The Algorithmic Clinician- AI's Revolution in Specialty Medicine

Editors
Asst. Prof. Dr. Hale KOKSOY
Asst. Prof. Dr. Usame Omer OSMANOGLU
Assoc. Prof. Dr. Hatice Seyma AKCA

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KİTAPTA BÖLÜM ADI: Artificial Intelligence in Pathology: Principles, Applications, and Future Perspectives

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02/01/2026

Konu : Uluslararası Yayınevi Belgesi

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3-Öğrenci eğitim merkezleri, yurtlan pansiyonları, yemekhaneleri, kafeteryaları, spor salonları, kütüphaneleri işletmek.

4-Konuları ile ilgili müzik kursları, bilgisayar kursları bu ve buna benzer eğitim alanında kurslar düzenlemek.

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6-İnsanın, özellikle okul öncesi çocukların bilgi, kültür, sanat ve mesleki yönden gelişmesi ve yetişmesi için özel teşebbüs olarak, Çocuk Yuvası, Ana Okulu ve Kreşler, Okul öncesi eğitim ve öğretim, Öğrenci etüt eğitim

her türlü sosyal ve kültürel hizmetlerde bulunmak, spor sergi ve her türlü faaliyetlerde bulunmak.

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16-Şirket Yurtiçinde ve Yurtdışında mümessillik, distribütörlük alabilir veya verebilir. Ardiye, özel antrepo.özel depo işletmeciliği ve taahhüt işleri ile uğraşabilir.

17-Şirket konuları ile ilgili yerli ve yabancı gerçek ve tüzel kişilerle işbirliği yaparak yeni şirketler kurabilir, kurulmuş şirketlere iştirak edebilir. Yurt içinde veya dışında temsilcilikler açabilir.

Şirket amaç ve konusunu gerçekleştirebilmek için konusu ile ilgili olarak:

A-) Şirketin faaliyet konusuna giren yatırımlarda bulunabilir, her

istikrazda bulunmak, bu mallar üzerinde irtifak irtikap hakları ile medeni kanun hükümleri gereğince bilcümle ayni ve nakdi haklarla ilgili her çeşit iltizami ve tasarruf işlemleri, aracılık yapmamak şartı ile yapmak. (Gümrük komisyonculuğu hariç) yukarıda gösterilen konulardan başka, ileride şirket için faydalı ve lüzumlu görülecek başka işlere girişilmek istendiği taktirde ortaklar kurulu kararına istinaden şirket bu işleri de yapabilecektir.

D-) Yurtiçi ve Yurtdışı fuar ve sergilere katılmak maksat ve mevzuuna dair ürünlerin tanıtımı, toptan alım, satım ve ticareti ile yurt içinde ve yurt dışında büro, şube, teşhir yerleri, mağazalar, dükkanlar açmak işletmek veya işlettirmek, konusuna giren işlerle ilgili taşıt araçları alır satar; kiralar veya kiraya verir.

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The Algorithmic Clinician: AI's Revolution in Specialty Medicine

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ÖNSÖZ

Yapay zeka (Artificial Intelligence, AI), son yıllarda tıbbın temel bilimlerinden klinik uygulamalarına kadar uzanan geniş bir alanda köklü bir dönüşüm sürecini başlatmıştır. Büyük ölçekli verilerin analizi ile makine öğrenmesi ve derin öğrenme temelli yaklaşımlar; tanı, tedavi, prognoz ve klinik karar destek süreçlerinde önemli ilerlemeler sağlamıştır. Bununla birlikte, tıpta yapay zekanın artan kullanımı yalnızca teknik bir gelişme olarak değil; etik sorumluluk, klinik muhakeme, hasta güvenliği ve insan merkezli sağlık hizmetleri bağlamında ele alınması gereken çok boyutlu bir dönüşüm olarak değerlendirilmelidir.

Bu kitap, tıpta yapay zekanın bilimsel temellerini, metodolojik altyapısını ve klinik uygulamalarını, disiplinler arası ve bütüncül bir bakış açısıyla ele almayı amaçlamaktadır. İçeriğinde; temel bilimlerde yapay zeka destekli analiz yaklaşımlarından çoklu omik verilerin yorumlanmasına, dijital patoloji ve tıbbi görüntüleme sistemlerinden klinik karar destek mekanizmalarına; cerrahi, yoğun bakım, halk sağlığı, genetik, psikiyatri ve etik boyutlara kadar uzanan güncel ve özgün konular yer almaktadır. Her bölümde, yapay zekanın sunduğu olanaklar kadar, sınırları, riskleri ve klinik sorumlulukları da dengeli bir biçimde ele alınmıştır.

Bu eserin temel amacı, yapay zekayı insan hekimliğinin yerine geçen bir unsur olarak değil; klinik deneyimi, bilimsel muhakemeyi ve etik duyarlılığı destekleyen tamamlayıcı bir araç olarak konumlandırmaktır. Bu doğrultuda kitap, algoritmik çıktılar ile klinik kararlar arasındaki ilişkinin eleştirel bir bakış açısıyla değerlendirilmesini teşvik etmekte; şeffaflık, açıklanabilirlik, veri güvenliği ve hasta mahremiyeti gibi temel etik ilkeleri merkeze almaktadır.

Bu kitap; hekimler, temel bilim araştırmacıları, sağlık alanında çalışan mühendisler, araştırmacılar ve lisansüstü öğrenciler için hem kuramsal hem de uygulamaya yönelik bir başvuru kaynağı olarak tasarlanmıştır. Amacımız, tıpta yapay zekanın olanaklarını bilimsel titizlik ve etik sorumluluk çerçevesinde ele alarak, gelecekteki araştırmalara ve klinik uygulamalara sağlam ve sürdürülebilir bir zemin oluşturmaktır.

Başta değerli editörlerimiz olmak üzere, Karamanoğlu Mehmetbey Üniversitesi'nden ve farklı üniversitelerden kitabın hazırlanmasına katkı sunan tüm akademisyenlere içtenlikle

teşekkür ederiz. Ayrıca bu kitabın oluşmasında desteklerini esirgemeyen Karamanoğlu Mehmetbey Üniversitesi Rektörü Sayın Prof. Dr. Mehmet Gavgalı'ya ve KMU Tıp Fakültesi Dekanı Sayın Prof. Dr. Pembe Oltulu'ya saygı ve şükranlarımızı sunarız.

Tıpta yapay zekanın, insan onurunu ve hasta yararını merkeze alan bir anlayışla gelişerek daha güvenli, etkili ve sürdürülebilir bir sağlık sistemine katkı sağlaması dileğiyle…

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Haziran, 2026

PREFACE

Artificial intelligence (AI) has initiated a profound transformation across a broad spectrum of medicine, from basic sciences to clinical practice. Advances in large-scale data analysis, machine learning, and deep learning have significantly improved diagnostic accuracy, treatment planning, prognostic assessment, and clinical decision support systems. Nevertheless, the increasing integration of artificial intelligence into medicine should be regarded not merely as a technological advancement but as a multidimensional transformation that must be addressed within the framework of ethical responsibility, clinical judgment, patient safety, and human-centered healthcare.

This book aims to present the scientific foundations, methodological infrastructure, and clinical applications of artificial intelligence in medicine from an interdisciplinary and holistic perspective. The chapters cover a wide range of contemporary topics, including AI-assisted analytical approaches in basic medical sciences, multi-omics data interpretation, digital pathology, medical imaging systems, clinical decision support mechanisms, surgical and intensive care applications, public health, medical genetics, psychiatry, and ethical considerations. Throughout the book, both the opportunities and the limitations, risks, and clinical responsibilities associated with artificial intelligence are discussed in a balanced manner.

The primary objective of this volume is to position artificial intelligence not as a replacement for human physicians but as a complementary tool that supports clinical experience, scientific reasoning, and ethical awareness. Accordingly, the book promotes a critical evaluation of the relationship between algorithmic outputs and clinical decision-making, emphasizing fundamental ethical principles such as transparency, explainability, data security, and patient privacy.

This book is designed as a theoretical and practical reference resource for physicians, basic science researchers, engineers working in healthcare, researchers, and graduate students. Our aim is to address the potential of artificial intelligence in medicine within a framework of scientific rigor and ethical responsibility, thereby providing a solid and sustainable foundation for future research and clinical applications.

We would like to express our sincere gratitude to the editors and to all academic contributors from Karamanoğlu Mehmetbey University and other institutions who participated in the preparation of this book. We also respectfully acknowledge the support of the Rector of Karamanoğlu Mehmetbey University, Prof. Dr. Mehmet Gavgali, and the Dean of the Faculty of Medicine, Prof. Dr. Pembe Oltulu.

With the hope that artificial intelligence in medicine will continue to evolve in a manner that prioritizes human dignity and patient benefit, contributing to a safer, more effective, and sustainable healthcare system…

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BASIC SCIENCES

CHAPTER 1

Next-Generation Hybrid Toxicology: Multimodal AI Integration Across Stem Cell–Based Models, Organ-on-a-Chip Systems, Animal Models, and Digital Twins

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1. Introduction: The Molecular Revolution in Toxicology

Since the beginning of the 21st century, toxicological research within the health sciences has encountered structural limitations in addressing emerging experimental challenges (1). This period has necessitated a fundamental transition from traditional observational methodologies to a data-driven, mechanistically based discipline (2). This "Molecular Revolution" facilitates a high-resolution characterization of xenobiotic interactions with biological systems by extending beyond macroscopic observations to encompass genomic, transcriptomic, and proteomic layers (3). This paradigm shift is further supported by the evolution of experimental platforms, where the transition from traditional animal models to advanced stem cell-based and in vitro systems provides more accurate representations of human physiological responses (4). Modern toxicology has evolved far beyond being a mere safety assessment tool. It has emerged as an interdisciplinary field of translational medicine that integrates the holistic perspective of systems biology with the predictive power of computational sciences.

This contemporary approach, which deconstructs molecular pathogenesis at both the cellular and systemic levels, uses artificial intelligence (AI) to transform large datasets into meaningful clinical outcomes (5). Consequently, biological systems are reconstructed in digital environments, allowing in vivo processes to be simulated through advanced in silico models (6).

1.1. Scope and Objective of the Chapter

In light of this transforming scientific landscape, the primary objective of this chapter is to elucidate the transformative impact of integrating Medical Biology and Artificial Intel-

ligence within the framework of next-generation toxicological research. This work analyzes how high-fidelity biomimetic systems, specifically induced Pluripotent Stem Cells (iPSCs) and Organ-on-a-Chip (OoC) technologies, establish a biological infrastructure for advanced algorithmic synthesis.

Another critical objective of this chapter is to present the conceptual foundations of Digital Twin technology, which can simulate complex homeostatic regulation and systemic feedback loops that traditional models cannot adequately explain. By merging biological insight with algorithmic power, this study aims to provide a comprehensive roadmap for precision toxicology applications. Ultimately, it discusses how this hybrid synergy enhances clinical safety, optimizes drug development processes, and initiates a new era in personalized healthcare.

1.2. From Descriptive to Predictive: Paradigm Shifts in Risk Assessment

Historically, toxicological risk assessment has been grounded in a descriptive foundation (6). This classical experimental approach is based on the principle of extrapolating data obtained from animal models subjected to high-dose exposure to human physiology (7). However, contemporary toxicogenomic data reveal significant limitations within this methodology (8). In particular, interspecies biological differences and the dose-response relationships governed by homeostatic mechanisms alter the predictive power and clinical relevance of traditional models (9). At this juncture, modern toxicology has moved away from purely observational methods and has adopted a data-driven architecture capable of predicting molecular aberrations and cellular signaling pathways.

Current literature now centers on the "Predictive Toxicology" framework (10). This approach examines the toxic process as an integrated whole, ranging from the initial molecular trigger (MIEs) to organ-level damage, within the context of "Adverse Outcome Pathways" (AOPs) (11). The most critical aspect of this transition is the integration of in silico (computational) models with in vitro (cellular) data. This synergy minimizes uncertainty in risk assessment and transforms the field into a proactive system capable of predicting toxicity at the molecular level (12).

1.3. The Role of Medical Biology: Advancing Bio-mimetic Models

Fundamental advancements in medical biology and tissue engineering are redefining the biological infrastructure of toxicology (13). Research utilizing human-derived Induced Pluripotent Stem Cells (iPSCs) has not only overcome ethical barriers but has also enabled the investigation of inter-individual genetic diversity and personalized sensitivities (14).

As a critical component of this process, Organ-on-a-Chip (OoC) technologies create microphysiological systems that emulate tissue-tissue interfaces, fluid dy-

namics, and mechanical stress (15). Unlike static cell cultures, these systems can model dynamic organismal responses, such as homeostasis and inflammation, with high fidelity (16). Consequently, medical biology has become the primary source of the high-quality, biologically relevant data essential for artificial intelligence algorithms.

1.4. Multimodal AI Framework: Synthesizing Heterogeneous Data Streams

At the core of the "Next-Generation" transition in toxicology are Multimodal Artificial Intelligence (AI) architectures that can process data from diverse sources simultaneously and seamlessly (17). Traditional machine learning models, which focus on unimodal datasets such as chemical structures (QSRR/QSAR) or isolated cellular images, often fail to account for the multi-layered and dynamic complexity of biological systems (18). This limitation precludes a comprehensive understanding of non-linear biological processes and systemic interactions (19). Factorial experimental design offers a strategic framework for deciphering these nonlinear interactions within biological systems (20).

Resolving biological complexity requires the Multimodal Framework to synthesize the following factors into a unified analytical plane:

Molecular Descriptors: Quantitative analysis of structure-activity relationships.

High-Content Imaging (HCI): Spatial analysis of cellular morphology and phenotypic alterations.

Multi-omic Datasets: Molecular signatures at genomic, transcriptomic, and metabolomic levels.

Clinical and Phenotypic Data: Retrospective and prospective data reflecting the systemic responses of the living organism. The integration of these heterogeneous data streams through a central computational engine is illustrated in Figure 1, showcasing the transition from diverse biological inputs to predictive digital outputs.

This comprehensive integration possesses the potential to transform static data into a dynamic simulation layer: Digital Twins. Digital Twin technology models the biological responses to xenobiotic exposure within the framework of homeostatic regulation and feedback loops that govern systemic integrity (21). It enables the high-fidelity representation of in vivo physiological processes within a digital environment. Consequently, this multidimensional methodology liberates toxicological decision-support mechanisms from traditional constraints, offering faster, cost-effective, and personalized precision-toxicology foresight aligned with the principles of modern medicine.

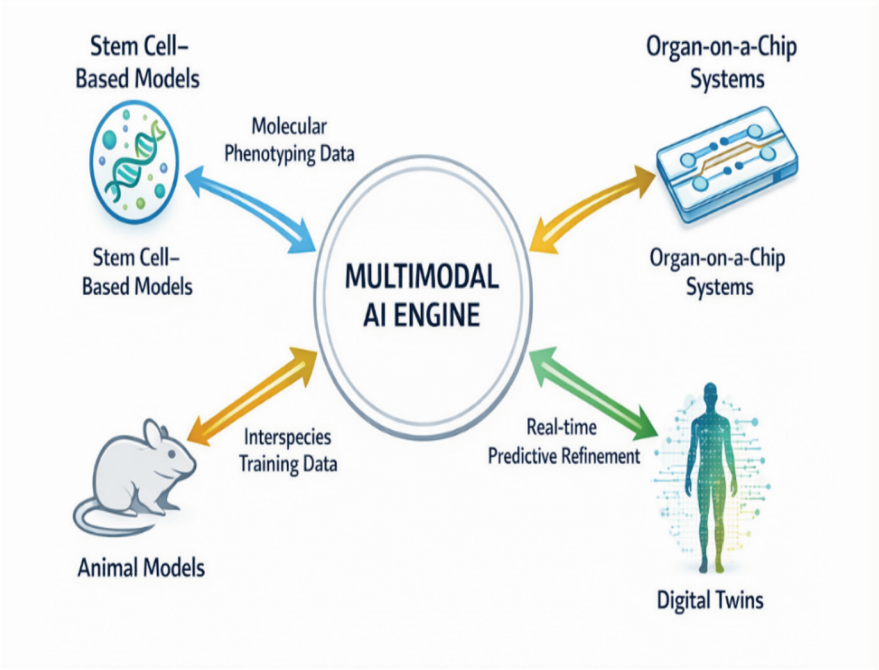


Figure 1. Conceptual Framework of the Hybrid Toxicology Ecosystem

2. Medical Biology Foundations: Signaling Pathways and Cellular Stress

The predictive capacity of artificial intelligence in toxicology depends on the precision with which molecular mechanisms are defined at the cellular level. This section examines the biological components of toxicity and the accelerating role of AI within these processes.

2.1. Toxicity Mechanisms

Xenobiotic exposure triggers a series of complex signaling pathways within the cell. Traditionally, toxicity was defined primarily through cell death or morphological changes. However, contemporary assessments increasingly prioritize sub-mechanisms such as oxidative stress, mitochondrial dysfunction, and DNA damage response (21-23). By analyzing the cross-talk between these multidimensional mechanisms, artificial intelligence can establish a systemic toxicity profile that transcends single-parameter observations.

2.2. Epigenetic Markers

Toxicity is not limited to genetic sequences; epigenetic modifications, such as DNA methylation, histone modifications, and changes in microRNA expression, reflect the long-term effects of exposure (22). These epigenetic alterations generally produce cumulative,

complex datasets. Artificial intelligence algorithms detect hidden patterns within these complex epigenomic maps, playing a critical role in predicting the transgenerational or long-term effects of exposure.

2.3. Molecular Targets: The Speed of AI in Novel Biomarker Discovery

The most transformative contribution of AI in this field is the radical acceleration of novel biomarker discovery. Traditional biomarker discovery relies on years of laboratory research, high-cost processes, and trial-and-error methodologies (23). In contrast, contemporary AI can scan multi-omic data to identify specific proteins or gene expression signatures associated with toxicity within weeks. This speed is derived not only from data-processing capacity but also from AI's ability to prioritize candidate molecules within biological pathways and from its in silico validation capabilities. Consequently, failure rates in the preclinical stages of drug development are minimized, allowing for the rapid definition of personalized safe dose ranges.

3. Advanced Cell Culture Systems and AI Integration

The primary reason for moving away from animal models traditionally considered the "gold standard" in toxicological research is their inability to represent human physiology accurately. To fill this gap, advanced cell culture systems have been integrated with artificial intelligence's data-mining capabilities. This synergy transforms toxicology from an empirical discipline into a predictive science.

3.1. iPSC and Three-Dimensional (3D) Models

Induced Pluripotent Stem Cell (iPSC) technology has resolved ethical debates and provided the opportunity to study a specific patient's genetic background in a laboratory environment (24). Traditional two-dimensional (2D) cultures are insufficient for reflecting in vivo conditions, as they cannot simulate cell-cell and cell-matrix interactions.

In contrast, iPSC-derived organoids and 3D spheroid models emulate tissue architecture and cellular behavior (25). By analyzing the complex signaling data obtained from these 3D models, AI models not only determine the effect of a drug on the target cell but also its interactions within the tissue integrity. The most critical point here is that iPSC technology provides a massive, "genetically diversified" training dataset for artificial intelligence.

3.2. Automated High-Content Screening (HCS)

In modern laboratories, HCS systems simultaneously image the cellular effects of thousands of compounds. However, these systems generate high-byte image data in every experiment. At this stage, "Deep Learning" algorithms come into play. Traditional analysis

methods focus on a limited number of morphological parameters (cell size, nuclear shape, etc.). AI-based HCS analysis, however, simultaneously evaluates thousands of phenotypic features that the human eye cannot detect (26). These algorithms identify "sub-lethal" changes early and grade a xenobiotic's toxic potential with much higher sensitivity. The application of probit analysis provides a mathematically rigorous approach for determining these sensitive toxicological thresholds (27).

3.3. Organ-on-a-Chip (OoC) Dynamics and Data Integration

OoC systems represent the most advanced stage of the 'hardware' layer in modern toxicology. These microengineered devices meticulously emulate the complex microphysiological environments of human organs, incorporating essential parameters such as interstitial fluid flow, oxygen gradients, and biomechanical stresses, including shear stress and cyclic stretching. Unlike traditional static 2D cultures, OoC platforms possess the unique capacity to model xenobiotic bioactivation and multi-organ crosstalk, such as the Liver-Kidney-Gut axis, which is crucial for understanding systemic toxicity and metabolic clearance (28).

The high-frequency, real-time data streams generated by these platforms constitute a vital dynamic input for advanced AI engines. By continuously monitoring subtle fluctuations in oxygenation, extracellular pH, and metabolite concentrations using integrated on-chip electrochemical and optical sensors, AI algorithms can construct a 'live' toxicity trajectory. This shift from endpoint-based analysis to continuous temporal monitoring allows for the detection of early-stage cellular stress before irreversible damage occurs. To achieve superior physiological fidelity, these hybrid platforms utilize AI-driven closed-loop feedback systems. These intelligent loops autonomously modulate microfluidic flow rates, nutrient delivery, and xenobiotic concentrations in response to real-time cellular signaling and metabolic demands. Such automated optimization ensures that the Digital Twin remains precisely synchronized with the biological 'wetware' response, effectively minimizing experimental artifacts and enhancing reproducibility (28-31).

The clinical applicability of these hybrid models, which bridge the critical gap between benchside bioengineering and bedside precision medicine, is further detailed in Table 1 across various medical specialties (29-31). By integrating patient-specific genetic backgrounds with real-time physiological monitoring, AI-driven OoC platforms transcend traditional high-throughput screening, evolving into powerful tools for predicting individualized drug responses and identifying safe therapeutic windows (29).

Table 1: Summary of Hybrid Model Components and Multimodal AI Integration Across Clinical Specialties (Note: Synthesized and adapted by the author based on the frameworks of Li et al. (2025), Deng et al. (2023), and Haddrick & Simpson (2019) (29–31).

Clinical Specialty	Hybrid Model Components	Multimodal AI Integration	Clinical & Research Goal
Ophthalmology	Retina-on-a-Chip + iPSC-derived Photoreceptors	Image-based AI for morphological analysis and Real-time Predictive Refinement	Screening for retinal drug toxicity and personalized treatment for macular degeneration.
Orthopedics	Bone-on-a-Chip + Biomechanical Sensors + Digital Twins	Data Fusion of mechanical stress sensors and predictive virtual simulations	Modeling implant integration and identifying osteotoxicity in new biomaterials.
Microbiology & Infectious Dis.	Lung/Gut-on-a-Chip + Pathogen Co-culture	Multimodal AI for pathogen-host interaction modeling and antimicrobial resistance prediction	Assessing drug permeability and inflammatory responses in complex microenvironments.
Neurology	Blood-Brain Barrier (BBB)-on-a-Chip + Neural Organoids	Molecular Phenotyping of neural signaling and interspecies translation from animal data	Evaluating neurotoxicity and drug delivery across the BBB for Alzheimer's and Parkinson's.
Oncology	Tumor-on-a-Chip + Patient-derived Organoids	Predictive Simulations for individual drug response and therapeutic resistance modeling	Personalized oncology and optimization of patient-specific chemotherapy regimens.
Cardiology	Heart-on-a-Chip + iPSC-Cardiomyocytes + Sensors	Real-time signal processing of electrophysiological data and digital twin modeling	Detecting pro-arrhythmic effects of non-cardiac drugs (Cardiotoxicity screening).

4. The Transition from Animal Models to Digital Twins

The most significant challenge in toxicology is the need to rely on data from biologically distinct species when assessing what is "safe for humans." However, digitized medical biology resolves this issue by establishing an "interspecies bridge."

Table 2: Structural and Functional Comparison: Traditional & Hybrid Toxicology Ecosystem (Note: Table 2 is synthesized and adapted from the integrated frameworks of Li et al. (32), Gangwal & Lavecchia (33), and FDA TranslAI (34).

Feature	Traditional Toxicology	Hybrid Toxicology Ecosystem
Primary Method	Primarily in vivo animal testing and static in vitro 2D cell cultures.	**Integrated** "Unified Ecosystem" combining Stem Cells, Organ-on-a-Chip, Animal Models, and Digital Twins.
Cost Efficiency	**High** (Extensive animal housing, long-term maintenance, and labor-intensive protocols).	**Optimized** (High initial R&D, but significant long-term savings through simulation-led refinement).

(Continued)

Table 2: Structural and Functional Comparison: Traditional & Hybrid Toxicology Ecosystem (Note: Table 2 is synthesized and adapted from the integrated frameworks of Li et al. (32), Gangwal & Lavecchia (33), and FDA TranslAI (34). (Continued)

Feature	Traditional Toxicology	Hybrid Toxicology Ecosystem
Timeframe	**Long** (Months to years for chronic toxicity and multi-generational studies).	**Rapid** (Accelerated by Real-time micro-physiological data and high-speed AI simulations).
Ethical Approval	**Highly Stringent** (Significant ethical hurdles due to extensive animal use; 3Rs challenges).	**Streamlined** (Focuses on Reduction and Replacement via human-specific digital and micro-models).
Human Translatability	**Low to Moderate** (Interspecies differences often lead to clinical trial failures).	**High** (Utilizes Human-specific genetic responses and real-time predictive refinement for human biology).
AI-Enabled Prediction Power	**Static/Minimal** (Limited to linear correlation and simple statistical modeling).	**Superior** (Multimodal AI Engine) (Continuous learning from Interspecies Training Data to provide high-fidelity toxicity forecasts).

4.1. Interspecies Bridging

The high failure rate in translating data from animal experiments to human clinical outcomes has necessitated a robust methodological shift in toxicology (32). Traditional methods attempt to map metabolic pathways in rodent physiology linearly to humans, often overlooking non-linear biological complexities. In contrast, using "interspecies training data," artificial intelligence predicts which molecular deviations observed in animal models accurately correspond to human physiological responses through advanced non-linear algorithms (33).

Rather than discarding historical animal data, this process creates a **"translation layer"** that harmonizes in vivo results with human-specific data from iPSC-derived organoids and Organ-on-a-Chip (OoC) systems. This approach aligns with the **FDA's TranslAI initiative**, which employs generative AI models to translate experimental findings across domains—such as organ systems and in vitro-to-in vivo extrapolation (IVIVE) thereby supporting cross-model toxicology prediction and reducing dependence on conventional animal testing protocols (34). The structural and functional differences between these conventional methodologies and the proposed integrated framework are detailed in the comparative analysis provided in Table 2.

4.2. The 3Rs Principle in the AI Era (Ethical Optimization)

Artificial intelligence has elevated the classical 3Rs principle (Replacement, Reduction, Refinement) to a new dimension. Traditionally, the 3Rs focus on reducing the use of animals. However, AI-supported hybrid models have the potential to replace animal use (35,36) completely. By "learning" from data from thousands of historical animal experiments, AI algorithms minimize the need for new animal testing to predict a novel molecule's toxicity. This development accelerates ethical committees' decision-making processes and gives rise to the concept of "precision ethics."

4.3. Digital Twins

Digital Twin technology represents the ultimate output of these integrated efforts. A digital copy of an individual or an organ system is constructed by synthesizing genetic data from iPSCs, physiological data from OoC platforms, and clinical history. Digital Twins adapt xenobiotic exposure not as a static risk score, but as a dynamic process that evolves. Through this technology, the effects of a drug or an environmental toxin can be tested in a digital universe before any contact with a living organism. This marks the transformation of toxicology from a "reactive" field (analyzing after the event) into a "proactive" structure (preventing damage before it occurs) (37).

5. Case Study: AI-Driven Nanotoxicology of Saffron-Functionalized CuO2 Nanoparticles

In this section, Crocus sativus-functionalized copper dioxide nanoparticles (CS-CuO_2NPs), synthesized via a green chemistry approach, are evaluated within an AI-driven nanotoxicological framework. This study integrates cell culture-based experimental biology with data-driven artificial intelligence to provide a model for future smart drug delivery and targeted nanotherapy systems.

5.1. Green Synthesis and Multimodal Characterization

The CS-CuO_2NPs were obtained via a sustainable, cost-effective green synthesis protocol that leveraged the reducing and stabilizing capacity of saffron stigma extract. The phenolic compounds, flavonoids, and carotenoids in the extract facilitate the controlled transformation of Cu^{2+} ions into CuO_2 nanoparticles.

Physicochemical Digital Descriptors: To form the input layer of the AI model, the structural and morphological properties were quantified using the following techniques:

UV–Vis Spectroscopy: Optical confirmation of nanoparticle formation.

FTIR: Analysis of surface interactions between saffron biomolecules and the CuO^2 core.

XRD: Determination of crystalline phase and lattice parameters.

SEM/ TEM: Assessment of particle size, distribution, and morphology.

5.2. Biological Evaluation and Apoptotic Response in SH-SY5Y Cells

The biological impact of CS-CuO_2NPs was evaluated on the human neuroblastoma cell line SH-SY5Y. This line serves as a critical proxy for neural networks and brain-related toxicity. The experimental assays measured cellular uptake, dose-dependent cytotoxicity, and oxidative stress responses.

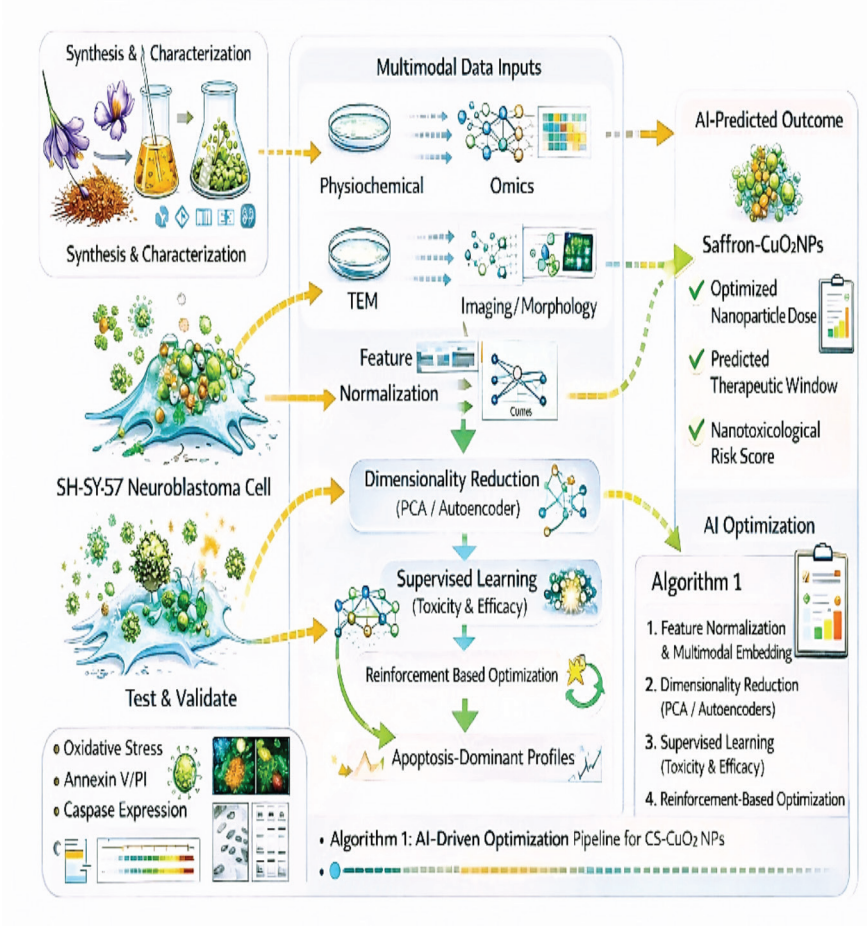


Figure 2. The Multimodal AI Integration Architecture for Nanotoxicological Optimization. The proposed architectural flow begins with the experimental characterization of green-synthesized CS-CuO2NPs, which is then integrated with the biological response data obtained from SH-SY5Y neuroblastoma cells. These multimodal data streams are processed by the XAI-NanoPredict computational engine, which utilizes MSE and Joint Optimization criteria to filter experimental noise. The final stage of the architecture defines the "Safe Therapeutic Window," enabling the transition from raw experimental observations to predictive, precision-based drug-delivery modeling.

Molecular Mechanisms of Programmed Cell Death: Apoptotic pathways were validated using Annexin V/PI staining and analyses of Caspase-3 and Caspase-9 expression. These molecular outputs confirmed that cell death occurred via controlled apoptosis rather than non-specific necrosis. These findings constitute the "Biological Response Layer" of the proposed AI architecture.

These findings constitute the 'Biological Response Layer' of the proposed AI architecture. To further refine the toxicological sensitivity of this layer, probit analysis was employed

to determine precise threshold levels and dose-response gradients, ensuring that sub-lethal apoptotic triggers are accurately distinguished from systemic background noise (27).

5.3. AI-Based Path Optimization and "XAI-NanoPredict" Framework

The hallmark of this study is the integration of traditional in vitro data into a predictive AI-driven framework. By analyzing multimodal data streams, the model moves beyond simple observation to proactive optimization. The architectural flow of this integration is visualized in Figure 3, which illustrates the transition from green synthesis and SH-SY5Y cellular response to the AI-driven optimization loop, identifying the ideal therapeutic window for smart drug delivery.

To operationalize this architecture, we propose Algorithm 1 (XAI-NanoPredict), which serves as the computational engine for calculating nanotoxicological risk scores and identifying optimal dosage. This algorithm facilitates with to systematic decision-making process by processing physicochemical descriptors and biological response layers simultaneously.

Methodological Foundation of the Optimization Pipeline: The structural integrity of this computational framework is grounded in advanced statistical optimization criteria. The structural integrity of XAI-NanoPredict is grounded in the MSE criterion for multiresponse robust design and the joint optimization of mean and standard deviation, ensuring that the calculated 'Safe Therapeutic Window' is robust to biological variability (39,40). This rigorous mathematical foundation allows the model to distinguish genuine toxicological signals from procedural artifacts, thereby enhancing the precision of the Nanotoxicological Risk Score.

This algorithm simultaneously processes the physicochemical descriptors of green-synthesized nanoparticles and biological response layers to define the "Safe Therapeutic Window mathematically".

Algorithm 1: XAI–NanoPredict Optimization Pipeline for CS–CuO2NPs

(Methodological Contribution for Citation)

I. Input (Data Acquisition Layer)

The algorithm accepts multimodal data streams concurrently:

- **Physicochemical Nanoparticle Descriptors:** Particle size (TEM/SEM), Zeta potential, crystalline phase (XRD), and surface functionalization data (FTIR/UV–Vis).
- **SH–SY5Y Biological Response Layer:** Dose–dependent cytotoxicity (IC_{50}), oxidative stress levels, and apoptotic markers (Caspase–3/9, Annexin V/PI).
- **High–Content Imaging Metrics:** Spatial analysis of cellular uptake kinetics and phenotypic alterations.

II. Optimization Objective

The core computational goal is to achieve a balance between safety and performance (23, 39–41):

- **Minimize:** Toxicology Score (T_{score})

- **Maximize:** Anticancer Efficacy (E_{eff})
- **Constraint:** Maintain the equilibrium between these two objectives using **Mean Squared Error (MSE)** and **Joint Optimization** criteria to filter experimental noise.

III. Execution Steps

- **Step 1: Multimodal Feature Embedding and Normalization** – Data from heterogeneous formats (images, numerical measurements, spectra) are integrated into a single analytical plane via the **MultiTox Framework** and normalized.
- **Step 2: Dimensionality Reduction via Autoencoder-based Latent Space Mapping** – Noise within high-dimensional biological datasets is filtered to map the most influential **"latent features."**
- **Step 3: Predictive Modeling of Multi-Responce Profiles-** The mapped latent features are processed throught robust predictive architectures to generate initial mathematical profiles for toxicity (Tscore) and efficacy(Eeff).
- **Step 4: Reinforcement-based Optimization Loop (Safe Therapeutic Window)** – Utilizing the **MSE criterion** (Köksoy, 2006) and the **joint optimization of mean and standard deviation** (Köksoy & Doganaksoy, 2003), the system is purified from experimental artifacts to determine the most stable and safe dosage range (39,40).
- **Step 5: Final Output Generation and XAI Reporting** – Generation of the final **Nanotoxicological Risk Score,** where the **Explainable AI (XAI)** justifies its decisions through biological rationales, such as specific pathway analysis.

IV. Output (Decision Layer)

- **Optimized Dose *(μg/ml)*:** The precise dosage providing maximum efficacy with minimum toxicity.
- **Predicted Therapeutic Impact:** A predictive assessment of treatment effectiveness supported by **digital twin simulations.**

5.4. Translational Perspective: From Lab to Clinic

This model provides a robust methodological bridge between Cell Culture, Artificial Intelligence, and Animal Models. The transition from static laboratory observations to a dynamic AI-driven framework represents a significant evolution in our research trajectory. While our previous studies used factorial experimental designs to deconstruct complex chemical interactions (20), the current AI-driven approach builds on this foundation by incorporating **real-time epigenetic feedback loops** (22). By evaluating the high-purity biological profile of **geographically indicated Safranbolu Saffron** against commercial alternatives, the model achieves a unique layer of specificity. This AI-filtered approach serves as a critical ethical and economic pre-filter, ensuring that only the most optimized nanotherapeutic candidates proceed to in vivo animal trials, thereby minimizing experimental risks and costs.

6. Multimodal Data Fusion and Algorithmic Challenges

The success of artificial intelligence in toxicology is not solely dependent on data volume; it is also fundamentally related to how these data are integrated (fused).

6.1. Integrating Heterogeneous Data

Toxicological datasets consist of fundamentally different formats, such as chemical structures, high-resolution cellular images, and multi-omic sequences. Integrating this heterogeneous structure into a single analytical plane requires 'Multimodal Data Fusion' algorithms (38, 42). By filtering noise and artifacts across different layers, AI perceives the effect of a xenobiotic on the cell as a holistic signal. The processing involved here is not merely placing data side by side but accurately representing the biological correlations between them through mathematical modeling. The mechanism by which multi-layered biological data are processed and synthesized by the AI engine based on the foundational architecture of the MultiTox model is detailed in Figure 2."

6.2. Explainable AI (XAI) in Toxicology: Beyond the Black Box

The integration of artificial intelligence into toxicological assessments often encounters a "trust barrier" due to the opaque nature of many complex algorithms. Traditional deep learning models frequently operate as "black boxes," providing high-accuracy toxicity predictions without explaining the underlying biological rationale. In clinical and regulatory contexts, a prediction of "toxic" is insufficient without an explanation of why and how that conclusion was reached.

Explainable AI (XAI) addresses this challenge by providing transparency to algorithmic decision-making processes (43). Within the proposed hybrid ecosystem, XAI does not merely output a risk score; it identifies the specific molecular features or cellular pathways that led to that score. For instance, an XAI framework can highlight which gene expression changes in an iPSC-derived organoid were most influential in predicting hepatotoxicity.

This interpretability is vital for the "Interspecies Bridging" process. By identifying the biological features that drive a prediction, researchers can determine whether the results are consistent with human or animal biology (43). Consequently, XAI transforms artificial intelligence from a blind prediction tool into an analytical partner that provides biological insights. This transparency is the key to gaining full acceptance from both the scientific community and regulatory bodies such as the FDA.

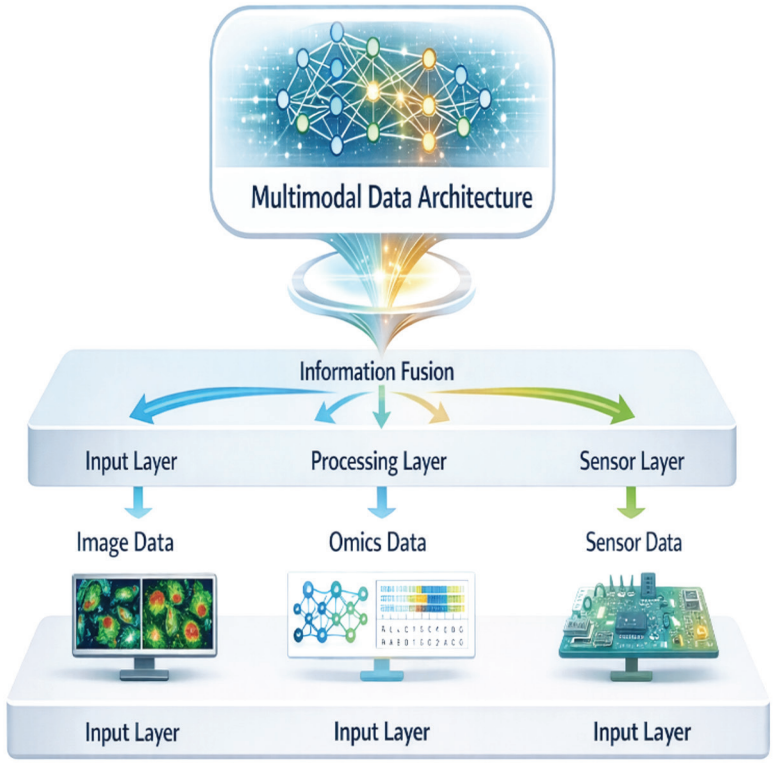


Figure 3. Multimodal Data Fusion Architecture (MultiTox Model)

7. Regulation, Standardization, and Personalized Toxicology

For next-generation models to transition from the laboratory to the clinic, they must be recognized by international regulatory authorities. This recognition is not merely a legal requirement but a fundamental step for the standardization of hybrid methodologies.

7.1. FDA Modernization Act 2.0

A historical turning point in toxicological research occurred with the enactment of the FDA Modernization Act 2.0. This legislation officially ended the 1938 requirement that all new drugs must be tested on animals before human clinical trials (44). This regulatory shift provides a formal mandate for the use of "New Approach Methodologies" (NAMs), such as Organ-on-a-Chip, iPSC models, and AI-driven simulations (45). This act does not merely suggest alternatives; it fundamentally redefines the legal infrastructure of drug safety by validating the predictive power of biomimetic and digital systems. The historical evolution from the mandatory animal testing era to the future "In Silico" vision, and the impact of these changes on the drug approval process, are summarized in Table 3.

7.2. Standardization and Validation

Despite the significant progress in legislative processes, the lack of standardized validation protocols remains a primary barrier to the widespread clinical and regulatory adoption of AI and Organ-on-a-Chip (OoC) models. The current landscape is characterized by a fragmented ecosystem in which diverse chip designs, varying microfluidic parameters, and proprietary AI algorithms are used across laboratories, severely complicating the reproducibility and cross-platform validation of toxicological data (46).

For these hybrid models to move beyond experimental "proof-of-concept" and gain full acceptance from regulatory bodies like the FDA, they must prove that they are as reliable, or more so, than the animal models they aim to replace. This transition requires not only technological innovation but also a "methodological bridge". Consequently, current research is intensely focused on establishing universal quality standards, such as Good Cell Culture Practice (GCCP 2.0) and standardized AI performance metrics, to ensure these systems provide the high-fidelity, reproducible evidence required for clinical applications. Without such rigorous standardization, the "trust barrier" between algorithmic predictions and biological reality will remain a significant obstacle to the era of personalized toxicology (47).

Table 3: The Evolutionary Shift in Toxicology Regulation (Adapted from 4, 43, 44, 46, 48).

Timeline / Milestone	Key Regulatory Shift	Facilitating Technology (Source)	Impact on Drug Approval Process
Pre-2022: Traditional Era	Mandatory animal testing for all IND (Investigational New Drug) applications.	**Animal Models (Primary focus for interspecies biological validation).**	High failure rates in clinical trials due to human-animal biological divergence (4).
Dec 2022: FDA Modernization Act 2.0	Elimination of the federal mandate for animal testing; acceptance of NAMs (New Approach Methodologies).	**Stem Cell–Based Models & Organ-on-a-Chip Systems (44).**	Allowed "human-specific genetic responses" to be submitted as primary safety data.
2025 - Present: Hybrid Integration	Shift towards "Weight of Evidence" (WoE) using integrated hybrid data streams.	**Multimodal AI Engine (Integration of omics and sensor data).**	Real-time Predictive Refinement enables faster identification of toxicity prior to human trials (43).
2025-2030: Future Vision: In Silico Era	Full acceptance of virtual clinical trials and digital evidence for rare diseases.	**Digital Twins & Predictive Virtual Simulations.**	Reduction in "Time-to-Market" by simulating long-term toxicity in virtual human cohorts (46).

7.3. Personalized Toxicology

The fundamental objective of this technological transformation is to conduct safety testing not for the "average person," but for a "specific individual." Models derived from an individual's iPSC cells and Digital Twin simulations can identify pharmacogenetic differences (drug-gene interactions) in advance. This approach elevates toxicology from a general safety assessment to a critical component of precision medicine applications (48).

Table 3 illustrates a profound shift in the pharmaceutical landscape, moving from traditional animal models toward a future defined by personalized, digital, and human-centric data. By replacing broad biological approximations with New Approach Methodologies (NAMs), the industry is transitioning from a reactive "trial and error" model to a proactive "predictive precision" model.

8. Conclusion: The Digital and Biological Transformation of Toxicology

As detailed throughout this study, toxicological science is evolving beyond its traditional observational roots to establish a new identity at the intersection of Artificial Intelligence (AI) and medical biology. The transition from rigid animal models to dynamic Digital Twins and personalized toxicity profiles represents more than a technical shift; it is a fundamental paradigm change in how we protect human health.

Artificial Intelligence serves as a "computational lens" for understanding complex biological systems by integrating iPSC-derived models, Organ-on-a-Chip (OoC) platforms, and multi-omic data streams. Regulatory milestones, most notably the FDA Modernization Act 2.0, solidify the legal foundation of this transformation. At the same time, Explainable AI (XAI), operationalized through models such as the XAI-NanoPredict proposed in this study, establishes a crucial bridge of trust between algorithmic predictions and biological reality. In conclusion, the historically "reactive" approach of analyzing xenobiotic effects after damage has occurred is being replaced by a "proactive" security system that simulates physiological effects in a digital universe before biological damage manifests. This hybridization of medical biology and AI will minimize risks in drug development and drastically reduce time-to-market for life-saving therapies. In the coming era, toxicology will function not merely as a risk-assessment discipline but as a digital security architecture that safeguards the quality of human life.

9. References

1. Stephens, M. L., et al. (2013). Evidence-based toxicology for the 21st century: opportunities and challenges. *ALTEX*, 30(1), 74–103. https://doi.org/10.14573/altex.2013.1.074
2. Jiang, X. C., Zhao, J. W., & Liu, J. X. (2025). Mechanistic insights and rational catalyst design in NOx electroreduction. *Nanoscale*, 17(26), 15628–15647. https://doi.org/10.1039/d5nr01682g
3. Zhao, Y., Yin, N., Yang, R., & Faiola, F. (2024). Recent advances in environmental toxicology: Exploring gene editing, organ-on-a-chip, chimeric animals, and in silico models. Food and chemical toxicology: an international journal published for the British Industrial Biological Research Association, 193, 115022. https://doi.org/10.1016/j.fct.2024.115022
4. Koksoy, H., & Kocabas, R. (2023). Stem Cell, Experimental Animals, and Cell Culture Studies in Diabetes. In: Current Multidisciplinary Approach to Diabetes Mellitus Occurrence Mechanism (pp. 125-142). Nobel Tıp Press. https://doi.org/10.69860/nobel.9786053359104.8
5. Manik, M. M. T. G., Mohonta, S. C., Karim, F., Miah, M. A., Islam, M. S., Chy, M. A. R., ... & Saimon, A. S. M. (2025). AI-driven precision medicine leveraging machine learning and big data analytics for genomics-based drug discovery. *Journal of Posthumanism*, 5(5), 4895-4915.
6. Bean, T. G. et al. (2024). Toxicological effects assessment for wildlife in the 21st century: Review of current methods and recommendations for a path forward. Integrated environmental assessment and management, 20(3), 699–724. https://doi.org/10.1002/ieam.4795
7. Kaplan, B. L. F., Hoberman, A. M., Slikker, W., Jr, Smith, M. A., Corsini, E., Knudsen, T. B., Marty, M. S., Sobrian, S. K., Fitzpatrick, S. C., Ratner, M. H., & Mendrick, D. L. (2024). Protecting Human and Animal Health: The Road from

Animal Models to New Approach Methods. *Pharmacological reviews*, 76(2), 251–266. https://doi.org/10.1124/pharmrev.123.000967

8. Davis, A. P., Wiegers, T. C., Sciaky, D., Barkalow, F., Strong, M., Wyatt, B., Wiegers, J., McMorran, R., Abrar, S., & Mattingly, C. J. (2025). Comparative Toxicogenomics Database's 20th anniversary: update 2025. *Nucleic acids research*, 53(D1), D1328–D1334. https://doi.org/10.1093/nar/gkae883
9. Koksoy, H., & Akca, H. S. (2026). Renal cell cytotoxicity and acute kidney injury: A clinical-biological evaluation of Maras powder (smokeless tobacco) induced nephrotoxicity in the emergency setting. *International Journal of Health Sciences of Northern Lights*, 5(3), 190–200. https://doi.org/10.5281/zenodo.18545418
10. Ajisafe, O. M., Adekunle, Y. A., Egbon, E., Ogbonna, C. E., & Olawade, D. B. (2025). The role of machine learning in predictive toxicology: A review of current trends and future perspectives. *Life sciences*, 378, 123821. https://doi.org/10.1016/j.lfs.2025.123821
11. Rim K. T. (2021). Application of the adverse outcome pathway framework to predict the toxicity of chemicals in the semiconductor manufacturing industry. *Molecular & cellular toxicology*, 17(3), 325–345. https://doi.org/10.1007/s13273-021-00139-4
12. Luechtefeld, T., Marsh, D., Rowlands, C., & Hartung, T. (2018). Machine Learning of Toxicological Big Data Enables Read-Across Structure Activity Relationships (RASAR) Outperforming Animal Test Reproducibility. *Toxicological sciences: an official journal of the Society of Toxicology*, 165(1), 198–212. https://doi.org/10.1093/toxsci/kfy152
13. Low, L. A., Mummery, C., Berridge, B. R., Austin, C. P., & Tagle, D. A. (2021). Organs-on-chips: into the next decade. *Nature Reviews*. Drug discovery, 20(5), 345–361. https://doi.org/10.1038/s41573-020-0079-3
14. Cerneckis, J., Cai, H., & Shi, Y. (2024). Induced pluripotent stem cells (iPSCs): molecular mechanisms of induction and applications. *Signal transduction and targeted therapy*, 9(1), 112. https://doi.org/10.1038/s41392-024-01809-0
15. Moore, M., Sriram, S., Ku, J., & Li, Y. (2026). Advances and Applications of Organ-on-a-Chip and Tissue-on-a-Chip Technology. *Bioengineering*, 13(1), 9. https://doi.org/10.3390/bioengineering13010009
16. Liu, X., Zhou, Z., Zhang, Y., Zhong, H., Cai, X., & Guan, R. (2025). Recent progress in organoids: Techniques, advantages, and applications. *Biomedicine & Pharmacotherapy*, 185, 117942.
17. Stahlschmidt, S. R., Ulfenborg, B., & Synnergren, J. (2022). Multimodal deep learning for biomedical data fusion: a review. Briefings in bioinformatics, 23(2), *bbab569*. https://doi.org/10.1093/bib/bbab569
18. Cherkasov, A. et al. (2014). QSAR modeling: where have you been? Where are you going to?. *Journal of medicinal chemistry*, 57(12), 4977–5010. https://doi.org/10.1021/jm4004285
19. Kitano H. (2002). Systems biology: a brief overview. Science (New York, N.Y.), 295(5560), 1662–1664. https://doi.org/10.1126/science.1069492
20. Koksoy, H., & Uraz, G. (2023). Biodegradation of 2, 4-D and trifluralin herbicides by the bacteria Pseudomonas spp. using factorial design of experiments. *Journal of International Environmental Application and Science*, 18(3), 87-99.
21. Lang, T., Lipp, A.-M., & Wechselberger, C. (2025). Xenobiotic Toxicants and Particulate Matter: Effects, Mechanisms, Impacts on Human Health, and Mitigation Strategies. *Journal of Xenobiotics*, 15(4), 131. https://doi.org/10.3390/jox15040131
22. Koksoy, H. (2025). Kanser Gelisimindeki Epigenetik Mekanizmalar I: DNA Metilasyonu, Histon Modifikasyonlari ve Kromatin Yapisi. In *Saglik & Bilim 2025: Kanserin Moleküler Temelleri* (1st ed., pp. 96–119). https://doi.org/10.59617/efepub2025204
23. Demrozi, F., Farmanbar, M., & Engan, K. (2025). Multimodal AI (MMAI) for Next-Generation Healthcare: Data Domains, Algorithms, Challenges, and Future Perspectives. *Current Opinion in Biomedical Engineering*, 100632.
24. Cerneckis, J., Cai, H., & Shi, Y. (2024). Induced pluripotent stem cells (iPSCs): molecular mechanisms of induction and applications. *Signal Transduction and Targeted Therapy*, 9(1), 112.
25. Park, S., Sharma, H., Kim, W., Gwon, Y., Kim, H., Choung, Y. H., & Kim, J. (2023). Microengineered organoids: reconstituting organ-level functions in vitro. *Organoid*, 3.
26. Chandrasekaran, S. N., Ceulemans, H., Boyd, J. D., & Carpenter, A. E. (2021). Image-based profiling for drug discovery: due for a machine-learning upgrade?. *Nature Reviews Drug Discovery*, 20(2), 145-159.
27. Koksoy, H., & Aslım, B. (2013). Determination of herbicide resistance in aquatic cyanobacteria by probit analysis. *Journal of Applied Biological Sciences*, 7(2), 37-41.
28. Gao, X., Wang, T., Huang, W., Liu, C., Zhang, Z., Deng, Y., & Huang, J. (2025). Multi-organ-on-a-chip: Modeling strategy, method, and biomedical applications. *Biomicrofluidics*, 19(4).
29. Li, B., Tang, Y., Huang, Z., Ma, L., Song, J., & Xue, L. (2025). Synergistic innovation in organ-on-a-chip and organoid technologies: Reshaping the future of disease modeling, drug development, and precision medicine. *Protein & cell*, pwaf058. Advance online publication. https://doi.org/10.1093/procel/pwaf058
30. Koksoy, H. (2026). A new frontier for in vitro biology: Retracing cell culture's path to organs-on-a-chip technology. *International Journal of Health Sciences of Northern Lights*, 5(3), 187–189. https://doi.org/10.5281/zenodo.18543705
31. Haddrick, M., & Simpson, P. B. (2019). Organ-on-a-chip technology: turning its potential for clinical benefit into reality. *Drug discovery today*, 24(5), 1217-1223.
32. Li, T., Chen, X., & Tong, W. (2024). Bridging organ transcriptomics for advancing multiple organ toxicity assessment with a generative AI approach. *NPJ digital medicine*, 7(1), 310. https://doi.org/10.1038/s41746-024-01317-z
33. Gangwal, A., & Lavecchia, A. (2025). Artificial intelligence in preclinical research: enhancing digital twins and organ-on-chip to reduce animal testing. *Drug discovery today*, 30(5), 104360. https://doi.org/10.1016/j.drudis.2025.104360

34. U.S. Food and Drug Administration (FDA). TranslAI Initiative. National Center for Toxicological Research; 2024. Available from: https://www.fda.gov/about-fda/nctr-research-focus-areas/translai-initiative
35. Azkona G. (2023). Implementing the 3Rs in Laboratory Animal Research-From Theory to Practice. Animals : an open access journal from MDPI, 13(19), 3063. https://doi.org/10.3390/ani13193063
36. Poh, W. T., & Stanslas, J. (2024). The new paradigm in animal testing - "3Rs alternatives". Regulatory toxicology and pharmacology : RTP, 153, 105705. https://doi.org/10.1016/j.yrtph.2024.105705
37. Woillard, J. B. et al. (2025). Digital pharmacological twins: Bridging multi-scale modelling and artificial intelligence for precision medicine: The DIGPHAT consortium. Therapie, S0040-5957(25)00112-X. Advance online publication. https://doi.org/10.1016/j.therap.2025.09.006
38. Park, J., & Lee, S. (2025). MoltiTox: a multimodal fusion model for molecular toxicity prediction. *Frontiers in toxicology*, 7, 1720651. https://doi.org/10.3389/ftox.2025.1720651
39. Köksoy, O. (2006). Multiresponse robust design: Mean square error (MSE) criterion. Applied Mathematics and Computation, 175(2), 1716-1729.
40. Köksoy, O., & Doganaksoy, N. (2003). Joint optimization of mean and standard deviation using response surface methods. *Journal of Quality Technology*, 35(3), 239-252.
41. Lin, Z., & Chou, W. C. (2022). Machine learning and artificial intelligence in toxicological sciences. *Toxicological Sciences*, 189(1), 7-19.
42. Demrozi, F., Farmanbar, M., & Engan, K. (2025). Multimodal AI (MMAI) for Next-Generation Healthcare: Data Domains, Algorithms, Challenges, and Future Perspectives. *Current Opinion in Biomedical Engineering*, 100632.
43. Singh, R., Zhou, K., & Auclair, J. R. (2025). Reimagining drug regulation in the age of AI: a framework for the AI-enabled Ecosystem for Therapeutics. *Frontiers in medicine*, 12, 1679611. https://doi.org/10.3389/fmed.2025.1679611
44. Zushin, P. H., Mukherjee, S., & Wu, J. C. (2023). FDA Modernization Act 2.0: transitioning beyond animal models with human cells, organoids, and AI/ML-based approaches. *The Journal of clinical investigation*, 133(21), e175824. https://doi.org/10.1172/JCI175824
45. Moon, H. R., Surianarayanan, N., Singh, T., & Han, B. (2023). Microphysiological systems as reliable drug discovery and evaluation tools: Evolution from innovation to maturity. *Biomicrofluidics*, 17(6), 061504. https://doi.org/10.1063/5.0179444
46. Marx, U. et al. (2016). Biology-inspired microphysiological system approaches to solve the prediction dilemma of substance testing. ALTEX, 33(3), 272–321. https://doi.org/10.14573/altex.1603161
47. Pamies, D. et al. (2022). Guidance document on Good Cell and Tissue Culture Practice 2.0 (GCCP 2.0). ALTEX,39,30–70. https://doi.org/10.14573/altex.2111011
48. Miedel, M. T., Schurdak, M. E., Stern, A. M., Soto-Gutiérrez, A., Strobl, E. V., Behari, J., & Taylor, D. L. (2025). Integrated Patient Digital and Biomimetic Twins for Precision Medicine: A Perspective. Seminars in liver disease, 45(4), 458–475. https://doi.org/10.1055/a-2649-1560

CHAPTER 2

Comparison of Traditional Statistical Methods with Machine Learning in Medicine

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1. Introduction

Although medical research has historically been shaped by traditional methods focusing on hypothesis testing, inferential statistics, and explaining causality (e.g., t-tests, ANOVA, linear and logistic regression), the exponential increase in clinical data has necessitated a paradigm shift in analytical methods (1). Particularly in complex fields where relationships between variables are generally non-linear, such as morphometric analysis, forensic medical identification, and medical imaging, data-driven machine learning (ML) algorithms offer a highly accurate predictive alternative by learning the inherent patterns within the data without adhering to predefined assumptions. Consequently, as medical analytics evolves toward establishing a balance between the 'explanatory' power of traditional statistics, which presents the effects of variables with p-values and confidence intervals, and the 'predictive' capability of ML; the analysis of the philosophical, technical, and clinical differences between these two approaches has become one of the most critical focal points of discussion in modern medicine (2).

Historically, medical research and knowledge generation have been conducted through small sample groups and controlled experiments within the framework of 'Evidence-Based Medicine' (EBM) principles. Traditional biostatistics, the gold standard in this 'small data' era, has focused on making inferences from restricted populations to the general public, determining whether the effect of a drug or a risk factor is statistically significant ($p < 0.05$), and excluding incidental findings. However, the concept of 'Big Data,' which entered medicine in the 21st century with the rise of 'Omics' technologies like genomics and proteomics, high-resolution medical imaging, and unstructured Electronic Health Records (EHR), has transformed data from being merely evidence into a colossal resource (3,4).

In the analysis of these massive data clusters, ML has shifted its primary focus from inference to prediction; and has entered the medical literature as a set of algorithms that 'learn' complex and non-linear relationships, which the human eye or traditional equations cannot detect, without the need to build a manual model (5). Understanding the fundamental philosophical and technical differences between traditional methods and this innovative approach, which generates individualized predictions for new patients by modeling hidden patterns in the dataset with mathematical functions, provides a critical academic framework to show clinicians and researchers which method is superior in which scenario (6).

2. Traditional Statistical Methods (TSM)

Traditional statistics primarily focuses on inferential statistics, generalizing from a sample taken from a population to the whole. Statistical models, which play the leading role in this inference process, function as fundamental tools that summarize the patterns in the data used (7). Regression models are among the most frequently used methods for this purpose, particularly in the medical literature. In a general framework, statistical models are used toward three primary objectives:

Discovering Causality: Although considered a fundamental tool for uncovering cause-and-effect relationships between events in various scientific fields, achieving this goal poses a significant practical challenge (8).

Making Predictions: Based on more practical reasons compared to causality research, it allows for predicting unknown situations in light of available data.

Describing Events: It is used to explain the structure and characteristics of existing data.

However, regardless of whether the task of a statistical model used in medical literature or other scientific disciplines is inference, prediction, or description, this traditional approach has a significant limitation: deep connections and relationships existing among variables in complex systems are generally ignored (9-10).

2.1. Logistic Regression

It is a frequently preferred method for predicting binary or multiclass outcomes, such as the presence or absence of a disease. Logistic regression models the probability of an event occurring using a combination of independent variables, offering high explainability. Each coefficient (Odds Ratio - OR) has clinical significance. It assumes an absence of multicollinearity among variables and a linear relationship between the logit and independent variables. Its performance decreases in incomplete or imbalanced datasets (11).

2.2. Linear Regression

Linear regression is a fundamental statistical method used to model the relationship between a dependent variable (target or outcome variable) and one or more independent

variables (explanatory or predictor variables). Its primary purpose is to draw the best-fitting straight line (regression line) that optimally represents the distribution of available data points and enables the prediction of future values (12).

2.3. Discriminant Function Analysis (DFA)

DFA is a multivariate statistical method that aims to construct mathematical functions (discriminant functions) that best distinguish groups from each other using continuous independent variables, based on observations whose belonging to two or more groups is already known. Its basic functions are to predict which group new observations, whose independent variable values are known, belong to and to determine which independent variables contribute most to the difference between groups (13).

Although DFA serves a similar purpose to logistic regression, it relies on stricter assumptions, such as the independent variables exhibiting a multivariate normal distribution and the groups having equal variance-covariance matrices (homogeneity). In medical literature, it is frequently used to categorize patients into diagnostic groups (healthy/sick) or to determine risk categories (14).

3. ML Algorithms

ML is a set of algorithms that enable systems to learn from data without being explicitly programmed (5). Some methods frequently preferred in medical diagnosis and prognostic modeling are summarized below:

3.1. Decision Tree (DT) and Random Forest (RF)

Decision trees create a tree structure by dividing data according to specific features. However, a single tree is prone to overfitting. The Random Forest algorithm consists of an ensemble of multiple decision trees and produces much more robust results by averaging predictions or using majority voting. Its ability to provide feature importance levels gives physicians an advantage in prioritizing clinical parameters (15).

3.2. Artificial Neural Networks (ANN)

Developed by drawing inspiration from the neuronal structure of the human brain, ANNs are particularly excellent at modeling non-linear relationships. They consist of input, hidden, and output layers. They achieve high accuracy rates in diagnosing complex medical images or multivariate morphometric measurements (15).

3.3. Support Vector Machines (SVR/SVM)

Support Vector Regression (SVR) and Classification (SVM) uses hyperplanes to separate data points. It is particularly successful in high-dimensional (where the number of fea-

tures exceeds the number of cases) clinical genetic data because it performs classification by maximizing margins (15).

3.4. Linear Regression Algorithm

From a ML perspective, Linear Regression is a fundamental supervised learning algorithm used to predict a continuous output value from labeled data. Although it is a method with statistical origins, in ML the focus is not on inferential analysis but on maximizing the generalization and prediction performance of the model on previously unseen data (15).

The algorithm models the relationship between input features (x) and target variable (y) in a linear plane. The learning process involves finding weighting coefficients (β) that minimize the square of the difference (cost function) between the predicted values and the actual values, usually using the Ordinary Least Squares (OLS) method or the Gradient Descent optimization algorithm, which is more efficient on large datasets (16,2).

3.5. Logistic Regression Algorithm

Logistic regression, although often confused with its namesake in traditional statistical methods, is a fundamental supervised learning algorithm used in ML literature, particularly for binary classification problems. The algorithm uses a logistic (sigmoid) function to model the relationship between input features and the probability of the target class occurring. Its main difference from traditional linear regression is that it compresses the output value from the range $[-\infty, +\infty]$ to the range $[0, 1]$. This allows the model's result to be interpreted as a probability value. The prediction process is typically carried out by assigning results above a certain threshold (e.g., 0.5) as "Class 1" and those below as "Class 0". In the context of ML, coefficients are usually optimized through Maximum Likelihood Estimation (MLE) and minimizing the Log-Loss (Cross-Entropy) function (18,2).

3.6. Elastic Net Regression

ElasticNet is a regularized regression method used especially in high-dimensional datasets (where the number of features exceeds the number of observations) and scenarios where there is high correlation (multicholinearity) among independent variables. This algorithm was developed as a hybrid of Lasso (L1) and Ridge (L2) regression methods (19). While Lasso regression has the ability to select features, it tends to select only one of the highly correlated groups of variables and reduce the others to zero. Ridge regression, on the other hand, keeps the variables in the model but reduces their coefficients. ElasticNet combines the penalty terms of these two methods in a linear combination, offering the advantages of both worlds: it can both produce sparse models (feature selection) and keep related variables in the model as a group (grouping effect) (20).

3.8. Ridge Regression

Ridge Regression (Tikhonov Regression) is a regularization method developed to address the overfitting and multicollinearity problems frequently encountered in multiple linear regression models. This algorithm uses a mechanism that penalizes the magnitude of the coefficients to control the complexity of the model. The algorithm works by adding an L2 penalty term to the traditional Least Squares (OLS) method. This penalty term consists of the sum of the squares of the coefficients of the independent variables multiplied by a setting parameter (λ or α). As the λ parameter increases, the coefficients of the model approach zero (but not exactly zero); this reduces the variance of the model while slightly increasing the bias, allowing the model to generalize better on new data outside the training data (21).

3.9. Lasso Regression

Lasso Regression (Least Absolute Shrinkage and Selection Operator) is an algorithm used in linear regression models for both regularization and feature selection. It is particularly preferred in high-dimensional datasets with a large number of independent variables, some of which have low contribution to the prediction, to improve model interpretability and prevent overfitting (2).

The algorithm's fundamental characteristic is the addition of an L1 penalty term to the cost function, which is the sum of the absolute values of the coefficients. Unlike Ridge regression, Lasso can reduce the coefficients of variables it deems insignificant to zero. This feature allows the algorithm to act as an automatic feature selector, enabling it to produce sparser and simpler models (2).

3.10. Naive Bayes Algorithm

Naive Bayes is a family of probabilistic classification algorithms based on Bayes' Theorem, focusing on the assumption of independence among features. The "naive" in the algorithm's name comes from the assumption that each feature in the dataset is completely independent of and equally influential on the existence of the target class (22).

While features in real-world data are often correlated, Naive Bayes, despite this simplified assumption, exhibits very high performance, especially in areas such as text classification, spam filtering, and medical diagnosis. The algorithm calculates the posterior probability for each class and assigns the data to the class with the highest probability. It stands out for its low computational cost and its ability to produce effective results even on small datasets (23).

3.11. Extreme Gradient Boosting (XGBoost)

Extreme Gradient Boosting (XGBoost) is a scalable and high-performance implementation of gradient boosting decision trees. Belonging to the ensemble learning family, this

algorithm builds a powerful prediction model by sequentially combining weak learners (typically shallow decision trees). The "Extreme" suffix stems from the algorithm's computational efficiency, speed, and ability to prevent overfitting (24).

The most fundamental difference between XGBoost and traditional gradient boosting methods is that it includes both L1 (Lasso) and L2 (Ridge) regularization terms in the cost function. Furthermore, it uses second-order Taylor expansion (Hessian) during the optimization of the loss function to perform more precise gradient updates. With features such as parallel processing, missing data management, and tree pruning, it is considered the "gold standard" in modern data science, especially in structured data (24).

3.12. K-Nearest Neighbour (K-NN)

K-Nearest Neighbor (K-NN) is a non-parametric and instance-based supervised learning algorithm used for both classification and regression problems. It is also referred to as a "lazy learner" in the literature because instead of deriving a general model (such as an equation or tree structure) from the data during the training phase, it stores all the training data in memory and performs the actual computation during the prediction (testing) phase. The algorithm's basic logic is based on the assumption that "similar objects are close to each other." When a new observation (e.g., a skeletal sample or clinical data) enters the system, the algorithm determines the observation's location in the feature space and finds its k nearest neighbors according to a chosen distance criterion. In classification tasks, the majority class among these k neighbors is assigned as the class of the new observation. In regression tasks, the average of the target values of the neighbors is taken (25).

3.13. Model Validation and Optimization

Clinical data are often unbalanced (e.g., the number of healthy individuals is much higher than the number of sick individuals). In this case, to improve the success of ML models, the minority class is synthetically replicated using algorithms such as SMOTE (Synthetic Minority Over-sampling Technique) (26).

To ensure that the model's performance is not random, methods such as K-Fold Cross-Validation are used. This approach divides the data into k parts, setting aside a different part for testing each time, allowing the model to yield statistically more robust results (27).

4. Performance Evaluation

Performance evaluation is the process of quantitatively measuring the ability of a developed ML model to generalize to new and unseen data beyond the training data. The success of the model is measured not only by the low error rate in the training data but also by the stability of its prediction performance on the test data. The evaluation process includes different metrics and validation strategies depending on the type of problem (classification or regression) (15).

4.1. Classification Metrics

In classification models, performance is generally analyzed using the following metrics derived from the Confusion Matrix (15):

Accuracy: The ratio of total correct predictions to all predictions.

Precision: How many of the predicted positives are actually positive.

Recall/Sensitivity: How many of the true positives are correctly predicted (a critical metric, especially in medical research).

F1-Score: The harmonic mean of precision and sensitivity; a more reliable indicator than accuracy in unbalanced datasets.

ROC-AUC: The area under the Receiver Operating Characteristic (ROC) curve; indicates the model's capacity to distinguish between classes.

4.2. Regression Metrics

In continuous value estimation, the following methods are used to measure the difference (error) between the predicted value ($\hat{y}$) and the actual value (y) (28):

MAE (Mean Absolute Error): The average of the absolute values of the errors.

MSE (Mean Squared Error): The average of the squares of the errors (It penalizes larger errors more).

RMSE (Root Mean Squared Error): The square root of the MSE; provides unit-based interpretability.

R^2 (Coefficient of Determination): Expresses how much of the variance in the dependent variable is explained by the independent variables.

5. Comparative Analysis

Traditional statistics and ML are not rivals, but complementary. Table 1 compares the key features of the two approaches from a medical perspective.

Table 1. Comparison of Traditional Statistics and Machine Learning in Medical Data Analysis

Feature	Traditional Statistical Methods (TSM)	Machine Learning (ML)
Primary Objective	Inference, Hypothesis Testing, Causality	Prediction, Pattern Recognition
Data Assumptions	Strict (Normality, Independence, etc.)	Flexible or None (Non-parametric)
Explainability	Very High	Variable
Data Size	Small/medium-scale	High performance with Big Data
Complex Relationships	Limited (Manual)	Very High (Automatic)
Error Management	Bias minimization	Variance and Overfitting balance

In the health literature, classification or regression studies can be found in many fields (29). Recently, ML methods have provided great support to these studies. The branches in which some studies were applied, performance metrics, sample size, and parameters used are given in Table 2. According to the results in this table, it is seen that ML methods take on a supportive-complementary role rather than replacing traditional statistical methods. In particular, ML methods play a saving role in the weakness of TSMs in nonlinear data structures and large datasets (30).

Table 2. Comparison of Traditional Statistics and Machine Learning Applications in Medical Literature

Study	Sample Size	Branch	Method	Performance Metrics	Variables
Osmanoglu et al. (30)	503	Forensic Sciences	Classification (ML)	Accuracy=0.85 AUC=0.85	4
Sweilum et al. (31)	261	Forensic Sciences	Classification (TSM)	Accuracy=0.89 AUC=0.84	4
Panga et al. (32)	110	Forensic Sciences	Classification (TSM)	Accuracy=0.86 AUC=0.91	6
Vatzia et al. (33)	100	Forensic Sciences	Classification (ML)	Accuracy=0.91 AUC=0.97	5
Ekizoglu et al. (34)	443	Forensic Sciences	DFA (TSM)	Accuracy=0.80 AUC=0.89	5
Yonguc et al. (35)	95	Forensic Sciences	Classification (ML)	Accuracy=0.90 AUC=0.92	4
Aytürk et al. (36)	540	Anatomy	Classification (ML)	Accuracy=0.85 AUC=0.85	6
Benazzi et al. (37)	114	Anatomy	DFA (TSM)	Accuracy=0.93 AUC=-	-
Zech et al. (38)	95	Anatomy	DFA (TSM)	Accuracy=0.79 AUC=-	-
Afrianty et al. (39)	91	Anatomy	Classification (ML)	Accuracy=0.86 AUC=-	-
Kumar et al. (40)	80	Anatomy	DFA (TSM)	Accuracy=0.86 AUC=-	-
Dülger et al. (41)	730	Gynecology Obstetrics	Regression (ML)	MAPE=8.87 MAE=284	7
Feng et al. (42)	7875	Gynecology Obstetrics	Regression (ML)	MAPE=6.10 MAE=199	4
Trujilo et al. (43)	250	Gynecology Obstetrics	Regression (ML)	MAPE=11.95 MAE=288	13
Osmanoglu et al. (44)	299	Cardiology	Classification (ML)	Accuracy=0.85 AUC=0.83	4
Celik et al. (45)	106	Pediatric Surgery	Classification (ML)	Accuracy=0.88 AUC=0.91	18
Keles et al. (17)	782	Anatomy	Classification (TSM)	Accuracy=- AUC=0.91	6
Emir et al. (46)	1447	Anesthesiology	Classification (ML)	Accuracy=0.91 AUC=0.90	10

TSM: Traditional Statistical Methods, ML: Machine Learning, DFA: Discriminant Function Analysis, AUC: Area Under the Curve

6. Conclusion and Future Perspectives

In medical sciences, ML is a powerful analytical tool that steps in where traditional statistics are limited, rather than replacing them. The ideal approach for clinicians and researchers is to choose the method according to the study's objective. If the primary goal is to understand the etiological significance of a risk factor and provide a plausible finding to the literature, then traditional statistics should be preferred; if the primary goal is to diagnose a disease or predict prognosis with the highest accuracy based on available clinical data, then ML should be chosen.

In the future, with the increased integration of Explainable AI (XAI) techniques into medicine, the "black box" perception of ML models will be broken, and they will become a routine tool in physicians' daily clinical decision-making processes.

7. References

1. Breiman L. (2001). Statistical modeling: The two cultures (with comments and a rejoinder by the author). Statistical science, 16(3), 199-231. https://doi.org/10.1214/ss/1009213726
2. Hastie T, Tibshirani R, Friedman J. (2009). The Elements of Statistical Learning: Data Mining, Inference, and Prediction (2nd ed.). Springer.
3. Beam AL, Kohane IS. (2018). Big Data and Machine Learning in Health Care. JAMA, 319(13), 1317–1318. https://doi.org/10.1001/jama.2017.18391
4. Obermeyer Z, Emanuel EJ. (2016). Predicting the future—big data, machine learning, and clinical medicine. The New England Journal of Medicine, 375(13), 1216-1219.
5. Osmanoğlu UÖ, Mutlu F, Gürsoy H, Şanlısoy S. (2019). Use of image processing and analysis in medicine and an application. Osmangazi Journal of Medicine, 41(1), 6-16. https://doi.org/10.20515/otd.426347
6. Topol EJ. (2019). High-performance medicine: the convergence of human and artificial intelligence. Nature Medicine, 25(1), 44-56. https://doi.org/10.1038/s41591-018-0300-7
7. Bzdok D, Altman N, Krzywinski M. (2018). Statistics versus machine learning. Nature Methods, 15(4), 233-234. https://doi.org/10.1038/nmeth.4642
8. Steyerberg EW. (2019). Clinical Prediction Models: A Practical Approach to Development, Validation, and Updating (2nd ed.). Springer.
9. Deo, R. C. (2015). Machine learning in medicine. Circulation, 132(20), 1920-1930.
10. Rajkomar A, Dean J, Kohane I. (2019). Machine learning in medicine. The New England Journal of Medicine, 380(14), 1347-1358.
11. Schober P, Vetter TR. (2021). Logistic Regression in Medical Research. Anesthesia & Analgesia, 132(2), 365-366. https://doi.org/10.1213/ANE.0000000000005247
12. Schneider A, Hommel G, Blettner M. (2010). Linear regression analysis: part 14 of a series on evaluation of scientific publications. Deutsches Ärzteblatt International, 107(44), 776. https://doi.org/10.3238/arztebl.2010.0776
13. Hair JF, Black WC, Babin BJ, Anderson RE. (2019). Multivariate data analysis.
14. Tabachnick BG, Fidell LS, Ullman JB. (2019). Using multivariate statistics (Vol. 6, pp. 497–516). Pearson.
15. Celik O, Osmanoglu UO. (2021). Investigation of Artificial Intelligence Applications Used in Scientific Studies in Healthcare. Journal of Multidisciplinary Developments. 6(1):44-53. ISSN 2564-6095. http://www.jomude.com/index.php/jomude/article/view/83
16. Bishop CM, Nasrabadi NM. (2006). Pattern recognition and machine learning (Vol. 4, No. 4, p. 738). New York: springer.
17. Keles A, Ayturk BG. (2026). A study on the morphometry and classification of variations of the suprascapular notch using computed tomography. Anat Sci Int 101, 183–192. https://doi.org/10.1007/s12565-025-00843-4
18. Hosmer Jr, DW, Lemeshow S, Sturdivant RX. (2013). Applied logistic regression. John Wiley & Sons.
19. Zou H, Hastie T. (2005). Regularization and variable selection via the elastic net. Journal of the Royal Statistical Society Series B: Statistical Methodology, 67(2), 301-320.
20. Friedman JH, Hastie T, Tibshirani R. (2010). Regularization paths for generalized linear models via coordinate descent. Journal of statistical software, 33, 1-22.
21. Hoerl AE, Kennard RW. (1970). Ridge regression: Biased estimation for nonorthogonal problems. Technometrics, 12(1), 55-67.
22. Mitchell TM. (1997). Does machine learning really work?. AI magazine, 18(3), 11-11.

23. Rish I. (2001). An empirical study of the naive Bayes classifier. In IJCAI 2001 workshop on empirical methods in artificial intelligence (Vol. 3, No. 22, pp. 41-46).
24. Chen T, Guestrin C. (2016). Xgboost: A scalable tree boosting system. In Proceedings of the 22nd acm sigkdd international conference on knowledge discovery and data mining (pp. 785-794).
25. Cover T, Hart P. (1967). Nearest neighbor pattern classification. IEEE transactions on information theory, 13(1), 21-27.
26. Chawla NV, Bowyer KW, Hall LO, Kegelmeyer WP. (2002). SMOTE: synthetic minority over-sampling technique. Journal of Artificial Intelligence Research, 16, 321-357.
27. Kohavi R. (1995). A study of cross-validation and bootstrap for accuracy estimation and model selection. In Ijcai (Vol. 14, No. 2, pp. 1137-1145).
28. Fawcett T. (2006). An introduction to ROC analysis. Pattern recognition letters, 27(8), 861-874.
29. Keleş A, Aytürk BG, Yılmaz HF, Osmanoğlu UÖ, Daşdelen D, Yeşildağ A. (2026). The Morphometric Relationship Between the Infraorbital Foramen and Key Midfacial Anatomical Landmarks. European Journal of Therapeutics, 32(2), 191–201. https://doi.org/10.58600/eurjther2891
30. Osmanoglu UO, Keleş A. (2026). Development of a sex estimation model using sternal morphometric parameters in a Turkish population. Australian Journal of Forensic Sciences, 1-15. https://doi.org/10.1080/00450618.2026.2644192
31. Sweilum OAH, Galal HKA, Habib RM. (2017). Determination of sex from the sternum and fourth rib measurements (a cross-sectional study (using thoracic computed tomography (ct) images. Egypt J Forensic Sci Appl Toxicol. 17(2):27–38. https://doi.org/10.21608/ejfsat.2017.46119
32. Panga SK, Sharma D, Wahi MK. (2025). Morphometric analysis of the human sternum for sex estimation: a quantitative approach in Forensic Medicine. Int J Curr Adv Res. 14(4):196–202. https://doi.org/10.24327/ijcar.2025.202.0043
33. Vatzia K, Fanariotis M, Bugajski M, Fezoulidis IV, Piagkou M, Vlychou M, Vassiou K, Vezakis I, Botis G, Papadodima S, et al. (2025). Assessing sternal dimensions for sex classification: insights from a Greek computed tomography-based study. Diagnostics. 15(13):1649. https://doi.org/10.3390/diagnostics15131649
34. Ekizoglu O, Hocaoglu E, Inci E, Bilgili MG, Solmaz D, Erdil I, Can IO. (2014). Sex estimation from sternal measurements using multidetector computed tomography. Med (Baltim). 93(27):e240. https://doi.org/10.1097/MD.0000000000000240
35. Yonguc GN, Kurtulus A, Bayazit O, Adıgüzel E, Unal I, Demir S, Acar K. (2015). Estimation of stature and sex from sternal lengths: an autopsy study. Anat Sci Int. 90(2):89–96. https://doi.org/10.1007/s12565-014-0235-0
36. Ayturk BG, Keles A, Osmanoglu UO. (2026). Sex estimation from sacral anatomy in Turkish adults: a machine learning–based analysis. Surg Radiol Anat 48, 96. https://doi.org/10.1007/s00276-026-03863-5
37. Benazzi S, Maestri C, Parisini S et al. (2009). Sex assessment from the sacral base by means of image processing. J Forensic Sci 54:249–254. https://doi.org/10.1111/J.1556-4029.2008.00947.X
38. Zech WD, Hatch G, Siegenthaler L et al. (2012). Sex determination from os sacrum by postmortem CT. Forensic Sci Int 221:39–43. https://doi.org/10.1016/j.forsciint.2012.03.022
39. Afrianty I, Nasien D, Haron H. (2022). Performance analysis of support vector machine in sex classification of the sacrum bone in forensic anthropology. Jurnal Teknik Informatika 15:63–72. https://doi.org/10.15408/JTI.V15I1.25254
40. Kumar J, Modi V. (2025). MRI-Based Sexual dimorphism in sacral morphometry: a forensic study in the central Indian population. SSR Inst Int J Life Sci 11:7229–7234. https://doi.org/10.21276/SSR-IIJLS.2025.11.2.35
41. Dülger Ö, Dursun A, Osmanoğlu UÖ. (2024). Fetal birth weight estimation with machine learning techniques in 15-40 weeks of pregnancy. Van Medical Journal. 31 (3):186-191. https://doi.org/10.5505/vmj.2024. 09797
42. Feng M, Wan L, Li Z, Qing L, Qi X. (2019). Feta weight estimation via ultrasound using machine learning. IEEE Access. 7:87783–87791
43. Trujillo O, Perez-Gonzalez J, Medina-Bañuelos V. (2020). Early Prediction of Weight at Birth Using Support Vector Regression. VIII Latin American Conference on Biomedical Engineering and XLII National Conference on Biomedical Engineering. CLAIB 2019. IFMBE Proceedings, vol 75. Springer.
44. Osmanoglu UO, Mutlu F. (2021). Prediction of Heart Failure Exitus with Machine Learning Classification Algorithms. Journal of Multidisciplinary Developments, 6(1):74-82. ISSN 2564-6095. Available at: <http://www.jomude.com/index.php/jomude/article/view/95>.
45. Çelik Ö, Aslan AF, Osmanoğlu UÖ, Cetin N, Tokar B. (2020). Estimation of renal scarring in children with lower urinary tract dysfunction by utilizing resampling technique and machine learning algorithms. Journal of Surgery and Medicine, 4(7), 573-577. https://doi.org/10.28982/josam.691768
46. Emir B, Ozmen E, Kilincer Bozgul SM, Acar C, Soyer N, Bozkurt D, Gonderen K, Efgan MG. (2026). XGBoost outperforms other machine learning models in diagnosing Sepsis-Associated Thrombocytopenia: a multicenter retrospective study. Front. Med. 13:1715551. https://doi.org/10.3389/fmed.2026.1715551

CHAPTER 3

An Innovative Hybrid Approach in the Stereological Analysis of Neurogenesis: An Artificial Intelligence–Assisted Automated Dissector and Cell Counting System

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1. Introduction

Neurogenesis is the process through which neural stem cells (NSCs) develop into fully functional mature neurons (1). For many years, it was believed that new neuron formation did not occur in the mammalian brain. However, postnatal neurogenesis was initially demonstrated in the rodent hippocampus and subsequently validated in the adult human hippocampus (2-4). In the adult mammalian brain, neurogenesis is known to persist mainly in two regions: the subgranular zone (SGZ) of the dentate gyrus in the hippocampus and the subventricular zone (SVZ) of the lateral ventricles. The process of new neuron formation occurring in these two regions is termed 'hippocampal neurogenesis' (5). In addition, evidence suggests that adult neurogenesis may also occur in other brain regions with specialized functions, including the neocortex of primates, the cerebellum of rabbits, the amygdala of mice, and the striatum of humans (6, 7). These findings have reinforced the understanding that the brain is not a static organ and can exhibit structural plasticity in specific regions throughout life. This has elevated the field of neurogenesis to a crucial position in contemporary neuroscience research. Despite these advances, the accurate quantitative evaluation of neurogenesis remains a methodological challenge.

Hippocampal neurogenesis is closely related to cognitive processes and can be affected by many physiological and pathological conditions, including neurodegenerative diseases, stress, and aging. In this context, extending the lifespan of cognitive health processes such as memory and learning is seen as a potential target (6, 8, 9). In the neurogenesis research, a range of histological and immunohistochemical markers are employed to identify recently formed neurons and progenitor cell populations. Cells are immunolabeled with markers including Ki-67 and bromodeoxyuridine (BrdU) for proliferation, doublecortin (DCX) for immature neurons/neural progenitors, and NeuN for mature neurons (10, 11),

and are subsequently counted under a light microscope. However, these manual counting methods have some methodological limitations. Researchers may favor denser or more distinct cell clusters (counting bias); the decision to include poorly stained or atypically morphological cells in the count is subjective (identification bias); high variability among observers leads to reproducibility problems; and manually counting thousands of cells is time-consuming and labor-intensive (12, 13).

Design-based stereology provides an unbiased and reliable framework for the quantitative estimation of three-dimensional (3D) biological structures using two-dimensional (2D) histological sections. The fact that the obtained data are independent of cell size and morphology and that a systematic random sampling approach is used in acquiring histological sections minimizes bias and systematic error. Due to these advantages, design-based stereological methods are widely accepted as the gold standard in quantitative neuromorphology (14-16). However, manual stereological analysis is still time-consuming, requires substantial expertise, and may be affected by observer-dependent variability.

In parallel with advances in digital pathology, artificial intelligence (AI)-based image analysis methods have increasingly been applied to histological image analysis (13, 17). In particular, deep learning (DL) approaches have shown promising results in the detection, segmentation, and classification of cells on microscopic images (18). These approaches provide faster and automated analysis but may have some limitations. Integration of AI-based image analysis methods with stereological counting principles has the potential to reduce analysis time as well as increase analysis sensitivity. Especially, DL-based segmentation models enable the automatic recognition and counting of cells (19). This section provides an overview of the theoretical foundations, methodological framework, hardware requirements, and future potential of this innovative hybrid approach for neurogenesis analysis.

2. Principles of Stereological Cell Quantification in Neuroscience

In neurogenesis research, accurate estimation of cell number is essential for interpreting structural and functional changes. Design-based stereology is a set of mathematical and statistical methods that provides unbiased quantitative estimation of 3D biological structures based on measurements obtained from 2D histological sections. In neuroscience research, these approaches are widely used to estimate structural parameters such as total cell number, volume, surface area, and length within defined anatomical regions. Unlike conventional morphometric methods, stereology does not rely on assumptions about the size, shape, orientation, or spatial distribution of the analyzed structures. This methodological robustness makes stereology particularly suitable for the quantitative analysis of heterogeneous biological tissues such as the brain (14, 20, 21).

Systematic random sampling (SRS) is a cornerstone of design-based stereology because it ensures that all parts of a biological structure have an equal probability of being included in quantitative analysis. This sampling strategy allows researchers to obtain un-

biased and reliable estimates of structural parameters such as total cell number or volume by examining only a fraction of the tissue within a defined region of interest. In practice, SRS is implemented by selecting sections at fixed, uniform intervals throughout the entire region of interest, while the first section is chosen using a random starting point. This systematic distribution increases sampling efficiency and results in lower coefficients of error compared with simple random sampling (22-24). Before initiating a study, a pilot study is essential to optimize sampling parameters, such as grid size and counting frame area, given the morphological heterogeneity of the brain region.

Among stereological techniques used in neuroscience, the optical disector method is one of the most widely applied approaches for estimating the numerical density of cells. The focus of a high-resolution microscope is moved along the z-axis of a thick tissue section within a predefined 3D probe. Cells are counted when a defined feature (typically the top of the nucleus or nucleolus) first comes into focus within this sampling volume. To ensure unbiased counting, strict forbidden line rules are applied to exclude cells that touch the exclusion boundaries of the counting frame. These counting principles ensure that the final estimate remains independent of the size, shape, or spatial orientation of the analyzed cells (15, 16, 25, 26).

To estimate the total number of cells within a defined brain region, the optical disector is commonly combined with the fractionator sampling principle, resulting in the optical fractionator method. In this approach, only a known fraction of the tissue is sampled, and the total number of particles (N) is calculated by multiplying the number of particles sampled (ΣQ−) by the inverse of the sampling fractions. An important advantage of this method is that it does not require estimation of the reference volume (Vref) and is therefore not affected by tissue shrinkage during histological processing. Relying solely on numerical density (Nv) can be misleading and may lead to the so-called "reference trap," where changes in cell density reflect changes in the reference volume (e.g., brain atrophy) rather than true changes in the absolute number of cells (14, 15, 27, 28).

These practical benefits have established design-based stereology as the preferred gold standard for quantitative cell analysis in neuroscience. They are widely used in studies investigating neuronal loss, neurogenesis, and structural plasticity in both experimental animal models and human brain tissue. By providing statistically reliable and repeatable counts, stereology has significantly improved our understanding of brain development, neurodegenerative diseases, and how the brain reacts to injury (29-33).

Despite these methodological strengths, conventional stereological methods have several important limitations. Although design-based stereology is built on unbiased principles, it is traditionally performed manually and requires extensive training, considerable time, and strict adherence to counting rules. As histological datasets become larger and more complex, manual stereological counting can become increasingly labor-intensive and prone to observer-dependent variability. Manual counting is affected by human factors such as subjectivity, recognition bias, and fatigue, which can lead to variability in results and limit reproducibility. These limitations have encouraged the development of hybrid computational approaches that combine DL-based image analysis with stereologi-

cal principles. This integration allows for more objective and efficient cell quantification while maintaining the principles of stereology. The automated stereology approach demonstrates a maximum error rate of less than 2% and a fivefold increase in efficiency in comparison with conventional stereology (31). Accordingly, AI-assisted approaches could be a promising solution to improve efficiency, objectivity, and scalability in quantitative neurogenesis research.

2.1. Digital Transformation in Neuromorphometry: From Automated Imaging to AI-Driven Analysis

Digitization has reshaped many areas of daily life, including the way tissues and cells are visualized at the microscopic level. Advances in digital technologies have improved tissue-based research by enabling digital microscopy and image analysis. In this way, histological slides can be stored as virtual images, viewed on computers instead of conventional microscopes, and analyzed and shared more efficiently (34). These developments have facilitated the transition from conventional microscopy to digital and computational analysis in histological research.

Stereology, particularly the optical fractionator, is one of the most commonly used unbiased methods for counting neurons in the whole brain or in specific brain regions. However, due to limitations such as time constraints, labor-intensive procedures, and researcher-related variability, there is a need for faster and more objective methods. Automated cell counting simplifies the data collection process, increasing efficiency and reducing the time required (35). However, automated image analysis software largely relies on predefined rules and may be insufficient when dealing with complex tissue structures. This limitation becomes more apparent in heterogeneous regions such as the hippocampus, where cell density and morphology vary considerably. In this context, AI-based approaches are considered a promising alternative. To be useful in practice, these methods need to be properly incorporated into research processes. The combination of human expertise and AI can improve efficiency. However, to fully benefit from digitalization, factors such as requirements analysis, careful planning, and structured implementation should be considered (36).

3. Conceptual Framework of the AI-Assisted Hybrid Stereology Approach

The AI-assisted hybrid stereology approach does not aim to replace the researcher, but rather to support and standardize the analytical process. Conventional image analysis methods are often limited when applied to complex brain regions such as the hippocampus, where cells are densely packed and frequently overlapping. In this context, DL methods provide a more flexible framework for handling such structural complexity.

In recent years, DL-based methods have been used for automated cell detection and segmentation in medical images (18, 19). These methods are particularly useful in complex tissues where conventional image analysis techniques are often insufficient. DL ap-

proaches have been successfully applied to the segmentation of fluorescently labeled neurons in both human and rat brains (37, 38). In addition, several studies have shown that automated cell counting based on DL can produce results comparable to stereological estimates, supporting their reliability as quantitative tools (31, 39, 40). For example, automated segmentation and quantification of pyramidal neurons in human hippocampal subregions have demonstrated an elevated level of agreement with manual stereological counting (29).

While DL-based methods offer effective tools for cell detection and segmentation, their use in quantitative analysis depends on the accuracy of the segmentation. The assessments of a trained researcher are crucial, particularly in regions where cell boundaries are unclear or staining is inconsistent. Instead of manually counting each cell, the researcher oversees the analytical process by verifying the algorithmic outputs, correcting misclassifications, and ensuring adherence to stereological rules. This hybrid approach aims to establish a structured digital workflow that preserves the accuracy of expert-based analysis while improving reproducibility and efficiency (41-43).

3.1. Methodological Workflow

The first stage of the hybrid workflow is the transformation of physical histological sections into high-resolution digital data. Tissue sections are obtained, stained with appropriate neurogenesis markers, and digitized to generate images suitable for quantitative analysis.

In the second stage, the region of interest is defined, and SRS is applied in accordance with design-based stereological principles. Rather than manually moving the microscope stage, the software automatically selects counting frames at uniform intervals across the digitized region of interest. Sections and sampling sites are selected with a random starting point, ensuring that all parts of the structure have an equal probability of being included in the analysis (30, 41, 44).

The third stage involves AI-assisted cell detection and segmentation within these sampled regions. DL-based models, particularly Convolutional Neural Networks (CNNs), are used to identify and segment labeled cells or nuclei. Following detection, stereological counting is performed by applying established rules such as inclusion and exclusion criteria within predefined counting frames (41).

Stereological methods such as the physical disector and optical fractionator can be used for 3D cell estimation. The optical fractionator integrates the disector principle with a fractionator sampling scheme, allowing for the estimation of the total cell number without being affected by tissue shrinkage or the need for reference volume measurements. The physical disector is implemented by comparing two aligned consecutive two-dimensional digital sections (the reference and the look-up sections). Cells are counted if they appear in one section but not in the other, ensuring that each cell is counted only once (25, 28, 45). However, this method requires precise digital alignment of sections and may be more labor-intensive.

Currently, the optical fractionator is preferred in most neurogenesis research conducted using a hybrid approach. In this method, a digital z-stack is generated by capturing a series of images at regular sampling intervals throughout the depth of a thick tissue section. Within this volumetric dataset, AI-based methods assist in identifying cells and determining the point at which each cell first comes into focus (top point) along the z-axis. This approach enables unbiased estimation of total cell number, independent of tissue shrinkage or changes in reference volume. In the automated implementation of the optical disector, AI-based analysis is used to identify this point along the z-axis. To preserve stereological principles, the software applies digital inclusion and exclusion boundaries (forbidden lines) to each 3D counting frame. Cells whose unique top point intersects an exclusion boundary are automatically excluded from the analysis, ensuring that the estimation remains independent of cell size, shape, or orientation (15, 41, 43, 45).

3.1.1. Quality Control and Validation

The final stage of the hybrid approach involves a quality control process to ensure the reliability of the AI-generated data. DL models improve analytical efficiency; however, human-in-the-loop validation remains essential for maintaining stereological standards and ensuring biological accuracy.

Automated cell detection systems may produce errors due to histological artifacts, such as non-specific staining or high cell density with overlapping nuclei. To address these issues, a trained researcher reviews a representative subset of the counting frames to assess whether the AI has correctly identified cell top points and applied the forbidden line rules appropriately. During this process, false positives (e.g., staining debris misidentified as cells) and false negatives (e.g., missed cells in dense regions) can be corrected. This approach ensures that the automated system functions as a support tool within an expert-guided analysis rather than as a fully autonomous process. During the implementation of a hybrid system, AI-based counting results are often compared with manual stereological estimates to assess their consistency (41, 43).

In design-based stereology, the reliability of the final estimate depends not only on the number of cells counted but also on the efficiency of the sampling scheme. To evaluate this, the coefficient of error (CE) is calculated for each subject. A low CE value (commonly ≤%5) indicates that the sampling density is sufficient to represent biological variability within the tissue. In addition, the coefficient of variation (CV) may be used to assess variability between subjects or experimental groups (28, 46, 47). In a hybrid system, the CE and CV reflect both the adequacy of systematic random sampling and the consistency of automated counting across different sections.

3.2. Hardware and Software Infrastructure for Hybrid Stereology

The effective implementation of an AI-assisted hybrid stereological system requires integrating high-precision optical hardware with advanced computational processing units. To maintain the design-based stereology principle, some hardware components are essential. A

motorized microscope stage with high-precision x–y–z control is required for SRS and digital z-stack acquisition in the optical disector. A high-resolution digital camera is necessary to capture clear histological details for AI-based segmentation. For real-time processing of DL models, a high-performance graphics processing unit (GPU) is critical to handle complex image recognition tasks efficiently. In addition, stable illumination systems and automated focus control contribute to image consistency and reproducibility (48, 49).

In addition to hardware components, software infrastructure plays a central role in integrating automated analysis with stereological principles. CNNs, specifically networks like U-Net or Mask R-CNN, are employed for the precise detection and segmentation of neurogenesis markers such as BrdU or DCX. To reduce variability in staining intensity and signal-to-noise ratio, automated color normalization and histogram equalization are used to improve consistency across slides. The software applies digital forbidden lines to each counting frame to ensure that AI-assisted counts are independent of cell size and shape (18, 43, 49-51).

An analysis pipeline includes image acquisition and preprocessing, segmentation, followed by the evaluation of cellular features and stereological counting. During preprocessing, steps such as noise reduction, contrast enhancement, and normalization are applied to improve segmentation performance. After segmentation, detected objects are evaluated based on their shape and staining characteristics to reduce false detections (52, 53).

In addition, preparation of annotated datasets and model development are important steps in AI-based systems. The performance of AI models depends on the quality of annotated datasets. These datasets are usually prepared through expert-guided labeling. Training and validation involve teaching the model to recognize cells and testing its performance. These processes are typically carried out using platforms such as TensorFlow or PyTorch, which support model development and evaluation (54, 55).

For integration with stereology, software tools may include modules for SRS, grid generation, and counting frame definition. In some cases, open-source platforms such as ImageJ or QuPath can be adapted to support semi-automated stereological analysis (44, 56). Overall, the effectiveness of a hybrid stereological system depends not only on hardware capacity but also on the interaction between imaging systems, computational tools, and user-guided validation processes.

4. Results

Recent developments in AI have significantly improved the functionality of automated image analysis in neuroscience. In particular, DL methods demonstrate significant potential for the detection, segmentation, and quantification of cells in histological images. Combining these techniques with stereological principles may contribute to more efficient and consistent quantitative analyses in neurogenesis research.

However, AI-based image analysis methods still have important limitations in neuroscience applications. In brain regions like the hippocampus, cells are often densely packed

and overlapping, complicating detection and segmentation. Variability in cell morphology, differences in staining quality, and low signal-to-noise ratios further increase this difficulty. In addition, the limited availability of well-annotated datasets restricts the performance of DL models. These challenges can lead to segmentation errors, especially when separating closely adjacent cells (57, 58). As a result, errors at the detection stage may affect subsequent quantitative analyses, highlighting the need for careful integration of AI methods with established stereological principles. Furthermore, variability in imaging conditions and the lack of standardized analysis pipelines complicate the application of these methods. Differences in staining protocols, image acquisition settings, and tissue preparation can influence model performance and limit the comparability of results across studies. The absence of consistent benchmarking strategies also makes it difficult to objectively evaluate and compare different analytical approaches.

Future work should focus on improving dataset quality, developing more robust annotation strategies, and increasing the interpretability of AI models. Integrating multiple imaging modalities may also help address the limitations of single-technique analysis (57, 58). Hybrid approaches that integrate AI-based image analysis with automated disector and cell-counting systems may provide a more consistent framework for quantitative neurogenesis research. Such approaches can enhance efficiency and reproducibility while preserving the unbiased nature of stereological methods. These systems may also facilitate the analysis of large-scale datasets and contribute to more reliable quantitative assessments in neuroscience research.

5. References

1. Wu, A., & Zhang, J. (2023). Neuroinflammation, memory, and depression: New approaches to hippocampal neurogenesis. Journal of Neuroinflammation, 20(1), 283.
2. Eriksson, P., Perfilieva, E., Björk-Eriksson, T., Alborn, A.-M., Nordborg, C., & Peterson, D. (1998). Neurogenesis in the adult human hippocampus. Nature Medicine, 4, 1313–1317.
3. Kim, T. A., Syty, M. D., Wu, K., & Ge, S. (2022). Adult hippocampal neurogenesis and its impairment in Alzheimer's disease. Zoological Research, 43(3), 481–496.
4. Altman, J., & Das, G. D. (1965). Autoradiographic and histological evidence of postnatal hippocampal neurogenesis in rats. Journal of Comparative Neurology, 124(3), 319–335.
5. Hagg, T. (2009). From neurotransmitters to neurotrophic factors to neurogenesis. The Neuroscientist, 15(1), 20–27.
6. Culig, L., Chu, X., & Bohr, V. A. (2022). Neurogenesis in aging and age-related neurodegenerative diseases. Ageing Research Reviews, 78, 101636.
7. Feliciano, D. M., Bordey, A., & Bonfanti, L. (2015). Noncanonical sites of adult neurogenesis in the mammalian brain. Cold Spring Harbor Perspectives in Biology, 7(10), a018846.
8. Kempermann, G., Song, H., & Gage, F. H. (2015). Neurogenesis in the adult hippocampus. Cold Spring Harbor Perspectives in Biology, 7(9), a018812.
9. Ming, G. L., & Song, H. (2011). Adult neurogenesis in the mammalian brain: Significant answers and significant questions. Neuron, 70(4), 687–702.
10. Lou, S., Gong, D., Yang, M., Qiu, Q., Luo, J., & Chen, T. (2024). Curcumin improves neurogenesis in Alzheimer's disease mice via the upregulation of Wnt/β-catenin and BDNF. International Journal of Molecular Sciences, 25(10).
11. Chen, J., & Guan, Z. (2022). Function of oncogene MYCN in adult neurogenesis and oligodendrogenesis. Molecular Neurobiology, 59(1), 77–92.
12. Nalluri, H. V., Graff, S. A., Maric, D., & Heiss, J. D. (2025). Optimizing colocalized cell counting using automated and semiautomated methods. Neuroinformatics, 23(2).
13. Varghese, F., Bukhari, A. B., Malhotra, R., & De, A. (2014). IHC profiler: An open-source plugin for quantitative evaluation of immunohistochemistry images. PLoS ONE, 9(5), e96801.

14. Schmitz, C., & Hof, P. R. (2005). Design-based stereology in neuroscience. Neuroscience, 130(4), 813–831.
15. West, M. J., Slomianka, L., & Gundersen, H. J. G. (1991). Unbiased stereological estimation of the total number of neurons in the subdivisions of the rat hippocampus using the optical fractionator. The Anatomical Record, 231(4), 482–497.
16. Gundersen, H. J., Bagger, P., Bendtsen, T. F., Evans, S. M., Korbo, L., Marcussen, N., et al. (1988). The new stereological tools: disector, fractionator, nucleator and point sampled intercepts and their use in pathological research and diagnosis. APMIS, 96(10), 857–881.
17. Baxi, V., Edwards, R., Montalto, M., & Saha, S. (2022). Digital pathology and artificial intelligence in translational medicine and clinical practice. Modern Pathology, 35(1), 23–32.
18. Litjens, G., Kooi, T., Bejnordi, B. E., Setio, A. A. A., Ciompi, F., Ghafoorian, M., et al. (2017). A survey on deep learning in medical image analysis. Medical Image Analysis, 42, 60–88.
19. Falk, T., Mai, D., Bensch, R., Çiçek, Ö., Abdulkadir, A., Marrakchi, Y., et al. (2019). U-Net: deep learning for cell counting, detection, and morphometry. Nature Methods, 16(1), 67–70.
20. West, M. J. (2012). Basic stereology for biologists and neuroscientists. Academic Press.
21. Evans, S. M., Janson, A. M., & Nyengaard, J. R. (2004). Quantitative methods in neuroscience: A neuroanatomical approach. Oxford University Press. Available from: https://doi.org/10.1093/acprof:oso/9780198505280.001.0001.
22. Gundersen, H. J., Jensen, E. B., Kiêu, K., & Nielsen, J. (1999). The efficiency of systematic sampling in stereology--reconsidered. Journal of Microscopy, 193(3), 199–211.
23. West, M. J. (1993). New stereological methods for counting neurons. Neurobiology of Aging, 14(4), 275–285.
24. Howard, V., & Reed, M. G. (2005). Unbiased stereology: Three-dimensional measurement in microscopy (2nd ed.). Garland Science.
25. Sterio, D. C. (1984). The unbiased estimation of number and sizes of arbitrary particles using the disector. Journal of Microscopy, 134(2), 127–136.
26. Gundersen, H. J. G. (1977). Notes on the estimation of the numerical density of arbitrary profiles: the edge effect. Journal of Microscopy, 111(2), 219–223.
27. Brændgaard, H., & Gundersen, H. J. G. (1986). The impact of recent stereological advances on quantitative studies of the nervous system. Journal of Neuroscience Methods, 18(1), 39–78.
28. Dorph-Petersen, K. A., Nyengaard, J. R., & Gundersen, H. J. G. (2001). Tissue shrinkage and unbiased stereological estimation of particle number and size. Journal of Microscopy, 204(3), 232–246.
29. Oltmer, J., Rosenblum, E. W., Williams, E. M., Roy, J., Llamas-Rodriguez, J., Perosa, V., et al. (2023). Stereology neuron counts correlate with deep learning estimates in the human hippocampal subregions. Scientific Reports, 13(1), 5884.
30. Reddy, D. S., Zhu, N., Challa, T., Gajjela, S., Desai, H., Ramakrishnan, S., et al. (2024). A comprehensive stereology method for quantitative evaluation of neuronal injury, neurodegeneration, and neurogenesis in brain disorders. Current Protocols, 4(12), e70053.
31. Alahmari, S. S., Goldgof, D., Hall, L., Phoulady, H. A., Patel, R. H., & Mouton, P. R. (2019). Automated cell counts on tissue sections by deep learning and unbiased stereology. Journal of Chemical Neuroanatomy, 96, 94–101.
32. Kaplan S, Onger ME, Altunkaynak BZ, Elibol E, Deniz OG, Karayiğit M, et al. Effects of spermine and the passive avoidance learning (PAL) following cerebral ischemia in chicks: Association with neuroprotection of pyramidal cells. J Chem Neuroanat. 2018;88:41-5.
33. Rağbetli MÇ, Aydınlıoğlu A, Koyun N, Yayıcı R, Arslan K. Total neuron numbers in CA1-4 sectors of the dog hippocampus. Indian Journal of Medical Research. 2010;131(6):780-5.
34. Aeffner, F., Adissu, H. A., Boyle, M. C., Cardiff, R. D., Hagendorn, E., Hoenerhoff, M. J., et al. (2018). Digital microscopy, image analysis, and virtual slide repository. ILAR Journal, 59(1), 66–79.
35. Penttinen, A. M., Parkkinen, I., Blom, S., Kopra, J., Andressoo, J. O., Pitkänen, K., et al. (2018). Implementation of deep neural networks to count dopamine neurons in substantia nigra. European Journal of Neuroscience, 48(6), 2354–2361.
36. Dawson, H. (2022). Digital pathology - rising to the challenge. Frontiers in Medicine, 9, 888896.
37. Iqbal, A., Sheikh, A., & Karayannis, T. (2019). DeNeRD: high-throughput detection of neurons for brain-wide analysis with deep learning. Scientific Reports, 9(1), 13828.
38. Vizcaíno, A., Sánchez-Cruz, H., Sossa, H., & Quintanar, J. L. (2022). Neuron cell count with deep learning in highly dense hippocampus images. Expert Systems with Applications, 208, 118090.
39. Alahmari, S. S., Goldgof, D., Hall, L. O., & Mouton, P. R. (2019). Automatic cell counting using active deep learning and unbiased stereology. In 2019 IEEE International Conference on Systems, Man and Cybernetics (SMC).
40. Ahmady Phoulady, H., Goldgof, D., Hall, L. O., & Mouton, P. R. (2019). Automatic ground truth for deep learning stereology of immunostained neurons and microglia in mouse neocortex. Journal of Chemical Neuroanatomy, 98, 1–7.
41. Alahmari, S., Goldgof, D., Hall, L. O., Dave, P., Ahmady Phoulady, H., & Mouton, P. R. (2018). Iterative deep learning based unbiased stereology with human-in-the-loop. In 2018 17th IEEE International Conference on Machine Learning and Applications (ICMLA) (pp. 665–670). IEEE.
42. Schmitz, C., Eastwood, B. S., Tappan, S. J., Glaser, J. R., Peterson, D. A., & Hof, P. R. (2014). Current automated 3D cell detection methods are not a suitable replacement for manual stereologic cell counting. Frontiers in Neuroanatomy, 8, 27.
43. Dave, P., Goldgof, D., Hall, L. O., Kolinko, Y., Allen, K., Alahmari, S., et al. (2022). A disector-based framework for the automatic optical fractionator. Journal of Chemical Neuroanatomy, 124, 102134.

44. Bankhead, P., Loughrey, M. B., Fernández, J. A., Dombrowski, Y., McArt, D. G., Dunne, P. D., et al. (2017). QuPath: Open source software for digital pathology image analysis. Scientific Reports, 7(1), 16878.
45. Kristiansen, S. L., & Nyengaard, J. R. (2012). Digital stereology in neuropathology. APMIS, 120(4), 327–340.
46. Gundersen, H. J. (1986). Stereology of arbitrary particles. A review of unbiased number and size estimators and the presentation of some new ones, in memory of William R. Thompson. Journal of Microscopy, 143(1), 3–45.
47. Gundersen, H. J., & Jensen, E. B. (1987). The efficiency of systematic sampling in stereology and its prediction. Journal of Microscopy, 147(3), 229–263.
48. Glaser, J., & Glaser, E. (2000). Stereology, morphometry, and mapping: The whole is greater than the sum of its parts. Journal of Chemical Neuroanatomy, 20, 115–126.
49. Ronneberger, O., Fischer, P., & Brox, T. (2015). U-Net: Convolutional networks for biomedical image segmentation. In N. Navab, J. Hornegger, W. M. Wells, & A. F. Frangi (Eds.), Medical image computing and computer-assisted intervention – MICCAI 2015 (Lecture Notes in Computer Science, Vol. 9351, pp. 234–241). Springer.
50. He, K., Gkioxari, G., Dollár, P., & Girshick, R. (2017). Mask R-CNN. In Proceedings of the IEEE International Conference on Computer Vision (ICCV) (pp. 2961–2969).
51. Zhu, Y., & Meijering, E. (2021). Automatic improvement of deep learning-based cell segmentation in time-lapse microscopy by neural architecture search. Bioinformatics, 37(24), 4844–4850.
52. Carpenter, A. E., Jones, T. R., Lamprecht, M. R., Clarke, C., Kang, I. H., Friman, O., et al. (2006). CellProfiler: image analysis software for identifying and quantifying cell phenotypes. Genome Biology, 7(10), R100.
53. Alahmari, S. S., Goldgof, D., Hall, L. O., & Mouton, P. R. (2024). A review of nuclei detection and segmentation on microscopy images using deep learning with applications to unbiased stereology counting. IEEE Transactions on Neural Networks and Learning Systems, 35(6), 7458–7477.
54. Abadi, M., Barham, P., Chen, J., Chen, Z., Davis, A., Dean, J., et al. (2016). TensorFlow: a system for large-scale machine learning. In Proceedings of the 12th USENIX Conference on Operating Systems Design and Implementation (OSDI 2016) (pp. 265–283).
55. Paszke, A., Gross, S., Massa, F., Lerer, A., Bradbury, J., Chanan, G., et al. (2019). PyTorch: An imperative style, high-performance deep learning library. In H. Wallach et al. (Eds.), Advances in Neural Information Processing Systems (Vol. 32). Curran Associates, Inc.
56. Schneider, C. A., Rasband, W. S., & Eliceiri, K. W. (2012). NIH Image to ImageJ: 25 years of image analysis. Nature Methods, 9(7), 671–675.
57. Maddalena, L., Antonelli, L., Albu, A., Hada, A., & Guarracino, M. R. (2022). Artificial intelligence for cell segmentation, event detection, and tracking for label-free microscopy imaging. Algorithms, 15(9), 313.
58. Wenderoth, L., Asemissen, A.-M., Modemann, F., Nielsen, M., & Werner, R. (2025). Transferable automatic hematological cell classification: Overcoming data limitations with self-supervised learning. Computer Methods and Programs in Biomedicine, 260, 108560.

CHAPTER 4

Biophysical Structure, Dynamics, and Function in Living Systems Modeling with Artificial Intelligence

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1. Introduction

Living systems arise from the interaction of many physical components across different spatial and temporal scales. This order spans atomic vibrations, macromolecular rearrangements, and cellular behavior, and it helps determine biological function (1,2). Experimentally obtained three-dimensional structures may reflect conformational diversity and low-population intermediate states only to a limited degree in some systems (3). Dynamic behaviors such as binding-unbinding processes, allosteric transitions, and thermal fluctuations can show quantitative links to functional outputs under suitable measurements (1, 4). No single model explains the full structure-dynamics-function relation (3).

Traditional approaches have often studied these three components separately. Structural, dynamic, and functional data are often collected at different levels of representation and time scales, making integration difficult (1, 3). Measurement noise, limited sampling, and poor access to long time scales add further limits (3).

In recent years, artificial intelligence-based methods have provided tools for learning multi-layered representations and statistical relationships from large and diverse datasets (5-7). Here, artificial intelligence is treated as a set of predictive models that learn input-output relations from data. These models usually learn statistical patterns rather than physical laws or causal mechanisms, so their outputs must be judged by the data used and the learning assumptions (8, 9). Deep learning models such as AlphaFold2 and RoseTTAFold show that sequence-based structure prediction can reach high accuracy under suitable data and model conditions (10-12). However, prediction success does not guarantee physical consistency or causal explanation (8, 9).

This study examines when artificial intelligence can produce meaningful results for biophysical structure, dynamics, and function under specific data, assumptions, and technical limits.

2. The Structure-Dynamics-Function Triad in Biophysics

2.1. Biophysical Structure in Living Systems

Biophysical structure refers to the spatial organization of biological systems. It should be defined with its scale, method, uncertainty, and physical conditions (4, 13). At the atomic scale, structure is defined by geometric and energetic constraints formed by bond lengths, bond angles, torsional degrees of freedom, and interatomic interactions (14). At larger scales, they shape proteins, nucleic acids, complexes, membranes, and organelles (4, 15). Structure is therefore a family of scale-dependent representations, and model resolution should match the biological question (3, 14).

Structural biology often does not provide structure directly as an image. It produces a model from measurement data, and this model carries method-specific uncertainty. The Protein Data Bank stores coordinates, metadata, and validation information (16). X-ray crystallography, NMR, and cryo-EM each have distinct limits, so integrative approaches are often needed (1, 3, 11, 17, 18).

Biomolecules are in continuous motion under thermal noise. For some systems, structure is better described as an ensemble of conformations than as one average form (15, 19). This is especially important for intrinsically disordered proteins and regions (20, 21). Maximum entropy-based methods are often used to define ensembles consistent with experiment (3).

2.2. Dynamics

Dynamics describes how biophysical structures change over time and the physical processes that drive these changes. It includes vibrations, conformational transitions, binding-unbinding processes, large rearrangements, and rare events across broad time scales (1, 15, 19, 22). No single method can access all of these scales at once, so dynamics is often studied indirectly through selected observables (1, 3, 16).

Different experimental techniques are sensitive to specific aspects of dynamic behavior. NMR can report motions on selected time scales, but it has resolution and sensitivity limits, especially in large systems (17). Single-molecule FRET can reveal heterogeneity, but it also reports only selected observable states (23). Experimental data, therefore, capture only projections of dynamics.

Computational biophysics aims to study time-dependent models of biomolecules at atomic detail, mainly through molecular dynamics (MD) simulations. MD provides a time-dependent atomic description under a given force field and initial conditions, but it is limited by accessible time scales and model assumptions (22, 24).

Reduced representations and statistical models are widely used to study these systems. MSMs describe dynamics through metastable states and transitions, but they require sufficient sampling and approximate validity of the Markov assumption (25, 26). tICA-based reduction and generative models are also used to summarize accessible ensembles (27, 28).

There are many studies in the biophysical literature showing that certain dynamic properties may be related to biological function (1, 22). However, it is often unclear whether a dynamic observation is causal for function or only associated with it (13). Transitions linked to function should therefore not be treated as direct causes without experimental validation (26).

Biophysical dynamics consists of partially observed, multi-scale, and model-dependent processes. Artificial intelligence can help reduce and summarize such data, but the learned patterns must be interpreted carefully (13, 24).

2.3. Function

Function is defined here as the measurable outputs produced by a biophysical system under specific environmental and experimental conditions. These outputs may include rate constants, affinities, force-displacement relations, or response measures, depending on the system and assay (29). Function in biophysics therefore has no single universal definition (1). Protein language models can predict selected functional quantities, but they learn statistical relations to measured outputs rather than function itself (5, 30). Functional observables must therefore be defined clearly (17).

Function depends on the system and on the measurement setup. The same system may therefore show different outputs under different protocols (29). Structure and dynamics may support function, but they are often not sufficient by themselves, and the relation is rarely one-to-one (1, 13, 22). A molecule may also have more than one role under different conditions, a property described as biological moonlighting (31). Functional data carry measurement noise and uncertainty, so prediction results should be interpreted with these limits in mind (6, 8, 17, 31, 32).

In this study, function is treated as measurement-dependent rather than absolute (13, 24).

2.4. The Concept of Model

In this section, a model is considered as a representation that selects specific aspects of a biophysical system to address a scientific question. Models are incomplete by nature, but they can still be useful (13). In biophysics, explanatory models emphasize physical assumptions and causal relations, whereas predictive models emphasize accurate outputs for specific data sets (8, 9). Artificial intelligence models usually belong to the predictive side, so high accuracy does not mean mechanistic explanation (24, 33).

Any model leaves out part of the system. In artificial intelligence, the choice of representation strongly limits what can be learned (13, 24). Model parameters are usually fit to data rather than derived from physical principles, which increases flexibility but also sensitivity to data quality (24, 33). Physics-informed learning can add useful constraints, but it does not guarantee physical consistency (34). Scientific value therefore depends on valid conditions, uncertainty, and careful control of overgeneralization (13, 28).

Artificial intelligence models should therefore be treated as tools with clear limits and conditions of validity.

3. Data Ecosystem: Biophysical Data Types That Make Artificial Intelligence Modeling Possible

Artificial intelligence models do not observe biophysical reality directly. They learn from data representations produced by experiments and simulations, so data type, quality, and conditions strongly limit model validity (12, 16, 24). Experimental data include structural, dynamic, and functional measurements, but they have limited resolution, measurement noise, and often report only time or population averages (3, 16-18, 23, 29).

Experimental outputs also depend strongly on temperature, pH, ionic strength, solvent conditions, and binding partners, so curation and metadata are essential (8, 35). Simulations, especially MD, can provide time-dependent atomic detail, but they also depend on force fields, boundary conditions, and initial states (22, 24). Learned patterns may therefore reflect model assumptions as well as system properties (36). Experimental and simulation data are often combined, but this hybrid use is not a validation step by itself and depends on how uncertainties are handled (3, 14, 37, 38).

Biophysical data sets are also imbalanced. Some proteins and motifs are overrepresented, while some structure types and dynamic behaviors are undersampled. This limits generalization, so model outputs should not be treated as direct descriptions of biophysical reality (8, 9, 33, 39).

4. Core Methods: The Artificial Intelligence Tool Box for Biophysics

Artificial intelligence methods learn biophysical systems through selected representations rather than as direct physical objects. Their abilities and limits are largely determined by the form of representation, the learning paradigm, and the handling of physical constraints. Different representations emphasize different system properties and may also cause information loss (13, 24). Sequence representations are especially common for proteins and nucleic acids. Because they use primary structure information, they allow work with large data sets without requiring experimental structural data. However, spatial relationships and physical interactions are not directly included in these representations. These properties can only be learned indirectly when data are sufficient and assumptions are appropriate (5, 30). Three-dimensional geometric representations use atomic coordinates, distance maps, or density maps, and they reflect the spatial nature of biophysical interactions more clearly. However, these representations are sensitive to resolution limits, alignment problems, and experimental uncertainties. Graph-based representations reflect the network-like structure of biomolecules by treating atoms or residues as nodes and interactions as edges. The graph

definition affects what the model can learn, and no representation is universally best (40, 41).

Artificial intelligence applications in biophysics are based on different learning paradigms. Supervised learning aims to learn clear input-output mappings such as structure-to-function prediction. It requires labeled data, which can be limited by label scarcity and experimental uncertainties (24). Self-supervised learning learns representations by using the internal structure of the data without explicit labels. It has become widely used in large biophysical data sets, especially in sequence-based models (5, 30). he biophysical meaning of these representations is often not clear and requires additional analysis (13). Generative models can produce possible structures, sequences, or conformations, but these outputs still require validation (42-45).

Biophysical systems show specific symmetry properties against spatial transformations such as rotation and translation (40). Geometric deep learning approaches therefore include these symmetries in their architectures. In particular, E(3)-equivariant graph neural networks can improve the learning of interatomic potentials and energy models in some cases, but they also increase model complexity and cost (46). Completely data-driven models can in some cases produce physically inconsistent outputs. To reduce this risk, physics-informed learning approaches have been developed, which integrate physical laws, constraints, or conservation principles into the learning process. These constraints can be applied through loss functions, architectural design, or data generation. However, they are not universal solutions, and poorly defined constraints can limit model performance and interpretability (34).

In biophysical applications, it is important to know how accurate a model is and when it is reliable. For this reason, uncertainty estimation, calibration, and detection of out-of-distribution samples are among the fundamental components of the artificial intelligence tool set. These approaches support more cautious interpretation of model outputs (33). Artificial intelligence methods in biophysics should be treated as tools for hypothesis generation and data interpretation.

5. Structure Modeling: Learning the Structure

Structure modeling aims to predict or represent the spatial organization of biophysical systems with data-driven approaches. It includes coordinate prediction and the identification of structural properties that can be extracted reliably from data. Artificial intelligence-based structure models usually take biomolecular sequences, partial structural constraints, or representations derived from experimental data as input. They produce three-dimensional coordinates, contact or distance relationships, and density-compatible structural representations (11, 40). Some current models predict protein structures from sequence alone and are used for hypothesis generation when experimental structures are not available (10, 11).

In structure modeling, problem formulation sets the limits of what the model can learn. The sequence-to-structure approach is strong when experimental structural data are not

available, but it assumes that sequence information contains indirect information about spatial organization. These methods use statistical regularities such as evolutionary covariance and deep representation learning (10, 11). Approaches such as RoseTTAFold combine sequence, contacts, and partial structural information (10). The structural outputs of artificial intelligence models depend strongly on representation and architecture choices. Sequence-based representations can use evolutionary information and statistical correlations, but they do not directly include atomic-level physical constraints. Geometric architectures that preserve spatial symmetries aim to represent interatomic interactions more consistently. E(3)-equivariant graph neural networks can improve accuracy and data efficiency in some cases, but their outputs still require physical and experimental evaluation (40, 41, 46).

The evaluation of structure models often depends on geometric similarity metrics such as RMSD and TM-score. These metrics summarize the spatial closeness between structures, but they do not show by themselves whether a model is biophysically meaningful. Local errors in functional regions may be hidden by global scores, so evaluation should also include local accuracy, agreement with experiments, physical consistency, and possible functional relevance (47). The reliability of structure models increases through independent validations performed with experimental data. Controls such as agreement with cryo-EM densities, consistency with NMR constraints, and agreement with the structural effects of known mutations strengthen the biophysical meaning of model outputs (14, 37, 38). The addition of experimental data as constraints is common, but uncertainties and data weights must be handled carefully (3).

The final aim of structure modeling is often functional interpretation. However, the transition from structure to function is not automatic. Similar structures may show different functions, while small local differences may produce major functional results. Functional inferences from structure models should therefore be treated as hypotheses unless they are supported by experimental validation (1, 13). Structure modeling is more reliable when combined with experiment and theory.

6. Dynamic Modeling: Learning Motion

Dynamic modeling aims to quantitatively describe the evolution of biophysical systems over time. It includes instantaneous structural changes and the statistical description of transition rates, transition probabilities, and connected states. In high-dimensional and noisy data, artificial intelligence often reduces these representations into simpler forms (22, 24). Biophysical dynamic data are mostly obtained in the form of time series. While molecular dynamics simulations produce the time-dependent change of atomic coordinates, experimental measurements generally report indirect projections of these coordinates (3). These data exist in a high-dimensional state space, and their direct interpretation is difficult (22). A main goal of dynamic modeling is to reduce this space into lower-dimensional coordinates with possible kinetic meaning (25). Deep learning-based approaches can help separate metastable states and extract kinetic relations between them (26, 28).

Artificial intelligence methods are widely used to generate low-dimensional representations from dynamic data. However, these representations do not have to be physically correct coordinates. In many cases, they are better treated as projections that approximate kinetic behavior or represent specific time scales (25, 27). The biophysical interpretation of latent spaces therefore requires careful evaluation. A latent dimension should be called a reaction coordinate only after additional tests and validation (25). Reduction methods that emphasize slow kinetic components are especially useful (27). An important approach in dynamic modeling is to express system behavior with discrete states and the transition probabilities between these states. Markov state models are an established example of this approach and aim to describe complex biomolecular dynamics through metastable states (26). Artificial intelligence methods can help identify states and transitions, but these models still depend on sufficient sampling and on the approximate validity of the Markov assumption (26, 28).

In biophysical systems, many functionally important processes occur as rare events. Large conformational transitions, folding-unfolding events, or binding processes are often represented only in a small part of the data. Artificial intelligence models are more sensitive to patterns that occur frequently in the data. If rare events are not sampled sufficiently, the model may not learn them (24). Longer simulations or special sampling strategies are therefore still needed (22). The reliability of dynamic modeling often depends on combining experimental and computational data. Experimental measurements can provide indirect constraints on the time scales and conformational regions that simulations should reproduce. Simulations can help identify structural and kinetic sources of experimental signals. Artificial intelligence methods can be used as analysis tools that connect these data types (14, 37, 38). However, this interaction does not by itself create validation, and the assumptions behind any apparent consistency should be stated clearly (13, 24).

Dynamic modeling learns only the sub-dynamic regimes that are sufficiently represented in the data. Its outputs should therefore be treated as data-driven representations with specific limits (24).

7. Function Modeling: Learning the Function

Function modeling aims to predict measurable outputs produced by biophysical systems under specific conditions. These outputs include catalytic rates, binding affinities, stability metrics, mechanical responses, or quantities related to signal transmission. Artificial intelligence-based approaches predict these outputs from sequence, structure, dynamic summaries, or their combinations. Function modeling is mainly correlation-based and does not explicitly represent causal mechanisms (5, 6, 13, 30, 32). The first step in function modeling is to define the predicted function clearly. Target variables may include rate constants or Michaelis-Menten parameters in enzyme kinetics, equilibrium constants or free energy differences in binding problems, force-displacement relationships in mechanical systems, and response amplitude or delay times in signal transmission (17, 29).

These quantities are experimentally defined and depend on the measurement protocol and physical conditions. Function modeling therefore predicts a quantity defined under specific settings rather than a universal function (13).

Artificial intelligence models do not measure function directly; they learn statistical associations between input representations and functional outputs. Sequence-based models can extract functional signals from evolutionary patterns, whereas structure-based models can use geometric features such as binding pockets or active sites. Dynamic summaries aim to capture links between timescales, transitions, and functional outputs (5, 25, 30, 39). For example, the DLKcat model predicts catalytic rate constants from enzyme sequences and should be judged with its training distribution and model assumptions in mind (32). However, function prediction is always limited by incomplete information. Systems with the same input representation can produce different functional outputs under different conditions. Many-to-one and one-to-many mappings are therefore common, and models may miss rare or condition-specific functions (13).

The most critical methodological point in function modeling is that correlation should not be interpreted as causality. A model learning a strong relationship between specific sequence or structural features and functional outputs does not mean that these features are the cause of the function. These relationships may reflect hidden variables or sampling bias (9). This warning also applies to function inferences based on artificial intelligence-generated structures, which should be tested with independent experiments whenever possible (33). Function modeling results should therefore be treated as hypotheses rather than final conclusions (13). Function modeling is often carried out on datasets that are limited in size and uneven in composition. Some protein families, ligand classes, or experimental conditions are overrepresented. This can support high performance within the training distribution but weak performance on out-of-distribution samples (5, 30). Results without external validation or condition-based tests should therefore be interpreted carefully. Function predictions carry both experimental uncertainties and model-derived errors. Predictions should therefore be reported with uncertainty intervals or confidence measures. Uncertainty estimation helps evaluate when the model is reliable and reduces overinterpretation (28).

Function modeling is therefore treated here as a predictive approach under specific data conditions, not as a full causal explanation of biophysical function (8, 9).

8. Inverse Problem and Design: Producing Structures Consistent with the Desired Function

The inverse problem approach is different from the forward problem in biophysical modeling. In the forward problem, system behavior or functional outputs are calculated from structure and physical parameters. In the inverse problem, a functional target is defined first. Then the aim is to search for structures, sequences, or parameter sets that may match this target. This approach is design-oriented and often uses predictive models to gener-

ate candidates within a defined solution space (36, 42, 43). Diffusion-based models are a current example in de novo protein design (42, 44). In the inverse problem, the mapping often shows a one-to-many structure. The same functional target can be realized by many different structures or sequences. This makes the inverse problem underdetermined in many cases. It therefore aims to define possible solution spaces under the target and constraints (3). Artificial intelligence-based design approaches produce probabilistic candidates that still require evaluation and validation (44, 45). One of the critical steps in the inverse problem is the clear definition of design targets and constraints. Functional targets such as binding affinity, stability threshold, and catalytic activity are often expressed as measurable quantities. Biophysical design must also consider thermodynamic stability, kinetic accessibility, chemical and structural realism, and experimental feasibility. Some constraints may be learned implicitly, but they often need explicit definition or later filtering (42, 45). Sequence design methods can produce sequences for a target structure, but these outputs still require separate evaluation of stability and function (43).

A common approach in artificial intelligence-assisted design is to create new structure or sequence candidates by using generative models. These models aim to produce examples similar to the distributions observed in the training data. They therefore often focus on in-distribution behavior and may be limited in generating unusual solutions (44). The generation stage is only the first screening step of the inverse problem. A critical stage is therefore the validation of generated candidates. This usually includes computational validation, cross-checking with forward modeling, and experimental tests. None of these steps is sufficient by itself, so inverse problem solutions are often developed in an iterative design-test-update cycle (45). An important risk in artificial intelligence-assisted design is treating model outputs as more reliable than they are. High prediction scores do not guarantee biophysical realism. Computationally suitable candidates should still be tested experimentally (44, 45). Inverse problem results should therefore be treated as hypotheses.

Inverse problem and design are among the most uncertain areas of biophysical modeling. Artificial intelligence can accelerate candidate generation and expand the search space, but biophysical validity and functional accuracy are not automatic (44, 45). Inverse problem outputs become meaningful only when they are evaluated with forward modeling, dynamic analysis, and experimental validation.

9. Validation, Benchmarking, and Reproducibility

Artificial intelligence models can produce reliable information in biophysics only under strong validation and benchmarking strategies. High accuracy or low error values alone are not sufficient for scientific validity. It also depends on the data used, the assumptions made, and the comparison procedure. Validation, benchmarking, and reproducibility are therefore central components of biophysical artificial intelligence studies (13). Validation aims to assess whether a model achieves a specific target. In biophysics, these targets are often diverse and problem-specific. Different problems, such as structure, dynamics, and

function modeling, require different validation criteria. Validation should therefore not rely only on numerical metrics; it should also state clearly what is being validated (13, 24). A common error is to validate models on data sets very similar to training data, which tests data set-specific learning more than real generalization (24). Independent and preferably experimental data sets are therefore important for biophysical validation (25).

The CAMEO platform, developed in the field of protein structure prediction, provides a standardized example for evaluating different methods on the same targets, with criteria, and independently of the developers (31). Such blind and continuous evaluation approaches show where methods are strong or limited. Benchmarking aims to compare the performance of a model with alternative methods. However, for these comparisons to be meaningful, they must be carried out on the same data, with the same evaluation criteria, and under the same assumptions. Otherwise, observed differences may reflect the experimental setup rather than real differences between methods (13). In biophysics, benchmarking should also ask whether the model captures relevant properties, where it fails, and whether the gain is scientifically useful. CASP addresses these questions by testing methods on unknown targets with common protocols (47). Consistency with experimental data is accepted as one of the strongest validation approaches for biophysical artificial intelligence models (13, 24). However, experimental validation is costly, time-consuming, and limited in scale. Computational methods are therefore widely used, but they do not replace experiment (24). Agreement with experimental data shows consistency, not proof of biophysical reality.

Reproducibility refers to the ability of a study to be reproduced by independent researchers using the same data and methods (8). In artificial intelligence studies, this principle requires detailed reporting of data sources, preprocessing steps, model architectures, hyperparameters, and sources of randomness (8, 9). In biophysical studies, poor reporting of experimental conditions, simulation protocols, and data filtering steps may make reproduction technically impossible (3, 35). Open data, open code, and standardized reporting principles are being emphasized increasingly to improve reproducibility. The FAIR principles (Findable, Accessible, Interoperable, Reusable) provide a widely adopted framework for biophysical data and model sharing (35). Their implementation may still face practical and institutional barriers. Reproducibility should therefore be treated as a goal that requires deliberate effort (8).

The value of model predictions depends on clear validation, fair benchmarking, and reproducibility.

10. Limits and Open Problems

Artificial intelligence-based biophysical modeling has improved the analysis of structure, dynamics, and function relationships. However, basic limitations remain. The success of high-capacity models has increased the need to state clearly when their outputs are reliable (13, 24). One of the clearest limitations of biophysical artificial intelligence models is

the lack of suitable data. Existing datasets are often concentrated around specific protein families, structure types, or systems that are easier to study experimentally. In contrast, intrinsically disordered proteins, rare conformational transitions, and complex multicomponent systems are often underrepresented (20, 21, 36). This imbalance can support high performance within the training distribution but reduce reliability in new or unusual systems. Collecting more data alone is therefore not sufficient; missing data types must also be identified clearly (11, 12, 48). Living systems are organized across multiple scales, from the atomic level to cellular and tissue scales (1, 2). In contrast, current artificial intelligence models usually operate at a single scale or between limited scales (24). Models with high atomic accuracy may miss larger-scale collective behaviors, while coarse-grained approaches leave out atomic details (49). This gap between scales remains a major open problem.

Artificial intelligence models often learn statistical regularities in data without directly representing physical laws. This may produce outputs that are hard to interpret physically or that lack consistency. Physics-informed learning aims to reduce this risk, but the choice of physical constraints and their level of use remain open research questions (34). In biophysics, physical consistency includes energy, kinetics, thermodynamic equilibrium, and sensitivity to environmental conditions (13, 22). Many biophysical artificial intelligence models are successful in systems similar to their training data, but their performance often decreases on out-of-distribution examples. This is especially critical in inverse problem and design, where rare or unseen solutions are often the goal (42, 45). Uncertainty estimation does not solve this problem fully, but it can identify predictions that require more cautious interpretation (48). How to measure and report generalizability remains open. Artificial intelligence models can learn strong statistical relationships between structure, dynamics, and function. However, it is often not possible to determine whether these relationships are causal. Causal inferences require intervention-based experiments or explicit mechanistic models. Artificial intelligence-based results should therefore not be presented as definitive explanations of biophysical mechanisms (9). Explainability methods can provide clues, but they do not demonstrate biophysical causality (33).

The field therefore remains actively developing. Open questions include when artificial intelligence is truly needed, how to balance model size with experiment-model integration, how to balance physical consistency with model flexibility, and when artificial intelligence outputs can be accepted as reliable biophysical knowledge.

11. Results

The examined examples and methods clearly show that artificial intelligence offers important possibilities in the analysis of biophysical systems. These possibilities should not be interpreted as automatic, universal, or directly causal explanations. Because AI models can work on large and heterogeneous data sets, they can address high-dimensional problems that are difficult for traditional approaches. Progress has been reported in structure

prediction, reduction of dynamic patterns, and discovery of statistical relations associated with function (5, 6, 25, 30, 32). These advances are based on data-driven generalizations rather than direct representations of physical laws or biophysical mechanisms (11, 13). A main point of this study is that AI models do not reproduce biophysical reality one-to-one. Their outputs depend on data representations, assumptions, and measurement or modeling conditions, so interpretation requires experimental evaluation and assessment of physical consistency (4, 13). The inverse problem and design approaches represent one of the most ambitious areas of AI use in biophysics. The ability to propose a structure or sequence from functional targets can accelerate research, but proposed solutions are not automatically biophysically stable, synthesizable, or experimentally valid. Design outputs should therefore be evaluated as experimental hypotheses (42, 45).

Issues of validation, benchmarking, and reproducibility are key criteria for the scientific value of AI-based biophysical studies. High performance metrics have limited value without appropriate validation and transparent reporting. Open data, open code, and standardized evaluation remain critical for the field (8, 31, 35). Artificial intelligence in biophysics should be treated as a complementary tool that works with experiment, theory, and computational modeling (8, 9, 13, 24). It is most useful when the questions, data, and assumptions are clearly defined.

12. References

1. Henzler-Wildman, K., & Kern, D. (2007). Dynamic personalities of proteins. Nature, 450(7172), 964-972. https://doi.org/10.1038/nature06522
2. Ramaswamy, S. (2010). The Mechanics and Statistics of Active Matter. Annual Review Condensed Matter Physics, 1, 323-345. https://doi.org/10.1146/annurev-conmatphys-070909-104101
3. Bonomi, M., Heller, G. T., Camilloni, C., & Vendruscolo, M. (2017). Principles of protein structural ensemble determination. Current opinion in structural biology, 42, 106-116. https://doi.org/10.1016/j.sbi.2016.12.004
4. Philips, R., Kondev, J., Theriot, J., Garcia, H. G. (2013). Physical Biology of the Cell. Garland Science, Taylor & Francis Group, London and New York.
5. Rives, A., Meier, J., Sercu, T., Goyal, S., Lin, Z., Liu, J., Guo, D., Ott, M., Zitnick, C. L., Ma, J., & Fergus, R. (2021). Biological structure and function emerge from scaling unsupervised learning to 250 million protein sequences. Proceedings of the National Academy of Sciences of the United States of America, 118(15), e2016239118. https://doi.org/10.1073/pnas.2016239118
6. Alley, E. C., Khimulya, G., Biswas, S., AlQuraishi, M., & Church, G. M. (2019). Unified rational protein engineering with sequence-based deep representation learning. Nature methods, 16(12), 1315-1322. https://doi.org/10.1038/s41592-019-0598-1
7. Gawlikowski, J., Tassi, C.R.N., Ali, M., Lee, J., Humt, M., Feng, J., Kruspe, A., Triebel, R., Jung, P., ,Roscher, R., Shahzad, M., Yang, W., Bamler, R., & Zhu, X. X. (2023). A survey of uncertainty in deep neural networks. Artif Intell Rev., 56(1), 1513-1589. https://doi.org/10.1007/s10462-023-10562-9
8. Sansone, S. A., McQuilton, P., Rocca-Serra, P., Gonzalez-Beltran, A., Izzo, M., Lister, A. L., Thurston, M., & FAIRsharing Community (2019). FAIRsharing as a community approach to standards, repositories and policies. Nature biotechnology, 37(4), 358-367. https://doi.org/10.1038/s41587-019-0080-8
9. Pearl, J. (2009). Causality, Models, Reasoning, and Inference (2nd Ed.). Cambridge University Press, New York, USA.
10. Baek, M., DiMaio, F., Anishchenko, I., Dauparas, J., Ovchinnikov, S., Lee, G. R., Wang, J., Cong, Q., Kinch, L. N., Schaeffer, R. D., Millán, C., Park, H., Adams, C., Glassman, C. R., DeGiovanni, A., Pereira, J. H., Rodrigues, A. V., van Dijk, A. A., Ebrecht, A. C., Opperman, D. J., … Baker, D. (2021). Accurate prediction of protein structures and interactions using a three-track neural network. Science (New York, N.Y.), 373(6557), 871-876. https://doi.org/10.1126/science.abj8754
11. Jumper, J., Evans, R., Pritzel, A., Green, T., Figurnov, M., Ronneberger, O., Tunyasuvunakool, K., Bates, R., Žídek, A., Potapenko, A., Bridgland, A., Meyer, C., Kohl, S. A. A., Ballard, A. J., Cowie, A., Romera-Paredes, B., Nikolov, S., Jain, R., Adler, J., Back, T., … Hassabis, D. (2021). Highly accurate protein structure prediction with AlphaFold. Nature, 596(7873), 583-589. https://doi.org/10.1038/s41586-021-03819-2

12. Varadi, M., Anyango, S., Deshpande, M., Nair, S., Natassia, C., Yordanova, G., Yuan, D., Stroe, O., Wood, G., Laydon, A., Žídek, A., Green, T., Tunyasuvunakool, K., Petersen, S., Jumper, J., Clancy, E., Green, R., Vora, A., Lutfi, M., Figurnov, M., … Velankar, S. (2022). AlphaFold Protein Structure Database: massively expanding the structural coverage of protein-sequence space with high-accuracy models. Nucleic acids research, 50(D1), D439-D444. https://doi.org/10.1093/nar/gkab1061
13. Gunawardena J. (2014). Models in biology: 'accurate descriptions of our pathetic thinking'. BMC biology, 12, 29. https://doi.org/10.1186/1741-7007-12-29
14. Liwo, A., Czaplewski, C., Sieradzan, A. K., Lubecka, E. A., Lipska, A. G., Golon, Ł., Karczyńska, A., Krupa, P., Mozolewska, M. A., Makowski, M., Ganzynkowicz, R., Giełdoń, A., & Maciejczyk, M. (2020). Scale-consistent approach to the derivation of coarse-grained force fields for simulating structure, dynamics, and thermodynamics of biopolymers. Progress in molecular biology and translational science, 170, 73-122. https://doi.org/10.1016/bs.pmbts.2019.12.004
15. Dill, K. A., & MacCallum, J. L. (2012). The protein-folding problem, 50 years on. Science (New York, N.Y.), 338(6110), 1042-1046. https://doi.org/10.1126/science.1219021
16. Berman, H. M., Westbrook, J., Feng, Z., Gilliland, G., Bhat, T. N., Weissig, H., Shindyalov, I. N., & Bourne, P. E. (2000). The Protein Data Bank. Nucleic acids research, 28(1), 235-242. https://doi.org/10.1093/nar/28.1.235
17. Clore, G. M., & Gronenborn, A. M. (1994). Multidimensional heteronuclear nuclear magnetic resonance of proteins. Methods in enzymology, 239, 349-363. https://doi.org/10.1016/s0076-6879(94)39013-4
18. Frank, J. (2006). Three-Dimensional Electron Microscopy of Macromolecular Assemblies. Oxford University Press, New York, USA.
19. Frauenfelder, H., Sligar, S. G., & Wolynes, P. G. (1991). The energy landscapes and motions of proteins. Science (New York, N.Y.), 254(5038), 1598-1603. https://doi.org/10.1126/science.1749933
20. Wright, P. E., & Dyson, H. J. (1999). Intrinsically unstructured proteins: re-assessing the protein structure-function paradigm. Journal of molecular biology, 293(2), 321-331. https://doi.org/10.1006/jmbi.1999.3110
21. Uversky V. N. (2014). Introduction to intrinsically disordered proteins (IDPs). Chemical reviews, 114(13), 6557-6560. https://doi.org/10.1021/cr500288y
22. Karplus, M., & McCammon, J. A. (2002). Molecular dynamics simulations of biomolecules. Nature structural biology, 9(9), 646-652. https://doi.org/10.1038/nsb0902-646
23. Rupp, B. (2010). Biomolecular Crystallography Principles, Practive, And Applications to Structural Biology. Garland Science, Talor & Francis Group, New York, USA.
24. Shaw, D. E., Maragakis, P., Lindorff-Larsen, K., Piana, S., Dror, R. O., Eastwood, M. P., Bank, J. A., Jumper, J. M., Salmon, J. K., Shan, Y., & Wriggers, W. (2010). Atomic-level characterization of the structural dynamics of proteins. Science (New York, N.Y.), 330(6002), 341-346. https://doi.org/10.1126/science.1187409
25. Noé, F., & Fischer, S. (2008). Transition networks for modeling the kinetics of conformational change in macromolecules. Current opinion in structural biology, 18(2), 154-162. https://doi.org/10.1016/j.sbi.2008.01.008
26. Chodera, J. D., & Noé, F. (2014). Markov state models of biomolecular conformational dynamics. Current opinion in structural biology, 25, 135-144. https://doi.org/10.1016/j.sbi.2014.04.002
27. Pérez-Hernández, G., Paul, F., Giorgino, T., De Fabritiis, G., & Noé, F. (2013). Identification of slow molecular order parameters for Markov model construction. The Journal of chemical physics, 139(1), 015102. https://doi.org/10.1063/1.4811489
28. Husic, B. E., & Pande, V. S. (2018). Markov State Models: From an Art to a Science. Journal of the American Chemical Society, 140(7), 2386-2396. https://doi.org/10.1021/jacs.7b12191
29. Bai, Y., Sosnick, T. R., Mayne, L., & Englander, S. W. (1995). Protein folding intermediates: native-state hydrogen exchange. Science (New York, N.Y.), 269(5221), 192-197. https://doi.org/10.1126/science.7618079
30. Elnaggar, A., Heinzinger, M., Dallago, C., Rehawi, G., Wang, Y., Jones, L., Gibbs, T., Feher, T., Angerer, C., Steinegger, M., Bhowmik, D., & Rost, B. (2022). ProtTrans: Toward Understanding the Language of Life Through Self-Supervised Learning. IEEE transactions on pattern analysis and machine intelligence, 44(10), 7112-7127. https://doi.org/10.1109/TPAMI.2021.3095381
31. Haas, J., Barbato, A., Behringer, D., Studer, G., Roth, S., Bertoni, M., Mostaguir, K., Gumienny, R., & Schwede, T. (2018). Continuous Automated Model EvaluatiOn (CAMEO) complementing the critical assessment of structure prediction in CASP12. Proteins, 86 Suppl 1(Suppl 1), 387-398. https://doi.org/10.1002/prot.25431
32. Li, F., Yuan, L., Lu, H., Li, G., Chen, Y., Engqvist, M. K. M., Kerkhoven, E. J., & Nielsen, J. (2022). Deep learning-based kcat prediction enables improved enzyme-constrained model reconstruction. Nat Catal., 5, 662-672. https://doi.org/10.1038/s41929-022-00798-z
33. Rudin C. (2019). Stop Explaining Black Box Machine Learning Models for High Stakes Decisions and Use Interpretable Models Instead. Nature machine intelligence, 1(5), 206-215. https://doi.org/10.1038/s42256-019-0048-x
34. 34 Raissi, M., Perdikas, P., & Karniadakis, G. E. (2019). Physics-informed neural networks: A deep learning framework for solving forward and inverse problems involving nonlinear partial differential equations. Journal of Computational Physics, 378, 686-707. https://doi.org/10.1016/j.jcp.2018.10.045
35. Wilkinson, M. D., Dumontier, M., Aalbersberg, I. J., Appleton, G., Axton, M., Baak, A., Blomberg, N., Boiten, J. W., da Silva Santos, L. B., Bourne, P. E., Bouwman, J., Brookes, A. J., Clark, T., Crosas, M., Dillo, I., Dumon, O., Edmunds, S., Evelo, C. T., Finkers, R., Gonzalez-Beltran, A., … Mons, B. (2016). The FAIR Guiding Principles for scientific data management and stewardship. Scientific data, 3, 160018. https://doi.org/10.1038/sdata.2016.18

36. Alber, F., Dokudovskaya, S., Veenhoff, L. M., Zhang, W., Kipper, J., Devos, D., Suprapto, A., Karni-Schmidt, O., Williams, R., Chait, B. T., Rout, M. P., & Sali, A. (2007). Determining the architectures of macromolecular assemblies. Nature, 450(7170), 683-694. https://doi.org/10.1038/nature06404
37. Boomsma, W., Ferkinghoff-Borg, J., & Lindorff-Larsen, K. (2014). Combining experiments and simulations using the maximum entropy principle. PLoS computational biology, 10(2), e1003406. https://doi.org/10.1371/journal.pcbi.1003406
38. Cavalli, A., Camilloni, C., & Vendruscolo, M. (2013). Molecular dynamics simulations with replica-averaged structural restraints generate structural ensembles according to the maximum entropy principle. The Journal of chemical physics, 138(9), 094112. https://doi.org/10.1063/1.4793625
39. Noé, F., De Fabritiis, G., & Clementi, C. (2020). Machine learning for protein folding and dynamics. Current opinion in structural biology, 60, 77-84. https://doi.org/10.1016/j.sbi.2019.12.005
40. Schütt, K., Kindermans, P. -J., Sauceda, H. E., Chmiela, S., Tkatchenko, A., & Müller, K.-R. (2017). SchNet: A continuous-filter convolutional neural network for modeling quantum interactions. 31st Conference on Neural Information Processing Systems (NIPS 2017), Long Beach, CA, USA.
41. Bronstein, M. M., Bruna, J., LeCun, Y., Szlam, A., & Vandergheynst, P. (2016). Geometric Deep Learning: Going beyond Euclidean data. IEEE Sig.Proc.Mag., 34(4), 18-42. https://doi.org/10.1109/MSP.2017.2693418
42. Anand, N. & Huang, P. -S. (2018). Generative Modeling for Protein Structures. 32nd Conference on Neural Information Processing Systems (NeurIPS 2018), Montréal, Canada.
43. Ingraham, J., Garg, V. K., Barzilay, R., & Jaakkola, T. (2019). Generative models for graph-based protein design. 33rd Conference on Neural Information Processing Systems (NeurIPS 2019), Vancouver, Canada.
44. Tripple, B. L., Yim. J., Tischer, D., Baker, D., Broderick, T., Barzilay, R., & Jaakkola, T. (2023). Diffusion Probabilistic Modeling Of Protein Backbones In 3d For The Motif-Scaffolding Problem. The Eleventh International Conference on Learning Representations (ICLR 2023), Kigali, Rwanda.
45. Dauparas, J., Anishchenko, I., Bennett, N., Bai, H., Ragotte, R. J., Milles, L. F., Wicky, B. I. M., Courbet, A., de Haas, R. J., Bethel, N., Leung, P. J. Y., Huddy, T. F., Pellock, S., Tischer, D., Chan, F., Koepnick, B., Nguyen, H., Kang, A., Sankaran, B., Bera, A. K., … Baker, D. (2022). Robust deep learning-based protein sequence design using ProteinMPNN. Science (New York, N.Y.), 378(6615), 49-56. https://doi.org/10.1126/science.add2187
46. Batzner, S., Musaelian, A., Sun, L., Geiger, M., Mailoa, J. P., Kornbluth, M., Molinari, N., Smidt, T. E., & Kozinsky, B. (2022). E(3)-equivariant graph neural networks for data-efficient and accurate interatomic potentials. Nature communications, 13(1), 2453. https://doi.org/10.1038/s41467-022-29939-5
47. Kryshtafovych, A., Schwede, T., Topf, M., Fidelis, K., & Moult, J. (2021). Critical assessment of methods of protein structure prediction (CASP)-Round XIV. Proteins, 89(12), 1607-1617. https://doi.org/10.1002/prot.26237
48. Hooker S. (2021). Moving beyond "algorithmic bias is a data problem". Patterns (New York, N.Y.), 2(4), 100241. https://doi.org/10.1016/j.patter.2021.100241
49. Noid W. G. (2013). Perspective: Coarse-grained models for biomolecular systems. The Journal of chemical physics, 139(9), 090901. https://doi.org/10.1063/1.4818908

CHAPTER 5

Multi-Omics Analyses and Artificial Intelligence Applications in Medical Biology

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1. Introduction

In recent years, advances in high-throughput technologies such as next-generation sequencing, mass spectrometry, and single-cell assays have led to a shift in biomedical research from traditional approaches focusing on a single "omics" layer to holistic multi-omics approaches that consider different biological layers together, such as the genome, epigenome, transcriptome, proteome, and metabolome (1-3). This technological transformation is based on the fact that cellular processes are the result of complex interactions between different molecular layers. For example, the fact that an increase in mRNA levels does not always translate into increased protein levels, or the repressive roles of microRNAs (miRNAs) on gene expression, highlights the inadequacy of analysing biological systems at a single level (4, 5). Therefore, multi-omics analyses play a critical role in understanding the molecular aetiology of diseases, identifying disease subtypes, discovering new biomarkers, and developing personalised treatment strategies.

However, the highly dimensional, heterogeneous, and noisy datasets that accompany multi-omics research limit the effectiveness of traditional statistical methods (6, 7). Artificial intelligence (AI) and machine learning (ML) methods offer an indispensable solution in overcoming these analytical challenges. AI-based approaches, thanks to their capacity to model complex and nonlinear relationships, make it possible to extract meaningful patterns from biomedical data, yielding successful results in the classification of disease subtypes, the prediction of treatment responses, and the identification of new therapeutic targets (3, 8, 9).

Currently, AI applications in medical biology extend beyond basic prediction models, facilitating the integration of many omics layers and enhancing the modelling of biological systems using sophisticated techniques such as ensemble learning, graph-based mod-

elling, and deep learning (10-12). Research, especially in oncology, demonstrates that AI-assisted multi-omics integration enhances tumour classification precision and improves the efficacy of clinical decision-making procedures (13, 14). Moreover, these comprehensive techniques are being increasingly utilised in cardiovascular, metabolic, neurodegenerative, and immunological disorders (5, 15, 16).

The combination of AI-powered analyses is accelerating personalised medicine applications. Molecular data is integrated with clinical phenotypes, medical images, and electronic health records. This comprehensive data combination provides a strong foundation for early diagnosis and individualised treatment decisions (5, 11, 17). However, critical hurdles still need to be overcome in this field. Data standardisation and model reproducibility are among the most important of these challenges. Furthermore, ethical regulations and issues regarding the full integration of systems into clinical processes remain relevant (11, 18).

This book chapter aims to provide a comprehensive framework, ranging from fundamental concepts to clinical applications, by examining the role of multi-omics approaches in medical biology, along with AI-based analysis strategies.

2. Overview of Omic Technologies

Omics technologies rely on high-throughput platforms that enable high-resolution analysis of biological systems at different molecular levels. Today, genomic, epigenomic, transcriptomic, proteomic, metabolomic, and microbiomic approaches are not only independent research fields but have also become fundamental components of multi-omics integration strategies. The combined evaluation of these data layers with AI-supported methods leads to significant advancements, particularly in translational medicine (3, 15, 17, 19).

2.1. Genomics and Epigenomics

Genomic analysis is a detailed examination of DNA sequences and structural variants. Single-nucleotide polymorphisms, copy number variations, indel mutations, and significant structural variants are the foundations of genomic research. Next-generation sequencing Technologies, including genome sequencing and whole-exome sequencing, as well as long-read sequencing techniques, are crucial in the molecular diagnosis of genetic diseases and in understanding clonal evolution in cancer genomics (20, 21). Furthermore, the integration of genomic data with ML improves clinical decision support systems, notably for analysing tumour mutation burden and signatures, and in determining targeted therapeutic strategies (14, 22, 23).

Epigenomics, on the other hand, encompasses mechanisms that regulate gene expression without altering the DNA sequence. Processes such as DNA methylation, histone modifications, and chromatin accessibility create dynamic regulatory layers sensitive to environmental factors. Single-cell epigenomic techniques and multimodal platforms enable the simultaneous analysis of the relationship between chromatin structure and gene

expression. AI analysis of this data significantly improves prognostic model accuracy, identifies early diagnostic biomarkers and distinguishes disease subtypes, particularly in cancer and neurological disorders (16, 19, 23, 24).

2.2. Transcriptomics

Transcriptomic analyses provide a comprehensive view of RNA expression profiles in biological samples. RNA sequencing technology has revolutionised transcriptomic research by enabling the identification of differential gene expression, alternative splicing, and fusion genes. Sequencing at the single-cell level offers the opportunity to examine cellular heterogeneity down to the finest detail (25). In addition, non-coding RNA types such as lncRNA, miRNA, and circRNA play a key role in gene regulation and are emerging as diagnostic biomarkers (26). Current studies demonstrate that combining AI-powered analyses with spatial and single-cell data provides a major advance in understanding the tumour microenvironment and cellular subgroups (19, 23).

2.3. Proteomics

Proteomics, the quantitative and qualitative analysis of proteins that directly regulate cellular functions, plays a critical role in biomarker discovery, drug targeting, and disease management today. Mass spectrometry (MS)-based technologies (especially LC-MS/MS) allow for detailed investigation of protein expression, post-translational modifications, and protein-protein interaction networks. AI applications, which find application in almost all stages of MS-based proteomics studies, have evolved from traditional ML algorithms to modern deep learning (DL) models, taking analysis performance to a higher level. DL approaches, in particular, have surpassed classical methods in spectrum estimation and modelling complex biological data (27-29).

AI-supported proteomic approaches are noteworthy as important tools in helping to solve biological complexity, discovering new biomarkers, and identifying specific drug targets. Translational research, where proteomic data is evaluated with multiple omics integration, also shows that it strengthens risk stratification and clinical predictions in various diseases such as oncological, neurological, and cardiovascular (14, 15, 28).

2.4. Metabolomics and Microbiomics

Metabolomics offers a functional reflection of cellular processes through the analysis of low molecular weight metabolites; Nuclear Magnetic Resonance (NMR) and LC-MS-based approaches play a critical role in identifying disease-related metabolite signatures and therapeutic responses (30). Similarly, microbiomics reveals host-microbial interactions and functional capacity in detail through 16S rRNA sequencing and shotgun metagenomic methods (31). According to recent research, evaluating this data in conjunction with multi-omics integration provides transformative benefits, especially in predicting metabolic syndrome, inflammatory diseases, and immunotherapy response (32).

The integration of multiple omics data with AI-based models has enabled us to move beyond the limited and reductionist nature of single omics approaches. Thus, diseases can now be redefined from a much broader and more comprehensive systems biology perspective. This technological synergy has also fundamentally changed the role of omics data, making it not only a tool for molecular identification but also a crucial component of clinical decision support systems. However, making biologically meaningful inferences and generating reliable hypotheses from these high-dimensional, heterogeneous, and incomplete datasets remains one of the most fundamental analytical challenges in the field (14, 17, 19, 32).

3. Integration Strategies in Multi-omics Approaches

Multi-omics approaches reveal the molecular mechanisms of diseases more comprehensively through the holistic integration of multi-layered biological data ranging from genomic variations to metabolic outputs. The inclusion of AI and ML methods in this process has significantly increased the predictive power of translational medicine (3, 14, 17, 19, 22).

3.1. Data Integration Models and Timing Strategies

Depending on the data structure and study design, the integration process can be categorised as horizontal, vertical, and diagonal (Figure 1).

- **Horizontal Integration:** This strategy, based on combining different cohorts belonging to the same omics layer, increases sample size and enhances the statistical power of analyses. However, systematic errors such as technical heterogeneity in data from different sources and batch effects necessitate the rigorous application of advanced normalisation techniques (6, 14, 33).
- **Vertical Integration:** This strategy is the simultaneous analysis of different omics layers (e.g., transcriptomics and proteomics) belonging to the same individual or sample group. In this dimension, which aims to model complex relationships ranging from genetic variations to phenotype, Deep Learning, Graph Neural Networks (GNNs), and Variational Autoencoders demonstrate superior performance in resolving inter-layer interactions (14, 17, 19, 33).
- **Diagonal Integration:** Combines heterogeneous sources with missing data through common mathematical representations. This approach offers flexibility, particularly in multi-centre studies where different protocols are applied, to ensure data integrity (17, 33). However, after this dimensional organisation of the data, the stage at which modalities are integrated in the analysis process is also of great importance.

In multi-omic studies, the stage at which different data layers such as genomics, transcriptomics, and proteomics are integrated plays a decisive role in the accuracy of the biolog-

ical inferences obtained. In this context, the integration methodologies applied are evaluated under three basic strategic approaches: early, intermediate, and late integration. (Figure 1).

- **Early Integration:** In this approach, all raw data from different sources (modalities) are combined into a single large dataset before the analysis phase. The model processes this combined set as a single input. It is easy to implement, but it can lead to the loss of original structural differences between the data (34, 35).
- **Intermediate Integration:** In this method, modalities are initially kept as separate entities. During the analysis process, the unique characteristics of each data type are preserved while the relationships between modalities are also learned. Ultimately, a "shared latent space" or an integrated model structure is created where all data meet on a common ground (34, 35).
- **Late Integration:** In this strategy, completely independent models are trained for each data type (e.g., genomic, proteomic, or clinical data). After each model generates its own prediction, these individual results are eventually combined (ensemble learning) to arrive at a final result. This method ensures that each data type best preserves its own internal dynamics, but it has a lower capacity to directly reflect molecular interactions (34, 35).

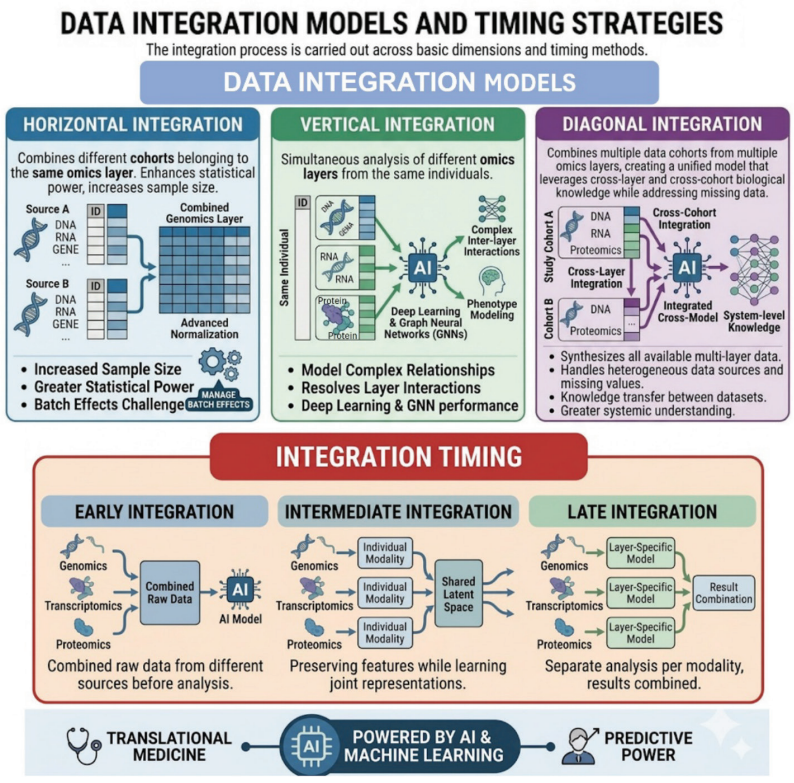


Figure 1. Schematic illustration of integration models and timing in multi-omics data integration. Nano Banana 2 was used to create the image.

The developed deep learning-based multimodal integration approaches enable more effective interpretation of information obtained from multi-omics data by combining these strategies.

3.2. Systems Biology and Functional Networks

Multi-omics integration involves the restructuring of biological networks as well as the merging of data. Several fundamental tools exist for understanding the functional relationships between multi-omics layers. Among these tools, gene regulatory networks, protein-protein interaction networks (PPI networks), and metabolic pathway maps are the most frequently referenced tools (10). Systems biology approaches allow us to simulate complex biological systems by integrating omics data with clinical, imaging, and phenotypic data, making it possible to create more comprehensive biological network maps (23). In this regard, biological complexity in system dynamics can be more accurately and consistently represented through multi-omics integration.

4. Fundamental Concepts and Learning Strategies of Artificial Intelligence and Machine Learning

The highly dimensional, heterogeneous, and often missing-value structure of multi-omics data necessitates advanced computational approaches that incorporate more flexible and scalable analytical methods beyond classical statistical techniques. In this regard, AI, the umbrella concept that enables computers to mimic human behaviour, and ML, a subset of AI that allows systems to learn from data without explicit programming, offer a powerful methodological framework for extracting meaningful patterns from biological data and generating new biological hypotheses through precise predictive models (3, 17).

Today, AI and multimodal AI have become essential tools in a wide variety of applications, such as pattern discovery in biological data, disease classification, prognosis prediction, and treatment response forecasting (8, 11). These approaches offer unique advantages, particularly in multi-omics datasets, for modelling nonlinear relationships and mapping complex interactions between variables. Indeed, the integration of deep learning (DL) and multimodal AI architectures into multi-omics has significantly improved clinical prediction performance and biological interpretation capacity (14, 19, 22). The fundamental learning strategies and analytical processes used to realise this potential of multi-omics data are detailed below.

AI, ML, and DL architectures offer a powerful methodological framework for extracting meaningful patterns from biological data, modelling complex nonlinear relationships, and generating new hypotheses [3, 17]. These approaches have become essential tools in critical areas such as disease classification, prognosis prediction, and treatment response forecasting, significantly enhancing biological interpretation capacity and clinically relevant predictions [8, 11, 14, 21, 24]. The fundamental learning strat-

egies and analytical processes that realise this potential offered by multiple omics data are discussed below.

4.1. Supervised and Unsupervised Learning

Machine learning paradigms are primarily classified into three main categories based on how biomedical data is processed:

- **Supervised Learning:** Supervised learning is widely preferred in solving clinical problems such as disease classification (e.g., benign/malignant differentiation), prognosis prediction (survival analyses), and treatment response prediction using labelled datasets (3, 14, 36). Logistic regression, support vector machines (SVMs), random forests, gradient boosting methods, and artificial neural networks are commonly used in biological classification problems (37). In multi-omics studies, these methods play an important role in identifying cancer subtypes, discovering biomarkers, and developing personalised treatment strategies. It has been reported that ensemble and deep learning models trained with multi-omics data provide higher accuracy in cancer subtype classification and immunotherapy response prediction compared to classical methods. Furthermore, in survival analyses, methods such as Random Survival Forest and DeepSurv, which are machine learning extensions of Cox regression, enhance clinical prediction performance through multi-omics data integration (14, 23).
- **Unsupervised Learning:** Unsupervised learning aims to uncover natural clustering and hidden patterns within data without a predefined (unlabeled) output variable. This paradigm plays a critical role, particularly in identifying molecular subtypes of diseases and revealing biological heterogeneity (14, 23). Methods such as K-means, hierarchical clustering, Gaussian Mixture Models, Non-Negative Matrix Factorisation (NMF), and Multi-omics Factor Analysis (MOFA) have enabled the identification of clinically significant new subgroups in complex diseases such as cancer (38). These approaches, combined with dimensionality reduction techniques, allow for the transformation of high-dimensional multi-omics data into more understandable and interpretable biological representations.
- **Reinforcement Learning:** Reinforcement learning (RL) is a machine learning approach that allows an agent to learn by interacting with a specific environment and receiving reward or punishment signals based on the consequences of its actions. In this method, the model learns the strategy that provides the highest total reward through trial and error without precise output labels. Therefore, unlike supervised and unsupervised learning, RL focuses on modelling dynamic decision-making processes. Although RL applications are still limited in biomedical research, and especially in multi-omics data analysis, it is attracting attention as a rapidly developing research area. These approaches have significant potential in areas such as modelling complex biological systems, developing adaptive treatment strategies, and optimising drug discovery processes (3, 14, 36).

4.2. Feature Selection and Dimensionality Reduction

Multi-omic datasets often contain a very high number of variables (features) despite limited sample sizes. This unbalanced structure increases the risk of overfitting models to training data and limits their generalizability. Therefore, feature selection and dimensionality reduction techniques are among the most critical components of biomedical data analysis. Methods that create simpler and more interpretable models by eliminating redundant variables, such as LASSO, play a significant role in identifying clinically applicable gene or protein panels, especially in biomarker discovery studies. In addition to LASSO, fundamental methods such as PCA (Principal Component Analysis), t-SNE (t-distributed Stochastic Neighbour Embedding), and UMAP (Uniform Multiple Approximation and Projection) are still considered the gold standard for distinguishing biologically significant signals (3, 14, 28).

4.3. Deep Learning

Deep learning (DL), a subfield of ML, relies on multilayer neural networks and has the capacity to automatically learn complex patterns in large datasets. Convolutional neural networks (CNN), recurrent neural networks (RNN), and autoencoder architectures are widely used in the analysis of biomedical data. While CNNs are primarily designed for image processing, they demonstrate high success in motif analysis in genomic sequences and the extraction of epigenetic signal patterns. RNN and Long Short-Term Memory (LSTM) structures are used to model dependencies in longitudinal multi-omics data, tracking processes such as disease progression. Autoencoder and Variational Autoencoder (VAE) architectures come into play in dimensionality reduction and low-dimensional "latent" representation learning stages. The main goal in these models is to minimise data reconstruction errors. In VAE models, the probabilistic distribution of the data is modelled by optimising the lower bound of evidence (ELBO). Current studies show that multimodal deep learning models integrating omics data with imaging and clinical data significantly improve analysis performance. For example, in the discovery of cancer subtypes, Generative adversarial networks (GANs), VAEs, convolutional autoencoders, transformers, self-supervised clustering, and graph convolutional networks have been used to create effective models for cancer subtypes and improve our understanding of the underlying biology (3, 14, 17, 27, 28, 33, 39).

In a multi-omics context, deep learning methods can provide more holistic representation learning by automatically extracting features from data obtained from different omics layers. In particular, autoencoder-based approaches are used to create more compact and biologically meaningful representations in noisy and high-dimensional omics data. Deep learning models are also effectively applied in multimodal integration studies, such as the simultaneous analysis of histopathological images and genomic data. Today, these architectures have evolved beyond data classification to include predicting biological structures, protein-ligand interactions, and gene correlation processes. These advanced

modells maximize clinical prediction performance and biological interpretation capabilities by processing omics data not only as statistical input but also as part of a complex biological language (3, 14, 28, 33, 39).

In general terms, artificial intelligence and machine learning approaches are leading the way in the development of precision medicine applications by enabling the integration of complex multi-omics data into clinical decision support systems. However, fundamental elements such as model interpretability, data standardisation, and ethical considerations will continue to be decisive factors in the safe and effective transfer of these advanced technologies to clinical practice.

5. AI-Powered Multi-omics Analysis

Multi-omics approaches enable a more holistic understanding of disease mechanisms by allowing the combined analysis of data from different biological layers such as genomics, transcriptomics, proteomics, and metabolomics. However, since these datasets are complex structures with high-dimensionality, heterogeneity, and technical variations, AI and ML methods have become increasingly important for effective analysis. AI-assisted multi-omics analyses are used in many stages, starting from data preprocessing and normalisation, to the integration of different omics layers, modelling of biological networks, and biomarker discovery.

5.1. The Strategic Importance of Data Preprocessing and Normalisation

The performance of AI models is directly dependent on data quality and standardisation. Multi-omics datasets require careful standardisation during the preprocessing phase due to their acquisition from different platforms (next-generation sequencing, mass spectrometry, microarray, etc.), measurements at different scales, and technical variability. Noise reduction, missing data imputation, outlier detection, and scaling (normalisation, standardisation) steps are critical for model reliability (6, 39, 40). Although AI applications in proteomics and metabolomics are rapidly advancing, compared to genomics, they are more commonly used in data preprocessing steps due to ongoing challenges in data standardisation and interpretability. The main reasons for this include small sample sizes and lack of interpretability (27, 39).

Non-biological technical variations, known as batch effects, are a significant problem, especially in multicentre or long-term studies. Failure to correct for these effects can lead to erroneous biological inferences. To correct for these effects, in addition to classical statistical methods, deep learning-based architectures such as Variational Autoencoders (VAE) and Generative Adversarial Networks (GAN) provide harmonisation while preserving the biological essence of the data. Furthermore, appropriate normalisation of each omics layer within itself before data integration increases the comparability of multiple data types (27, 39).

5.2. Advanced AI Models in Multi-omics Integration

In multi-omics integration, AI models enable more holistic biological interpretations by combining information from different biological layers into a common representation space. One of the most frequently used approaches in this context is autoencoder (VAEs) based models. Autoencoders can learn the common variational structure of different omics layers while reducing high-dimensional data to lower-dimensional, meaningful representations (39). Multimodal deep learning architectures can more accurately identify disease subtypes by processing genomic, transcriptomic, and proteomic data together (27).

Graph-based learning approaches analyse biological relationships within a structural context by modelling gene-gene, protein-protein, or gene-disease interaction networks. Methods such as Graph Neural Networks (GNNs) contribute to the identification of functional modules and disease-associated network regions by enabling information propagation through nodes (genes/proteins) and edges (interactions) in biological networks. AlphaFold3 and genomic language models (gLMs) are offering significant advances in predicting protein-ligand interactions and gene co-regulation, demonstrating the potential of deep learning in biological analysis (10, 39).

Bayesian network models, by representing probabilistic dependencies, allow for the modelling of causal or conditional relationships between variables. Bayesian frameworks offer significant advantages in modelling possible pathways ranging from genetic variations to transcriptomic changes and phenotypic outcomes in multi-omics data (39).

6. Clinical and Translational Applications

6.1. Use of Artificial Intelligence and Multi-omic Analysis in Biomarker Discovery

The discovery of biomarkers is an interesting yet challenging area of contemporary biomedicine. For early detection of diseases, prediction of disease course, estimation of treatment response and identification of therapy resistance, the search for measurable, reliable and reproducible markers is necessary. The problem arises from the fact that biology could not be deduced to a single layer that produces straightforward results. Not all changes in an organism's DNA are reflected equally at the RNA level, such that increased levels of specific RNAs do not correlate directly with protein abundance, and a particular change to protein concentrations may have negligible effects on the metabolic phenotype. This is where the multi-omic approach comes into play. Together, genomic, transcriptomic, proteomic, epigenomic and metabolomic data provide a comprehensive view of the disease. Integrating genetic, transcriptomic, proteomic, epigenomic, and metabolomic data yields a more comprehensive understanding of disease. However, this generates increased analytical complexity that could be translated into significant insights by artificial intelligence and machine learning (41, 42).

Research is no longer solely focused on the differences at single gene level but now asks the questions of which multilayered pattern is clinically useful and which data combination

produces a more clinically-suitable signature. Big data initiatives and AI-based integration methods can derive single molecule and crossomics biomarker panels but data heterogeneity, reproducibility and clinical validation issues still remain as major problems (41).

6.1.1. Why is the classical biomarker search insufficient?

The traditional method for identifying biomarkers depends on one specific parameter. Indicators such as HER2, AFP, EGFR mutations, or PD-L1 expression have significantly influenced clinical practices. Nevertheless, many of these markers prove to be effective in particular patient subgroups in specific contexts. As the disease biology becomes more complex, individual markers encounter their constraints. The multi-omic methods merge subtle signals, which results in more robust, contextual and clinically relevant profiles. Additionally, this strategy can improve reproducibility by conducting cross-validation among various omics levels (41).

On the other hand, the problem grows with the amount of data. The scenario, where the number of variables is much greater than the sample size, is almost the natural state of omics studies. In this case, classical univariate tests either remain overly conservative or produce a large number of false positives. Machine learning is powerful in finding patterns in big data. However, the risk of overfitting is also high in small and noisy biomedical datasets. In other words, the model sometimes learns not the disease, but the random noise in the study. Therefore, biomarker discovery is no longer just a matter of correct prediction, but it is also a matter of sparsity, that is, the selection of a small but meaningful number of features and reliability, which means whether the selected features are truly reliable (42, 43).

The contribution of AI is not only to classification. First, it aligns and normalises the data, handles missing values, and then separates common and modality-specific signals. Then it reduces the dimensionality, captures the relationships among samples or features, and extracts patterns associated with clinical outcomes. This sometimes takes the form of response and non-response prediction with supervised learning, sometimes the separation of patient subgroups with unsupervised learning, and sometimes mechanism analysis with network-based models. In particular, similarity network fusion, canonical correlation-based approaches, matrix factorisation, autoencoders, and graph neural networks are prominent tools in this field (41, 44).

There is an important distinction here. Some methods combine data at an early stage, some process each omics layer separately, then combine them at the latent level, and some perform fusion at the decision level. Which approach is appropriate depends on the nature of the data, the sample size, and the clinical question being asked. Therefore, there is no single best model. A good model is one that is biologically plausible, statistically robust, and clinically transferable (41).

6.1.2. Methods from DIABLO to MOGONET, from Stabl to StabilityCCA

The evolution of methods in this field clearly demonstrates how biomarker discovery has changed. DIABLO was developed to address two important challenges simultaneously.

First, identifying traits that distinguish between phenotypic groups and second, detecting traits that share information across various omics data blocks. Unlike approaches that focus solely on separating classes, DIABLO also questions whether the selected variables participate in a coordinated cross-omics signal. This point is important because many biomarkers are not particularly meaningful when examined individually, but can become biologically informative when they are part of an integrated transcriptomic, epigenetic, proteomic, or metabolic model. In its original publication, DIABLO was introduced as a multi-omics integration method capable of selecting subsets of molecular variables while discriminating between phenotypic groups, and demonstrated its capacity to recover signatures composed of mRNAs, miRNAs, CpGs, proteins, and metabolites. From a biomarker research perspective, DIABLO is attractive because it often produces compact and interpretable signatures rather than simply providing a final predictive value. This feature can facilitate the transition from computational results to biological interpretation. The selected variables can be examined in relation to pathways known to clinical experts or laboratory researchers, and the reproducibility of cross-omics signatures can be tested in independent cohorts. This offers a practical advantage over some highly inflexible black-box models. DIABLO is particularly suitable for designs where paired omics measurements from the same individuals are available, especially when both classification and mechanistic interpretation are desired. However, as with other component-based methods, the interpretability of DIABLO does not automatically guarantee robustness, as the result depends heavily on the choice of settings and preprocessing steps (45).

The significance of MOGONET lies in its quite different methodological design. Instead of focusing primarily on hidden shared components, MOGONET performs omics-specific learning for each omics layer and then integrates information between omics types for the final classification. As described in the original Nature Communications article, this method combines omics-specific learning with crossomics correlation learning to address multiple omics classification problems. The authors reported that MOGONET performed better than many other supervised integrative methods in different biomedical applications and was also able to identify biomarkers in multiple omics data types. A particularly noteworthy feature of MOGONET is its use of graph convolutional networks. Graph-based learning is useful in cases where relationships between samples provide significant information that cannot be captured solely by raw feature values. By generating sample graphs in each omics layer,

MOGONET preserves local similarity structures, and these local structures can correspond to disease states or biological subtypes. This is one reason why graph-based deep learning is gaining increasing interest in multiple omics analysis. Such methods can capture structured relationships that are difficult to represent in ordinary tabular models. In biomarker discovery, MOGONET demonstrates that deep learning can be useful not only for direct prediction but also for prioritising informative features in mRNA, DNA methylation, and miRNA layers (46).

Stabl focuses on a different problem, which is reliability and sparse biomarker selection. The methodological rationale is quite simple. Classical canonical correlation analy-

sis identifies the projections of two maximally correlated datasets, making it suitable for detecting shared structure across different data types. Stability selection applies repeated decays, usually through subsampling, to assess how consistently variables are selected. Therefore, StabilityCCA is particularly useful when the research objective is to identify interconnected features across omics layers rather than maximising instantaneous classification performance. This is a significant contribution to biomarker discovery. For example, if two metabolites and a set of transcriptomic or microbial variables are repeatedly selected together in resampled datasets, this model can provide stronger confidence than a long list of features found only once by a highly optimised classifier. The main limitation is that StabilityCCA is not primarily designed for supervised clinical prediction. It should be better understood as a method for the stable discovery of shared structure and subsequent prioritisation of candidate biomarkers that can be tested with predictive models (47).

StabilityCCA addresses another recurring problem in contemporary omics studies, that although a large number of candidate biomarkers are initially identified, only a small fraction remains convincing after replication and validation. Stabl is a methodological framework for selecting a sparse and reliable set of biomarkers by combining noise injection in multivariate prediction modelling with data-driven signal-to-noise thresholding. The importance of this approach is quite practical. In translational workflows, it is often far more beneficial to obtain a concise list of 5 to 20 robust biomarkers instead of an unstable panel of 200 candidates. A smaller panel is easier to test and validate, more suitable for diagnostic workflows, and more easily interpretable in biological terms. Stabl was developed with this translational reality in mind. Its aim is not only to optimise performance but also to increase the likelihood that the final selected features are small in number, stable against degradation, and reliable enough to be advanced to clinical trials. This feature makes Stabl extremely important in biomarker discovery under rigorous translational expectations. Conceptually, this framework is also important because it emphasises that biomarker modelling should not be evaluated solely by AUC, accuracy, or similar metrics. The number of selected features should also be evaluated in terms of the reproducibility of these features in different environments and the capacity of the signature to remain useful beyond the original discovery cohort (43).

MOFA+ can be considered a distinct class of analytical frameworks and is best described as an unsupervised probabilistic factor analysis approach. It was developed to offer a comprehensive and scalable solution for integrating multimodal data, particularly in complex multi-group and single-cell environments. The framework reconstructs data and identifies major axes of variation in a data set. This is particularly valuable in still poorly characterised biological systems. Before identifying disease-classifying biomarkers, it is often necessary to understand what forms of structured variation are present in the data. These may include batch effects, treatment-related changes, lineage effects, cellular state differences, or disease-associated gradients. MOFA+ offers a systematic way to identify these latent dimensions. In biomarker discovery processes, it is primarily used in the hypothesis generation phase. Latent factors can then be correlated with survival, treatment response, clinical characteristics, or cellular phenotypes. Features with high loadings on

biologically relevant factors can be selected as candidate biomarkers or used to guide subsequent supervised modelling. Consequently, MOFA+ has had a broad impact, although it is not a narrowly predictive biomarker discovery tool. Its role is to organise the data structure before a distinctive signature is selected (48).

Taken together, these methods demonstrate that different tools reflect different priorities in multi-omics biomarker research. DIABLO emphasises interpretable supervised cross-omics signatures. MOGONET emphasises high-capacity supervised integration with graph-based deep learning. StabilityCCA emphasises stable detection of shared cross-view structure. Stabl highlights sparse and reliable translation signatures. MOFA+ focuses on exploratory representation learning in complex multimodal data. There is no single method that can be considered optimal in every context. The most appropriate choice depends on whether the study is exploratory or predictive, the presence or absence of phenotype labels, the required degree of interpretability, and whether the main challenge is classification, trait stability, or biological discovery (43, 46-49).

6.1.3. Biomarker Identification in Various Diseases

- **Colorectal cancer:** Colorectal cancer is one of the most fruitful areas for multi-omics biomarker research. Zafari et al. emphasise that the integrated analysis of genomic, transcriptomic, proteomic, and metabolomic layers in CRC provides a powerful framework for the discovery of novel diagnostic, prognostic, and therapeutic biomarkers. The same study argues that singular omics analyses miss the interlayer relationship. Therefore, candidates found with integrated analysis are more biologically significant (50). This general framework becomes more concrete in the case of early-onset colorectal cancer. The analysis of the tumour tissue microbiome and plasma metabolome together using DIABLO revealed that when the metabolome-based classifier was used with the microbiome-based classifier, the AUC value increased. Furthermore, the study revealed correlations between metabolites, including glycerol, pseudouridine, cholesterol, and xylitol and specific microbial taxa. Such results show that biomarker discovery is no longer about single-molecule hunting but about hunting relationships along the host-microbiome-metabolite axis (51).
- **Immunotherapy:** Immunotherapy has revolutionised oncology, but the patient selection remains problematic. Although markers such as TMB, PD-L1, MSI, or MMR are useful in clinical practice, they are not sufficient on their own. This is because the immunotherapy response is shaped not only by the tumour cell genome but also by the tumour microenvironment, immune infiltration, pathway activity, and intercellular communication networks. Therefore, machine learning is increasingly focused on generating more complex and sensitive response signatures, particularly by combining multi-omic data. The review shows that a wide variety of data types, from single-nucleotide variant (SNV) data to RNA-seq, single-cell RNA data to clinical variables, are used for immunotherapy response prediction. Some studies have achieved significant AUC values using only RNA data, while others have used a combination of RNA, SNV and clinical data. The key point is that model performance often improves not from

raw features, but from high-level features such as tumour-infiltrating lymphocytes, pathway activity, and cell-to-cell communication. In other words, AI does not just compress data, but it translates it into a more biologically meaningful language (52).

- **Liquid biopsy:** Liquid biopsy represents a highly promising and clinically important area of multi-omic biomarker discovery. The concurrent analysis of circulating tumour DNA (ctDNA), circulating tumour cells, extracellular vesicles, microRNAs, proteomic and metabolomic indicators from blood or urine offers an appealing framework for early diagnosis, detection of minimal residual disease and treatment assessment. However, the data types are fragmented, analytes exhibit diversity, and procedures are variable. A recent review that examines AI-supported multi-omic liquid biopsy research in genitourinary cancers shows both the potential and limitations in the area. In cases of advanced prostate cancer, most studies indicate a detection rate exceeding 60% for ctDNA-based methods. Nonetheless, challenges such as small cohorts, absence of external validation, batch variability and lack of explainability issues limit clinical applications (53). This table is important because liquid biopsy demonstrates that discovering biomarkers is not merely about identifying a new signal and that the signal must be explored across multiple centres in a reproducible and standardised manner.
- **Breast, Lung, and Beyond-Composite Panel Thinking:** The multi-omics biomarkers are now evolving from single-gene markers to multilayer composite panels. An approach using AdaBoost, a multilayer perceptron, along with logistic regression integrated cancer markers, cell-free DNA levels and variations in copy number from a study involving 92 lung cancer patients and 80 healthy controls, providing higher diagnostic accuracy compared to analyses based on single markers. A multi-omics signature combining whole slide images, cancer-associated fibroblast signatures, and clinical data delivers greater prognostic accuracy in breast invasive ductal carcinoma. These examples show that multi-omics biomarkers can be further enhanced when they incorporate both laboratory findings and imaging along with clinical information (41).

Although this narrative is oncology-centric, the generalizability of the methodology is also crucial. A recent review on Alzheimer's disease shows that the integration of multi-omics and artificial intelligence can be used similarly not only in cancer, but also in other complex diseases requiring early diagnosis, patient classification, and biomarker discovery. The problem is still the same, that the data being high-dimensional, noisy, and heterogeneous. The solution is also similar by including random forest, SVM, variational autoencoder, graph neural network, transformer, and network-based methods. Thus, multi-omics artificial intelligence actually offers a framework specific to complexity, rather than to the disease (54).

The most compelling aspect of this field is its ability to combine very weak signals and transform them into clinically meaningful panels. The most problematic aspect is the susceptibility to misrecognition. Heterogeneous data types, missing values, different sensitivities of different platforms, the coexistence of continuous and discrete variables in the

same model, feature count imbalance between omics layers, and small sample sizes pose serious problems. Multi-omics integration can amplify false positives; overfitting is even more prevalent, especially when working with single-cell and spatial data (41).

Machine learning is good at finding patterns in big data, but this pattern can sometimes be a local mechanism specific to the training dataset. Discovery that cannot be reproduced in independent cohorts is not a clinical biomarker. Therefore, regularisation, cross-validation, external validation, control of false discovery rates, and explainable artificial intelligence are indispensable. As long as the model remains a black box, the physician will only have limited confidence in it (42).

The importance of methods like Stabl should also be seen here. Because what is needed in the clinic is not an impressive but fragile model with hundreds of features with a reliable, explainable, and verifiable panel consisting of a few candidate markers. The future of biomarker discovery likely lies not in fancier models, but in more robustly selected shortlists (43).

The use of artificial intelligence in biomarker discovery and multi-omics analysis has ceased to be a methodological luxury in biomedical research. It has increasingly become a necessary analytical backbone. The reason is clear. Disease biology is multi-layered, clinical needs are increasingly sensitive, and data are larger and more complex than humans can comprehend alone. Artificial intelligence offers powerful tools to unravel this complexity. But its real value lies not in high accuracy rates, but in its ability to produce reliable and portable biomarkers. Today, we have integration-oriented methods like DIABLO, graph-based classifiers like MOGONET, reliable feature pickers like Stabl, and stability-prioritising tools like StabilityCCA. Yet, the final word has not yet been spoken. The real test for this field is not to produce more models, but to achieve better validation, better standardisation, and stronger clinical implementation. When it achieves this, multi-omics AI will not only be a technology that analyses data, but a way of thinking that reframes biology and treatment (41, 53).

6.2. The Use of Artificial Intelligence and Multi-omics Analysis in Cancer

Cancer biology is too complex to be understood solely from a single molecular perspective. Alterations in the genome, in RNA equivalents, protein levels, epigenetic regulation and metabolic pathways interact with one another yet they do not convey identical information. As a result, in recent years a multi-omic strategy that involves the integrative assessment of genomic, transcriptomic, proteomic, epigenomic, and metabolomic data, has emerged as a leading field of study in oncology. However, this strategy bears significant impediments, including data abundance, variability, absent measurements and difficulties in interpretation. This is where artificial intelligence and machine learning became relevant by data classification and clarification of connections between the omics layers, accelerating the biomarker discovery, identification of tumour subtypes and anticipation of treatment responses (41, 55). Early fusion, intermediate fusion, and late fusion strategies, combined with autoencoders, variational autoencoders, graph neural networks, genera-

tive models, and multimodal deep learning structures, make it possible to read cancer as a more relational system. Specifically, completing missing data, establishing patient similarity networks, learning latent biological representations, and developing explainable risk signatures are characteristic features of this new era (34, 56).

Single-omics approaches often capture only a portion of the biological story. For example, detecting a driver mutation does not tell you the extent to which it's reflected in RNA, protein, or phenotype. Multi-omics integration, however, evaluates traces of the same disruption across different layers. Artificial intelligence provides the computational framework that makes this integration possible. Tasks such as dimensionality reduction, feature selection, supervised and unsupervised classification, patient clustering, survival modelling, and drug susceptibility prediction have now become standard components of this field (34, 57).

At this point, high accuracy is not the only important factor. From a clinical oncology perspective, the real value lies in whether the model has biological meaning, whether it can be replicated in different cohorts, and whether it can be used for decision support. In other words, a very good-looking AUC value has limited value if there is no external validation or if the patterns on which the model is based cannot be explained biologically. Current literature emphasises that generalizability and explainability are as essential as performance for clinical translation (53, 58).

6.2.1. Application Examples in Cancer

- **Colorectal cancer:** Colorectal cancer (CRC) is one of the strongest areas demonstrating why multi-omics integration is necessary. The combined analysis of genomic, transcriptomic, proteomic, and metabolomic layers in CRC accelerates the discovery of new diagnostic, prognostic, and therapeutic biomarkers. In this context, artificial intelligence and machine learning are used not only to generate candidate molecule lists but also to translate the correlations between different omics layers into clinical benefit.

  One of the early milestones in this field is the colon and rectal cancer proteogenomics study showing the combination of genomic data with proteomic data in TCGA-characterised CRC samples, underlies that the changes observed at the DNA level are not always reflected in the protein level in the same way. In other words, it revealed that the distance between genomic change and functional outcome is more complex than previously thought (59). Moreover, studies demonstrated that the proteogenomic approach in colon cancer can not only explain the biology but also reveal new therapeutic opportunities (60). A subsequent study which analysed the metastatic progression process in primary CRC through proteome-based subtypes and signatures, suggested that metastasis biology should be read not only through genomic changes but also through protein-level network rearrangement (61). Thus, CRC has become a model domain in multi-omics AI applications, extending from "diagnosis to treatment sensitivity".

- **Breast Cancer:** Breast cancer is one of the rare tumour types where imaging, digital pathology, and multi-omic data can be combined in the same clinical workflow. Therefore, AI-powered multimodal analyses produce more visible clinical outcomes here. The combined use of mammography, ultrasound, MRI, digital pathology, and multi-omic data provides a powerful framework for subtype diagnosis, immune microenvironment assessment, immunotherapy response, and drug resistance prediction (62).

  This approach has a more concrete application in triple-negative breast cancer. A high accuracy in TNBC subtyping was reported by combining mRNA, miRNA, DNA methylation, gene mutation, and MRI data with deep learning. The value of the study lies not only in its high success rate in cross-validation but also in its ability to deliver strong performance in the out-test set; this suggests that multi-omic integration can produce more robust representations than single-omics models (63).

  In addition, a study created a multimodal cellular and spatial map by combining four different spatial expression methods with single-cell or single-nucleus RNA sequencing on 67 biopsies from 60 metastatic breast cancer patients. This study strongly demonstrated that metastatic breast cancer should be understood not only by its cellular composition but also by its spatial organisation and microenvironmental order in different anatomical regions (64). Such studies suggest that in the future, multi-omic AI models may be able to answer not only the question of "which subtype?" but also "which niche, which cellular neighbourhood, which metastatic behaviour?"
- **Lung cancer:** The multi-omic literature on lung cancer is extremely instructive in terms of the clinical value of AI-assisted proteogenomic integration. Genomic, epigenomic, deep proteomic, phosphoproteomic, and acetylproteomic data were examined together in 110 lung adenocarcinomas and 101 matched adjacent tissue samples. The study identified four subgroups using multi-omics clustering which were associated with variables such as driver mutations, country, and gender, and presented potential therapeutic gaps (65). This is a strong example showing that multi-omics integration can be used not only for biological classification but also for therapeutic target discovery. Similarly, in small cell lung cancer (SCLC) four subtypes were identified by performing proteogenomic characterisation in 112 untreated cases and suggested different therapeutic sensitivities for each of these subtypes. Prognostic markers such as HMGB3 and CASP10 were also identified. The association between ZFHX3 mutation and high immune infiltration was also highlighted. Thus, multi-omics analysis brought together both prognostic and therapeutic layers within the same model in SCLC, an aggressive and biologically complex tumour type (66).
- **Hepatocellular Carcinoma:** Artificial intelligence and multi-omic analysis are also progressing together in hepatocellular carcinoma. Hepatocellular carcinoma (HCC) subtypes were modellled and survival, and immunotherapy response were analysed through a common signature developed using numerous machine learning combinations. The fact that the low-risk group showed better overall survival and better immu-

notherapy response reveals the potential of multi-omic risk signatures to become clinical decision support (67). Taking this line further, the HCC ecosystem was analysed with single-cell, spatial, and bulk transcriptomic data. This framework, established from six HCC cases and one control liver tissue sample, showed that intratumour heterogeneity primarily stems from HCC cell diversity and that this diversity extends to the genome-transcriptome-proteome-metabolome network. The study also reported that HCC cells direct tumour-associated macrophages to pro-tumour phenotypes (68). Such multilayer designs may pave the way for AI-assisted microenvironment-focused treatment strategies in HCC in the future.

- **Ovarian cancer:** Ovarian cancer is one of the tumours that particularly needs multi-omic modelling due to the difficulty of early diagnosis and high mortality. An accuracy of more than 90% in transcriptional subtype classification by integrating mono-, di-, and tri-omic data with variational autoencoder (VAE) and Maximum Mean Discrepancy VAE (MMD-VAE) based deep learning architectures in ovarian cancer was reported previously. The latent representations were also highlighted for survival analysis. This study is important because it shows that deep learning can not only generate predictions but also move high-dimensional data into a more meaningful biological representation space (69).
- **Pancreatic Cancer:** Pancreatic cancer is an area where classical bulk analyses are insufficient due to its dense stroma and immunosuppressive microenvironment. A study focused on analysing the tumour microenvironment in pancreatic cancer using single-cell multi-omics analysis and showed that this approach revealed cellular diversity, immunosuppression, and tumour-stroma interactions more objectively (70). Such studies show that multi-omics artificial intelligence is beginning to look not only at the tumour cell but also at the tumour ecosystem. Another study revealed the spatial variation of more than 5000 proteins in the pancreatic tumour microenvironment by performing single-cell resolution spatial proteomic analysis guided by multicolour imaging in centimetre-scale tissue sections. Such high-content studies are increasing the contribution of AI-assisted spatial analyses to the discovery of new biomarkers and targets in challenging tumours such as pancreatic cancer (71).
- **Immunotherapy:** Immunotherapy is perhaps the most critical application area of multi-omics AI. Classical markers such as PD-L1, TMB, MSI, and MMR are useful but they are often insufficient on their own. This is because the immunotherapy response is shaped not only by the tumour mutation burden but also by the tumour microenvironment, immune cell composition, epigenetic structure, and transcriptional programs. Li et al. (2024) show that machine learning creates more powerful models in predicting immunotherapy response by combining genomic, transcriptomic, and other omics layers (52). Similarly, systematic reviews also show that the number of AI-based biomarker studies in immuno-oncology is rapidly increasing. However, this shows that most of these are still retrospective. Therefore, the direction of the field is now shifting from individual biomarkers to "meta-biomarkers" that combine different data types (58).

6.2.2. Methodological Innovation: Overcoming Data Deficiency with Enhanced Multi-omics

One of the significant bottlenecks in the field is the deficiency and infrequent measurement in multi-omics datasets. A notable example addressing this problem is the unsupervised deep learning model called Multi-omic Synthetic Augmentation (MOSA). This model, developed on the Cancer Dependency Map, was able to synthetically enhance multi-omics profiles, increasing the number of multi-omics profiles by 32.7%, creating a more complete resource for 1523 cancer cell lines, and contributing to the identification of less studied mechanisms associated with drug resistance. Additionally, the multi-omics features are critical for cell clustering and biomarker discovery through SHapley Additive exPlanations-based interpretation was also demonstrated (72). Such methods address data deficiency not only as a technical problem but also as an opportunity for biological discovery.

When these examples are read together, three significant patterns become apparent. First, multi-omics AI is moving beyond mere subtype classification but it is starting to model more complex endpoints including treatment gaps, drug resistance, the structure of microenvironment, and metastatic behaviour. Second, the field is transitioning from the integration of bulk data to the single-cell and spatial multi-omics. Lastly, AI models are evolving through increasing demands for explainability, comprehensive data, and applicability in clinical settings (34, 41).

Nevertheless, there are fundamental constraints. Limited sample sizes, batch effects across different platforms, incomplete data, overfitting, lack of sufficient external validation, and difficulties in biological interpretation are slowing the transition of the field into clinical practice. The true impact of AI in clinical oncology will be measured solely by remarkable accuracy levels, but rather by prospective validation, reproducibility across multiple centres, and its capacity to assist in decision-making processes (53, 58).

The use of AI in cancer and multi-omics analysis is undergoing a transformation from the research level to clinical decision support. Examples ranging from colorectal cancer to lung cancer, breast cancer to pancreatic and ovarian cancer, demonstrate that processing different omics layers together can produce far richer clinical meaning than genomic reading alone. Next-generation studies take into account not only the tumour cell but also the microenvironment, spatial relationships, and dynamic networks that emerge under therapeutic pressure. The real breakthrough in the coming period will lie not in developing more complex algorithms, but in better data standardisation, stronger external validation, and the ability to build more explainable models. Then, multi-omics AI could truly become one of the backbones of precision oncology.

6.3. The Use of Artificial Intelligence and Multi-omics Analysis in Personalised-Medicine and Precision Medicine

Personalised medicine has long been described as “a unique approach for each patient”, precision medicine, however, has taken this idea to a more operational, more measurable

level. The basic goal is the same to bring the right patient together with the right treatment at the right time. But what makes this possible is no longer just clinical observation, it is the ability to read genomic, transcriptomic, proteomic, metabolomic, epigenomic, imaging, electronic health record, and even behavioural data together. In the last decade, this data explosion has transformed precision medicine from a promise into a real clinical program. At the same time, it has created a new problem of how to transform such diverse, high-dimensional, and noisy data into meaningful, reliable, and actionable decisions. Artificial intelligence has emerged as one of the strongest answers to this question (73-75).

The appeal of precision medicine today is that it does not reduce the patient to a diagnostic label. Two patients with the same histopathological diagnosis may have completely different molecular subtypes, the response or toxicity profile of two patients taking the same drug can vary dramatically. Therefore, the modern approach attempts to build a multi-layered chain from symptom to molecule, and from molecule to clinical decision. Multi-omics analyses, in particular, form the backbone of this chain. Because the mere existence of a mutation is not enough. It is also necessary to know how that change is reflected in RNA, protein, metabolism, and phenotype. At this point, Artificial intelligence, becomes an analytical framework that extracts order, relationships, and predictions from data structures that are too complex for the human mind to process alone (41, 75).

AI is simultaneously changing three things in precision medicine. First, the way data is integrated. Genomic and clinical data are no longer two columns side-by-side; they are treated as complementary modalities processed in a common latent space. Second, disease classification. Classical classifications are increasingly being replaced by more refined molecular subtypes. Third, decision support. Models don't just say "risk is high"; they also seek answers to questions such as "which patient might benefit from which drug, who might experience toxicity, and who should be tested?" (73, 75).

In this transformation, specific techniques have become prominent. DIABLO represents a supervised integration approach that seeks to identify biomarkers and molecular signatures by choosing specific sets of features that carry common information in multiple omics data and enhance phenotypic differentiation. Research indicates it can propose both established and novel biomarkers at the mRNA, miRNA, CpG, protein, and metabolite levels (45). Conversely, MOGONET uses both omics features and networks of inter-sample similarity by bringing graph convolutional networks into multi-omics classification. It has shown the potential for effective classification and biomarker identification in Alzheimer's disease, low-grade glioma, kidney cancer, and breast cancer subtypes (46). These two examples illustrate effectively how the direction of the field is progressing from mere accuracy toward the production of integrated signatures with biological meaning.

6.3.1. Oncology

Precision medicine's most visible success in the clinic is still in oncology. One of the historical symbols of this is the introduction of trastuzumab in HER2-positive breast cancer. This example showed that within the broad heading of cancer, a subgroup of treatment-sensitive molecules can be identified. Subsequently, a broad field opened up,

ranging from monoclonal antibodies to small molecule inhibitors and targeted immunotherapies (75).

But the most interesting part is that these successes are now based more on composite and multilayer panels than on individual biomarkers. Multi-omic strategies are being used for diagnosis, prognosis, treatment selection, and drug response prediction in lung, breast, colorectal, melanoma, and ovarian cancers and that multi-gene and cross-omic panels offer stronger clinical value than single-gene markers. Combining patient-derived organoids with multi-omic data and artificial intelligence has initiated a new phase, particularly in predicting drug susceptibility and resistance (41).

6.3.2. Non-Oncology Examples: Precision Medicine Is Not Just Cancer

Although precision medicine is often equated with oncology, its methodological expansion is also noteworthy in other fields. The same approach is now visible in cardiovascular medicine, perinatology, and pharmacogenomics, where disease biology is layered, patient trajectories are variable, and single markers often explain only a small part of the clinical picture. In these areas, AI is mainly useful for integration, risk stratification, and pattern recognition across heterogeneous data types rather than for some dramatic replacement of clinical judgment.

- **Cardiovascular medicine:** Cardiovascular disease is a good example of why reductionist models often become insufficient. Atherosclerosis, heart failure, arrhythmia, and thrombo-inflammatory syndromes do not arise from one pathway only. They involve inherited susceptibility, lipid handling, vascular remodelling, inflammation, endothelial dysfunction, metabolism, and environmental exposures acting together over time. Patient-based profiles were created by combining transcriptomic data with SNP information and clinical-demographic characteristics; they generated a signature consisting of 27 transcriptomic features and SNPs using a minimum redundancy–maximum relevance approach. The fact that the best-performing model was the Bayesian hyperparameter-adjusted XGBoost shows that precision medicine can make risk stratification more individualised in this area as well. Furthermore, making the basis on which the model makes decisions visible through SHAP analyses is a significant gain in terms of clinical confidence (76).

  A more recent review focused on atherosclerotic cardiovascular disease and argued that genomics, epigenomics, transcriptomics, proteomics, and metabolomics are all contributing pieces, with machine learning and AI increasingly used to connect them for molecular phenotyping and future precision diagnostics. This matters in practice because cardiovascular risk prediction has already reached a point where conventional clinical variables, while still essential, do not always capture residual biological heterogeneity. Machine learning is being explored not only to improve prediction accuracy, but also to identify subgroups, novel biomarker combinations, and outcome-specific risk profiles (77, 78).

  The disease subtyping is increasingly based on AI-assisted multi-omics and Electronic Health Record (EHR) integration not only in cancer but also in areas such as

cardiometabolic diseases, neurodegenerative diseases, and infections. For example, a heavily interferon-associated subgroup has been identified from peripheral blood gene expression patterns in systemic lupus erythematosus. This subtype subsequently provided the biological rationale for therapies targeting the IFN signalling pathway, such as anifrolumab. This example is a striking illustration of the direct precision medicine chain extending from biomarker to treatment (75). The same trend is seen in conditions such as type 2 diabetes and coronary artery disease. Frameworks combining biomarker and genomic information with longitudinal EHR data have begun to define patient subgroups that go beyond classical clinical categories. Such subtyping can be important not only for prognostic differentiation but also for planning more personalised decisions such as lifestyle interventions, drug selection, and monitoring intensity (75).

A similar trend exists in the field of Alzheimer's disease. A recent review summarises how integrating genomic, transcriptomic, proteomic, metabolomic, and microbiomic data with artificial intelligence offers new possibilities for early diagnosis, patient classification, mechanism analysis, and drug targeting; and how many methods, from classical machine learning to variational autoencoders, graphical neural networks, and transformer models, are being brought into this field. This literature reminds us that precision medicine means not only "targeted therapy in cancer" but also multi-layered patient modelling in complex diseases (54).

- **Perinatology:** Perinatology is a quieter but very important frontier. The clinical need is obvious including preeclampsia, preterm birth, neonatal sepsis, necrotising enterocolitis, bronchopulmonary dysplasia, and fetal growth disorders are biologically complex, time-sensitive, and often poorly predicted by standard clinical variables alone. Multi-omics combined with AI may support earlier risk identification in neonatal intensive care and maternal-fetal medicine by integrating genomics, proteomics, metabolomics, microbiome data, and clinical information (79). Marić and colleagues developed machine-learning models using six omics datasets from a longitudinal pregnancy cohort and reported that early-pregnancy urine metabolite models performed well, while an integrated multi-omics model performed better than single-omics approaches in their data. The data suggest that the biological signal of preeclampsia begins earlier and is more distributed across layers than routine monitoring can capture, but it is not yet a standard screening tool (80).

  Preterm birth research points in a similar direction. The DREAM Preterm Birth Prediction Challenge Consortium reported that maternal blood multi-omics could be used to predict gestational age and, in some settings, spontaneous preterm birth, with plasma proteomic random-forest models performing better than whole-blood transcriptomic models for some preterm birth tasks (81). A later study showed that multi-omic maternal signals could be associated with epidemiologic factors contributing to preterm birth in low- and middle-income settings, again using machine learning. These studies do not solve preterm birth prediction yet but they show that pregnancy should be read as a dynamic biological system, not as a sequence of disconnected

clinic visits (82). There is also a broader pediatric angle. A recent review described genomics-first care increasingly being layered with transcriptomics, proteomics, metabolomics, and other data types in pediatric precision medicine. That matters because perinatal and pediatric medicine often deal with rare diseases, developmental timing, and rapidly changing physiology. In such settings, multi-omics is not only about finer classification but it is about finding the disease at all, or understanding why one infant decompensates while another, with a similar bedside profile, does not (83).

Perinatology also shows the limits of the field very clearly. Cohorts can be small. Sampling schedules vary. Gestational timing matters a lot. Validation cohorts are not always large or ethnically broad, and the cost and logistics of repeated omics sampling are non-trivial. So, the field is promising, but fragile in places. Some models are impressive, but the road to robust clinical implementation is longer than the performance metrics alone may suggest.

- **Biobank-scale precision medicine:** The new phase of precision medicine is biobank-level studies that go beyond single-centre cohorts. One of the most notable examples of this is the MILTON framework developed on the UK Biobank. Garg et al. developed a machine learning approach that uses biomarkers, quantitative features, and proteomic data to predict 3,213 disease phenotypes. The study demonstrated that this framework can be used to enhance both disease prediction and genetic association analyses on 484,230 sequenced genome samples and 46,327 matched plasma proteomic samples. The fact that the models surpassed existing polygenic risk scores in many cases, amplifying 88 known gene-disease signals while revealing 182 additional associations, suggests that precision medicine is being redefined not only at the patient's bedside but also at the population scale (84).

  The significance of this example is not solely due to its numerical size. When biobank-based models can predict as-yet-undiagnosed "cryptic" cases, they offer a new toolset for preventive medicine, genetic discovery, and health system planning. Thus, precision medicine here means not just personalised treatment, but personalised risk prediction and more accurate cohort identification. This is the broader aspect of the concept, expanding from the clinical to public health.
- **Pharmacogenomics:** One of the most concrete areas where precision medicine is applied to daily clinical practice is pharmacogenomics. The drug response is often not a single-gene, Mendelian event but polygenic factors, comorbidities, polypharmacy, lifestyle, metabolite profile, and environmental interactions work together. Therefore, pharmacogenomics is no longer limited to single-gene tests; it is shifting towards large-scale genomic and non-genomic data integration. Artificial intelligence is also stepping in to solve this complexity (85). Multi-omics integration can move pharmacogenomics beyond single-gene interpretation toward a more complete model of drug response, while also outlining the practical barriers, including data harmonisation, explainability, regulation, and the uneven representation of populations in current datasets. That last issue is especially important. A pharmacogenomic model is not very precise if it is precise only for the populations that were easiest to study (86). A more concrete picture of

the transition was provided by the study on 100 whole-exome datasets, including 50 cardiovascular patients and 50 healthy individuals, on 1,800 pharmacogenes and identified 4,539 rare variants, including 115 damaging non-synonymous variants. Although comprehensive clinical pharmacogenomics profiling from exome data is feasible, the interpretation inconsistencies across available tools still complicate implementation (87). Pharmacovariome scanning, used whole pharmacogene resequencing together with deep computational analysis and machine learning for functional analysis of variants in less-studied drug-related genes. This addressed a real bottleneck that is common panel-based pharmacogenomics is useful, but it leaves a long tail of rare or uncertain variants unresolved. Multi-omics and AI are being used here as tools for interpretation, prioritisation, and functional inference (88).

This section of precision medicine also depends heavily on integration with clinical systems. Drug response is not encoded only in biology, but it is also shaped by indication, organ function, interacting medications, adherence, and time. For that reason, the future of AI-enabled pharmacogenomics will require a tighter connection between omics and electronic health records, decision support systems, and clinician-facing reporting frameworks. The primary tool for this transition in the clinic is clinical decision support systems. A systematic review by Farmaki et al. identified 19 pharmacogenomic clinical decision support systems used in clinical practice; most were active type, embedded in electronic health records, using preemptive genotyping, and based on guidelines such as Clinical Pharmacogenetics Implementation Consortium (CPIC) and U.S. Food and Drug Administration (FDA). The same study reports that pharmacogenomic clinical decision support systems development is still geographically uneven, with most initiatives remaining US-centric, and that broader, standardised applications are needed globally (89). This example clearly demonstrates that precision medicine means not only generating algorithms but also securely embedding them into clinical workflows.

Recently, the discussion on generative AI has strongly entered the precision medicine literature. In 27 studies examining the use of generative AI in personalised medicine, the most frequently used models were generative adversarial networks (GANs), followed by variational autoencoders (VAEs). These models were most often used in drug response prediction, treatment effect estimation, biomarker discovery, and patient stratification. One of their biggest promises is their ability to generate synthetic but realistic patient data, which can partially overcome data scarcity and privacy issues. This could provide a significant advantage, especially for rare diseases, small cohorts, and unbalanced datasets (90). However, caution is needed here. Generating synthetic data does not mean generating clinical reality. The success of generative AI depends on the quality of the training data, how much bias is transferred, and the explainability of the model. Producing representations that appear "convincing" in clinical practice but are biologically problematic can have serious consequences, especially in high-risk areas such as treatment selection. Therefore, generative AI is a promising tool for precision medicine but it is not yet an unsupervised automation engine (90).

The precision medicine literature is full of impressive accuracy rates. But the biggest barrier to transition to clinical practice is not a lack of performance; it is a lack of trust, standardisation, and generalizability. The major necessities, including usability, transparency, workflow compatibility, trust, and an ethical-legal framework, are crucial for the success of AI-powered clinical decision support systems. The physician wants to know not just what the algorithm says, but why it says what it says and how it aligns with clinical guidelines. Therefore, explainability is no longer a luxury, but a condition for adoption (91).

Formal semantic deficiencies, limited systematic evaluation, lack of standardised information models, narrow scope validation, and significant manual workload are major limitations (89). The ethical dimensions, such as privacy, patient-physician relationship, provider training, acceptability, and oversight, also bear the fundamental risks in the area (85). In short, the fundamental question facing precision medicine is no longer "can we calculate this?" but "can we use it fairly, understandably, reliably, and sustainably?"

Personalised medicine and precision medicine are shifting healthcare from a symptom-centric model to a data-centric but patient-focused model. Multi-omics analyses provide the biological language of this transformation; artificial intelligence builds the analytical engine that translates this language into clinical decision-making. HER2-positive breast cancer in oncology, host-microbiome-metabolome relationships in colorectal cancer, meta-biomarkers in immunotherapy, biobank-level disease prediction, cardiovascular risk stratification, multilayered modelling of neurodegenerative diseases, and pharmacogenomic clinical decision support systems demonstrate different facets of this transformation. The common thread is clear: the patient is now being analysed not just by their diagnosis, but also by their molecular pattern, clinical profile, environmental burden, and potential treatment response.

Nevertheless, caution is necessary. The true value of precision medicine will lie not in producing sophisticated models, but in its ability to make repeatable, explainable, and useful decisions in the clinic. In the coming years, the real difference will not be made by more sophisticated algorithms, but by cleaner data, better multi-centre validation, stronger standardisation, and more humane clinical integration. Artificial intelligence is poised to be the driving force in this process. But ultimately, biology, clinical reasoning, and patient benefit will have the final say (Figure 2).

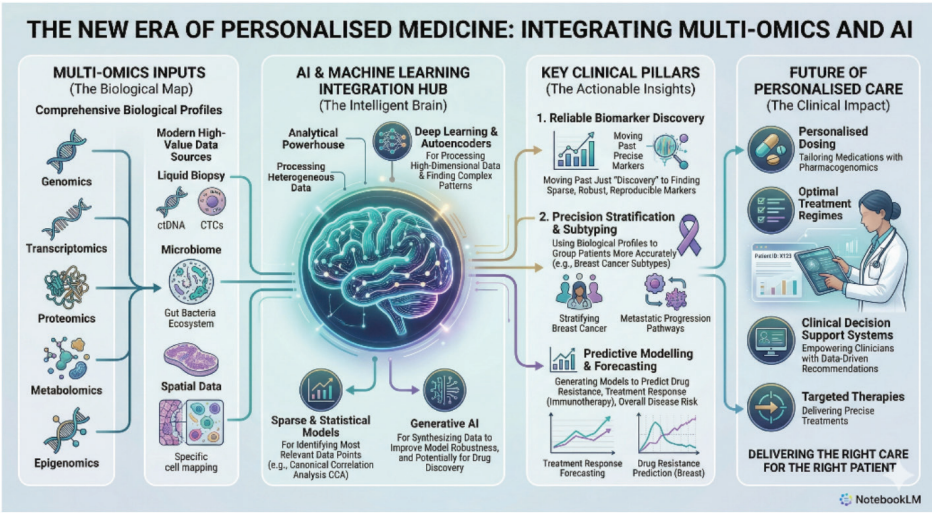


Figure 2. Integrated Model for AI-Enhanced Multi-omics in Personalised Medicine. This diagram illustrates the process of converting high-dimensional biological information into practical clinical outcomes. Detailed molecular profiles, including genomics, transcriptomics, proteomics, metabolomics and epigenomics, along with contemporary data sources such as liquid biopsies and spatial information, are integrated into a centralised AI system. Utilising cutting-edge computational techniques such as deep learning, graph neural networks, and sparse statistical modelling, the framework uncovers strong biomarker candidates and facilitates patient stratification, and aiding in the prediction of treatment responses. These insights are eventually implemented in clinical settings through pharmacogenomics-informed dosing and decision-support systems, guaranteeing the delivery of targeted, optimised treatment plans customised for each individual patient. The figure is prepared using Notebook LM and modified using Nano Banana Pro.

7. Conclusion

Biomedical investigation has completely embraced the multi-omic era, moving beyond simplistic methods and addressing the intricacies of life at various levels. This massive dataset, ranging from the genome to the metabolome, constitutes the language of biology, while artificial intelligence (AI), along with machine learning, acts as the fundamental analytical mechanism, transforming the biological language into meaningful clinical narratives.

Recently, we have arrived at a stage where we can evaluate the patient not merely through symptoms or a single genetic mutation but comprehensively, taking into account their molecular profile, environmental effects, and dynamic cellular networks. Particularly, in fields like multiple cancers, neurodegenerative and cardiovascular diseases, the integration of AI-driven analyses is converting personalised medicine from a promise into a tangible clinical practice.

The true achievement of precision medicine will depend not solely on developing more complex algorithms, but also on guaranteeing that these models are standardised, reproducible and explainable. The pathway to future advancements will focus on not the

volume of data, but more on achieving data uniformity and conducting multi-centre validations.

In the end, the integration of multi-omics and artificial intelligence is not just a set of technologies but represents a crucial mindset that is reframing biology and therapeutic processes. This collaborative approach of biological information and algorithmic power will continue to evolve healthcare from a reactive response to illness into a proactive patient-focused practice of treatment.

8. References

1. Hasin, Y., Seldin, M., Lusis, A. (2017). Multi-omics approaches to disease. *Genome Biol*, 18(1):83. https://doi.org/.10.1186/s13059-017-1215-1
2. Karczewski, K. J., Snyder, M. P. (2018). Integrative omics for health and disease. *Nat Rev Genet*, 19(5):299-310. https://doi.org/.10.1038/nrg.2018.4
3. Acharya, D., Mukhopadhyay, A. (2024). A comprehensive review of machine learning techniques for multi-omics data integration: challenges and applications in precision oncology. *Brief Funct Genomics*, 23(5):549-560. https://doi.org/.10.1093/bfgp/elae013
4. Biswas, N., Chakrabarti, S. (2020). Artificial Intelligence (AI)-Based Systems Biology Approaches in Multi-Omics Data Analysis of Cancer. *Front Oncol*, 10:588221. https://doi.org/.10.3389/fonc.2020.588221
5. Subramanian, I., Verma, S., Kumar, S., Jere, A., Anamika, K. (2020). Multi-omics Data Integration, Interpretation, and Its Application. *Bioinform Biol Insights*, 14:1177932219899051. https://doi.org/.10.1177/1177932219899051
6. Leek, J. T., Scharpf, R. B., Bravo, H. C., Simcha, D., Langmead, B., Johnson, W. E., . . . Irizarry, R. A. (2010). Tackling the widespread and critical impact of batch effects in high-throughput data. *Nat Rev Genet*, 11(10):733-739. https://doi.org/.10.1038/nrg2825
7. Stephens, Z. D., Lee, S. Y., Faghri, F., Campbell, R. H., Zhai, C., Efron, M. J., . . . Robinson, G. E. (2015). Big Data: Astronomical or Genomical? *PLoS Biol*, 13(7):e1002195. https://doi.org/.10.1371/journal.pbio.1002195
8. Libbrecht, M. W., Noble, W. S. (2015). Machine learning applications in genetics and genomics. *Nat Rev Genet*, 16(6):321-332. https://doi.org/.10.1038/nrg3920
9. Camacho, D. M., Collins, K. M., Powers, R. K., Costello, J. C., Collins, J. J. (2018). Next-Generation Machine Learning for Biological Networks. *Cell*, 173(7):1581-1592. https://doi.org/.10.1016/j.cell.2018.05.015
10. Zitnik, M., Nguyen, F., Wang, B., Leskovec, J., Goldenberg, A., Hoffman, M. M. (2019). Machine Learning for Integrating Data in Biology and Medicine: Principles, Practice, and Opportunities. *Inf Fusion*, 50:71-91. https://doi.org/.10.1016/j.inffus.2018.09.012
11. Topol, E. J. (2019). High-performance medicine: the convergence of human and artificial intelligence. *Nat Med*, 25(1):44-56. https://doi.org/.10.1038/s41591-018-0300-7
12. Hein, Z. M., Guruparan, D., Okunsai, B., Che Mohd Nassir, C. M. N., Ramli, M. D. C., Kumar, S. (2025). AI and Machine Learning in Biology: From Genes to Proteins. *Biology (Basel)*, 14(10). https://doi.org/.10.3390/biology14101453
13. Rappoport, N., Shamir, R. (2018). Multi-omic and multi-view clustering algorithms: review and cancer benchmark. *Nucleic Acids Res*, 46(20):10546-10562. https://doi.org/.10.1093/nar/gky889
14. Li, L., Sun, M., Wang, J., Wan, S. (2024). Multi-omics based artificial intelligence for cancer research. *Adv Cancer Res*, 163:303-356. https://doi.org/.10.1016/bs.acr.2024.06.005
15. Lin, M., Guo, J., Gu, Z., Tang, W., Tao, H., You, S., . . . Jia, P. (2025). Machine learning and multi-omics integration: advancing cardiovascular translational research and clinical practice. *J Transl Med*, 23(1):388. https://doi.org/.10.1186/s12967-025-06425-2
16. Dhankhar, S., Mujwar, S., Garg, N., Chauhan, S., Saini, M., Sharma, P., . . . Rani, N. (2024). Artificial Intelligence in The Management of Neurodegenerative Disorders. *CNS Neurol Disord Drug Targets*, 23(8):931-940. https://doi.org/.10.2174/0118715273266095231009092603
17. Vitorino, R. (2024). Transforming Clinical Research: The Power of High-Throughput Omics Integration. *Proteomes*, 12(3). https://doi.org/.10.3390/proteomes12030025
18. Ren, Y., Bai, H., Wang, J., Yang, Y., Wang, Y. (2026). Deep Learning-Enabled Multi-Omics Integration: A New Frontier in Precise Drug Target Discovery. *Biology (Basel)*, 15(5). https://doi.org/.10.3390/biology15050410
19. Yiu, T., Chen, B., Wang, H., Feng, G., Fu, Q., Hu, H. (2025). Transformative advances in single-cell omics: a comprehensive review of foundation models, multimodal integration and computational ecosystems. *J Transl Med*, 23(1):1176. https://doi.org/.10.1186/s12967-025-07091-0
20. Logsdon, G. A., Vollger, M. R., Eichler, E. E. (2020). Long-read human genome sequencing and its applications. *Nat Rev Genet*, 21(10):597-614. https://doi.org/.10.1038/s41576-020-0236-x

21. Warburton, P. E., Sebra, R. P. (2023). Long-Read DNA Sequencing: Recent Advances and Remaining Challenges. *Annu Rev Genomics Hum Genet*, 24:109-132. https://doi.org/.10.1146/annurev-genom-101722-103045
22. Morabito, A., De Simone, G., Pastorelli, R., Brunelli, L., Ferrario, M. (2025). Algorithms and tools for data-driven omics integration to achieve multilayer biological insights: a narrative review. *J Transl Med*, 23(1):425. https://doi.org/.10.1186/s12967-025-06446-x
23. Marouf, A. A., Rokne, J. G., Alhajj, R. (2025). Integrating Multi-Omics and Medical Imaging in Artificial Intelligence-Based Cancer Research: An Umbrella Review of Fusion Strategies and Applications. *Cancers (Basel)*, 17(22). https://doi.org/.10.3390/cancers17223638
24. Ramesh, D., Manickavel, P., Ghosh, S., Bhat, M. (2025). The Integration of Multi-omics With Artificial Intelligence in Hepatology: A Comprehensive Review of Personalized Medicine, Biomarker Identification, and Drug Discovery. *J Clin Exp Hepatol*, 15(6):102611. https://doi.org/.10.1016/j.jceh.2025.102611
25. Wu, X., Yang, X., Dai, Y., Zhao, Z., Zhu, J., Guo, H., Yang, R. (2024). Single-cell sequencing to multi-omics: technologies and applications. *Biomark Res*, 12(1):110. https://doi.org/.10.1186/s40364-024-00643-4
26. Statello, L., Guo, C. J., Chen, L. L., Huarte, M. (2021). Gene regulation by long non-coding RNAs and its biological functions. *Nat Rev Mol Cell Biol*, 22(2):96-118. https://doi.org/.10.1038/s41580-020-00315-9
27. Mann, M., Kumar, C., Zeng, W. F., Strauss, M. T. (2021). Artificial intelligence for proteomics and biomarker discovery. *Cell Syst*, 12(8):759-770. https://doi.org/.10.1016/j.cels.2021.06.006
28. Liu, R., Wang, Q., Zhang, X. (2024). Identification of prognostic coagulation-related signatures in clear cell renal cell carcinoma through integrated multi-omics analysis and machine learning. *Comput Biol Med*, 168:107779. https://doi.org/.10.1016/j.compbiomed.2023.107779
29. Guo, T., Steen, J. A., Mann, M. (2025). Mass-spectrometry-based proteomics: from single cells to clinical applications. *Nature*, 638(8052):901-911. https://doi.org/.10.1038/s41586-025-08584-0
30. Johnson, C. H., Ivanisevic, J., Siuzdak, G. (2016). Metabolomics: beyond biomarkers and towards mechanisms. *Nat Rev Mol Cell Biol*, 17(7):451-459. https://doi.org/.10.1038/nrm.2016.25
31. Integrative, H. M. P. R. N. C. (2019). The Integrative Human Microbiome Project. *Nature*, 569(7758):641-648. https://doi.org/.10.1038/s41586-019-1238-8
32. Rozera, T., Pasolli, E., Segata, N., Ianiro, G. (2025). Machine Learning and Artificial Intelligence in the Multi-Omics Approach to Gut Microbiota. *Gastroenterology*, 169(3):487-501. https://doi.org/.10.1053/j.gastro.2025.02.035
33. Benabbou, N., Abik, M., Baichoo, S. (2026). Integrative multi-omics and machine learning/deep learning approaches in cancer knowledge discovery: A scoping review. *Cancer Treat Res Commun*, 47:101136. https://doi.org/.10.1016/j.ctarc.2026.101136
34. Ballard, J. L., Wang, Z., Li, W., Shen, L., Long, Q. (2024). Deep learning-based approaches for multi-omics data integration and analysis. *BioData Min*, 17(1):38. https://doi.org/.10.1186/s13040-024-00391-z.
35. Occhipinti, A., Verma, S., Doan, L. M. T., Angione, C. (2024). Mechanism-aware and multimodal AI: beyond model-agnostic interpretation. *Trends Cell Biol*, 34(2):85-89. https://doi.org/.10.1016/j.tcb.2023.11.002
36. Gupta, R., Srivastava, D., Sahu, M., Tiwari, S., Ambasta, R. K., Kumar, P. (2021). Artificial intelligence to deep learning: machine intelligence approach for drug discovery. *Mol Divers*, 25(3):1315-1360. https://doi.org/.10.1007/s11030-021-10217-3
37. Kourou, K., Exarchos, T. P., Exarchos, K. P., Karamouzis, M. V., Fotiadis, D. I. (2015). Machine learning applications in cancer prognosis and prediction. *Comput Struct Biotechnol J*, 13:8-17. https://doi.org/.10.1016/j.csbj.2014.11.005
38. Hoadley, K. A., Yau, C., Hinoue, T., Wolf, D. M., Lazar, A. J., Drill, E., . . . Laird, P. W. (2018). Cell-of-Origin Patterns Dominate the Molecular Classification of 10,000 Tumors from 33 Types of Cancer. *Cell*, 173(2):291-304 e296. https://doi.org/.10.1016/j.cell.2018.03.022
39. Nunes, F. V. M., Behrens, L. M. P., Weimer, R. D., Goncalves, G. F., da Silva Fernandes, G., Dorn, M. (2025). Deep learning methods and applications in single-cell multimodal data integration. *Mol Omics*, 21(6):545-565. https://doi.org/.10.1039/d5mo00062a
40. McKenzie, M., Irac, S. E., Chen, Z., Moradi, A., Jenner, A., Nguyen, Q., Rashidieh, B. (2026). Integrative spatial omics and artificial intelligence: transforming cancer research with omics data and AI. *Semin Cancer Biol*, 119:65-82. https://doi.org/.10.1016/j.semcancer.2026.01.002
41. Jiang, Z., Zhang, H., Gao, Y., Sun, Y. (2025). Multi-omics strategies for biomarker discovery and application in personalized oncology. *Mol Biomed*, 6(1):115. https://doi.org/.10.1186/s43556-025-00340-0
42. Ng, S., Masarone, S., Watson, D., Barnes, M. R. (2023). The benefits and pitfalls of machine learning for biomarker discovery. *Cell and Tissue Research*, 394(1):17-31. https://doi.org/.10.1007/s00441-023-03816-z
43. Hédou, J., Marić, I., Bellan, G., Einhaus, J., Gaudillière, D. K., Ladant, F.-X., . . . Gaudillière, B. (2024). Discovery of sparse, reliable omic biomarkers with Stabl. *Nature Biotechnology*, 42(10):1581-1593. https://doi.org/.10.1038/s41587-023-02033-x
44. Ran, D., Li, J., Zhao, M., Du, L., Zhang, Y., Zhu, J. (2025). Artificial intelligence integrates multi-omics data for precision stratification and drug resistance prediction in breast cancer. *Front Oncol*, 15:1612474. https://doi.org/.10.3389/fonc.2025.1612474
45. Singh, A., Shannon, C. P., Gautier, B., Rohart, F., Vacher, M., Tebbutt, S. J., Lê Cao, K.-A. (2019). DIABLO: an integrative approach for identifying key molecular drivers from multi-omics assays. *Bioinformatics*, 35(17):3055-3062. https://doi.org/.10.1093/bioinformatics/bty1054

46. Wang, T., Shao, W., Huang, Z., Tang, H., Zhang, J., Ding, Z., Huang, K. (2021). MOGONET integrates multi-omics data using graph convolutional networks allowing patient classification and biomarker identification. *Nat Commun*, 12(1):3445. https://doi.org/.10.1038/s41467-021-23774-w
47. Pusa, T., Rousu, J. (2024). Stable biomarker discovery in multi-omics data via canonical correlation analysis. *PLoS One*, 19(9):e0309921. https://doi.org/.10.1371/journal.pone.0309921
48. Argelaguet, R., Arnol, D., Bredikhin, D., Deloro, Y., Velten, B., Marioni, J. C., Stegle, O. (2020). MOFA+: a statistical framework for comprehensive integration of multi-modal single-cell data. *Genome Biol*, 21(1):111. https://doi.org/.10.1186/s13059-020-02015-1
49. Li, X., Ma, J., Leng, L., Han, M., Li, M., He, F., Zhu, Y. (2022). MoGCN: A Multi-Omics Integration Method Based on Graph Convolutional Network for Cancer Subtype Analysis. *Front Genet*, 13:806842. https://doi.org/.10.3389/fgene.2022.806842
50. Zafari, N., Bathaei, P., Velayati, M., Khojasteh-Leylakoohi, F., Khazaei, M., Fiuji, H., . . . Avan, A. (2023). Integrated analysis of multi-omics data for the discovery of biomarkers and therapeutic targets for colorectal cancer. *Comput Biol Med*, 155:106639. https://doi.org/.10.1016/j.compbiomed.2023.106639
51. Jayakrishnan, T. T., Sangwan, N., Barot, S. V., Farha, N., Mariam, A., Xiang, S., . . . Kamath, S. D. (2024). Multi-omics machine learning to study host-microbiome interactions in early-onset colorectal cancer. *npj Precision Oncology*, 8(1):146. https://doi.org/.10.1038/s41698-024-00647-1
52. Li, Y., Wu, X., Fang, D., Luo, Y. (2024). Informing immunotherapy with multi-omics driven machine learning. *NPJ Digit Med*, 7(1):67. https://doi.org/.10.1038/s41746-024-01043-6
53. Eskandar, K. (2025). Artificial intelligence and multi-omics integration in liquid biopsy for genitourinary cancers: a systematic scoping review. *Int Urol Nephrol*. https://doi.org/.10.1007/s11255-025-04912-5
54. Ren, F., Wei, J., Chen, Q., Hu, M., Yu, L., Mi, J., . . . Wu, A. (2025). Artificial intelligence-driven multi-omics approaches in Alzheimer's disease: Progress, challenges, and future directions. *Acta Pharm Sin B*, 15(9):4327-4385. https://doi.org/.10.1016/j.apsb.2025.07.030
55. Nicora, G., Vitali, F., Dagliati, A., Geifman, N., Bellazzi, R. (2020). Integrated Multi-Omics Analyses in Oncology: A Review of Machine Learning Methods and Tools. *Front Oncol*, 10:1030. https://doi.org/.10.3389/fonc.2020.01030
56. Valous, N. A., Popp, F., Zörnig, I., Jäger, D., Charoentong, P. (2024). Graph machine learning for integrated multi-omics analysis. *Br J Cancer*, 131(2):205-211. https://doi.org/.10.1038/s41416-024-02706-7
57. Cai, Z., Poulos, R. C., Liu, J., Zhong, Q. (2022). Machine learning for multi-omics data integration in cancer. *iScience*, 25(2):103798. https://doi.org/.10.1016/j.isci.2022.103798
58. Prelaj, A., Miskovic, V., Zanitti, M., Trovo, F., Genova, C., Viscardi, G., . . . Pedrocchi, A. L. G. (2024). Artificial intelligence for predictive biomarker discovery in immuno-oncology: a systematic review. *Ann Oncol*, 35(1):29-65. https://doi.org/.10.1016/j.annonc.2023.10.125
59. Zhang, B., Wang, J., Wang, X., Zhu, J., Liu, Q., Shi, Z., . . . Liebler, D. C. (2014). Proteogenomic characterization of human colon and rectal cancer. *Nature*, 513(7518):382-387. https://doi.org/.10.1038/nature13438
60. Vasaikar, S., Huang, C., Wang, X., Petyuk, V. A., Savage, S. R., Wen, B., . . . Zhang, Z. (2019). Proteogenomic Analysis of Human Colon Cancer Reveals New Therapeutic Opportunities. *Cell*, 177(4):1035-1049.e1019. https://doi.org/.https://doi.org/10.1016/j.cell.2019.03.030
61. Tanaka, A., Ogawa, M., Zhou, Y., Namba, K., Hendrickson, R. C., Miele, M. M., . . . Roehrl, M. H. A. (2024). Proteogenomic characterization of primary colorectal cancer and metastatic progression identifies proteome-based subtypes and signatures. *Cell Reports*, 43(2). https://doi.org/.10.1016/j.celrep.2024.113810
62. Ran, D., Li, J., Zhao, M., Du, L., Zhang, Y., Zhu, J. (2025). Artificial intelligence integrates multi-omics data for precision stratification and drug resistance prediction in breast cancer. *Frontiers in Oncology*, Volume 15 - 2025. https://doi.org/.10.3389/fonc.2025.1612474
63. Yang, S., Wang, Z., Wang, C., Li, C., Wang, B. (2024). Comparative Evaluation of Machine Learning Models for Subtyping Triple-Negative Breast Cancer: A Deep Learning-Based Multi-Omics Data Integration Approach. *J Cancer*, 15(12):3943-3957. https://doi.org/.10.7150/jca.93215
64. Klughammer, J., Abravanel, D. L., Segerstolpe, Å., Blosser, T. R., Goltsev, Y., Cui, Y., . . . Wagle, N. (2024). A multi-modal single-cell and spatial expression map of metastatic breast cancer biopsies across clinicopathological features. *Nature Medicine*, 30(11):3236-3249. https://doi.org/.10.1038/s41591-024-03215-z
65. Gillette, M. A., Satpathy, S., Cao, S., Dhanasekaran, S. M., Vasaikar, S. V., Krug, K., . . . Shi, Z. (2020). Proteogenomic Characterization Reveals Therapeutic Vulnerabilities in Lung Adenocarcinoma. *Cell*, 182(1):200-225.e235. https://doi.org/.https://doi.org/10.1016/j.cell.2020.06.013
66. Liu, Q., Zhang, J., Guo, C., Wang, M., Wang, C., Yan, Y., . . . Zhang, P. (2024). Proteogenomic characterization of small cell lung cancer identifies biological insights and subtype-specific therapeutic strategies. *Cell*, 187(1):184-203.e128. https://doi.org/.10.1016/j.cell.2023.12.004
67. Li, M., Liu, Q., Gao, J., Liu, L., Tao, R., Wang, Z., . . . Zhang, S. (2025). Multi-omics and machine learning refine HCC molecular subtypes and prognosis based on liquid-liquid phase separation related genes. *Sci Rep*, 15(1):44884. https://doi.org/.10.1038/s41598-025-28551-z
68. Ye, J., Lin, Y., Liao, Z., Gao, X., Lu, C., Lu, L., . . . Liang, R. (2024). Single cell-spatial transcriptomics and bulk multi-omics analysis of heterogeneity and ecosystems in hepatocellular carcinoma. *npj Precision Oncology*, 8(1):262. https://doi.org/.10.1038/s41698-024-00752-1

69. Hira, M. T., Razzaque, M. A., Angione, C., Scrivens, J., Sawan, S., Sarker, M. (2021). Integrated multi-omics analysis of ovarian cancer using variational autoencoders. *Scientific Reports*, 11(1):6265. https://doi.org/.10.1038/s41598-021-85285-4
70. Fu, Y., Tao, J., Liu, T., Liu, Y., Qiu, J., Su, D., . . . Zhao, Y. (2024). Unbiasedly decoding the tumor microenvironment with single-cell multiomics analysis in pancreatic cancer. *Molecular Cancer*, 23(1):140. https://doi.org/.10.1186/s12943-024-02050-7
71. Xu, Y., Wang, X., Li, Y., Mao, Y., Su, Y., Mao, Y., . . . Tian, R. (2024). Multimodal single cell-resolved spatial proteomics reveal pancreatic tumor heterogeneity. *Nature Communications*, 15(1):10100. https://doi.org/.10.1038/s41467-024-54438-0
72. Cai, Z., Apolinário, S., Baião, A. R., Pacini, C., Sousa, M. D., Vinga, S., . . . Gonçalves, E. (2024). Synthetic augmentation of cancer cell line multi-omic datasets using unsupervised deep learning. *Nature Communications*, 15(1):10390. https://doi.org/.10.1038/s41467-024-54771-4
73. Johnson, K. B., Wei, W. Q., Weeraratne, D., Frisse, M. E., Misulis, K., Rhee, K., . . . Snowdon, J. L. (2021). Precision Medicine, AI, and the Future of Personalized Health Care. *Clin Transl Sci*, 14(1):86-93. https://doi.org/.10.1111/cts.12884
74. Abdelhalim, H., Berber, A., Lodi, M., Jain, R., Nair, A., Pappu, A., . . . Ahmed, Z. (2022). Artificial Intelligence, Healthcare, Clinical Genomics, and Pharmacogenomics Approaches in Precision Medicine. *Front Genet*, 13:929736. https://doi.org/.10.3389/fgene.2022.929736
75. Rodriguez-Martinez, A., Kothalawala, D., Carrillo-Larco, R. M., Poulakakis-Daktylidis, A. (2025). Artificial intelligence in precision medicine: transforming disease subtyping, medical imaging, and pharmacogenomics. *Emerg Top Life Sci*, 8(2):73-82. https://doi.org/.10.1042/etls20240011
76. DeGroat, W., Abdelhalim, H., Peker, E., Sheth, N., Narayanan, R., Zeeshan, S., . . . Ahmed, Z. (2024). Multimodal AI/ML for discovering novel biomarkers and predicting disease using multi-omics profiles of patients with cardiovascular diseases. *Scientific Reports*, 14(1):26503. https://doi.org/.10.1038/s41598-024-78553-6
77. Nordestgaard, L. T., Wolford, B. N., de Gonzalo-Calvo, D., Sopić, M., Devaux, Y., Matic, L., . . . Magni, P. (2025). Multiomics in atherosclerotic cardiovascular disease. *Atherosclerosis*, 408:120414. https://doi.org/.https://doi.org/10.1016/j.atherosclerosis.2025.120414
78. Kasartzian, D.-I., Tsiampalis, T. (2025). Transforming Cardiovascular Risk Prediction: A Review of Machine Learning and Artificial Intelligence Innovations. *Life*, 15(1):94
79. Pammi, M., Aghaeepour, N., Neu, J. (2023). Multiomics, artificial intelligence, and precision medicine in perinatology. *Pediatr Res*, 93(2):308-315. https://doi.org/.10.1038/s41390-022-02181-x
80. Marić, I., Contrepois, K., Moufarrej, M. N., Stelzer, I. A., Feyaerts, D., Han, X., . . . Aghaeepour, N. (2022). Early prediction and longitudinal modeling of preeclampsia from multiomics. *Patterns (N Y)*, 3(12):100655. https://doi.org/.10.1016/j.patter.2022.100655
81. Tarca, A. L., Pataki, B., Romero, R., Sirota, M., Guan, Y., Kutum, R., . . . Costello, J. C. (2021). Crowdsourcing assessment of maternal blood multi-omics for predicting gestational age and preterm birth. *Cell Rep Med*, 2(6):100323. https://doi.org/.10.1016/j.xcrm.2021.100323
82. Espinosa, C. A., Khan, W., Khanam, R., Das, S., Khalid, J., Pervin, J., . . . Aghaeepour, N. (2023). Multiomic signals associated with maternal epidemiological factors contributing to preterm birth in low- and middle-income countries. *Sci Adv*, 9(21):eade7692. https://doi.org/.10.1126/sciadv.ade7692
83. Mani, S., Lalani, S. R., Pammi, M. (2025). Genomics and multiomics in the age of precision medicine. *Pediatr Res*, 97(4):1399-1410. https://doi.org/.10.1038/s41390-025-04021-0
84. Garg, M., Karpinski, M., Matelska, D., Middleton, L., Burren, O. S., Hu, F., . . . Vitsios, D. (2024). Disease prediction with multi-omics and biomarkers empowers case–control genetic discoveries in the UK Biobank. *Nature Genetics*, 56(9):1821-1831. https://doi.org/.10.1038/s41588-024-01898-1
85. Haga, S. B. (2024). Artificial intelligence, medications, pharmacogenomics, and ethics. *Pharmacogenomics*, 25(14-15):611-622. https://doi.org/.10.1080/14622416.2024.2428587
86. Zack, M., Stupichev, D. N., Moore, A. J., Slobodchikov, I. D., Sokolov, D. G., Trifonov, I. F., Gobbs, A. (2025). Artificial Intelligence and Multi-Omics in Pharmacogenomics: A New Era of Precision Medicine. *Mayo Clin Proc Digit Health*, 3(3):100246. https://doi.org/.10.1016/j.mcpdig.2025.100246
87. Tafazoli, A., van der Lee, M., Swen, J. J., Zeller, A., Wawrusiewicz-Kurylonek, N., Mei, H., . . . Miltyk, W. (2022). Development of an extensive workflow for comprehensive clinical pharmacogenomic profiling: lessons from a pilot study on 100 whole exome sequencing data. *Pharmacogenomics J*, 22(5-6):276-283. https://doi.org/.10.1038/s41397-022-00286-4
88. Tafazoli, A., Mikros, J., Khaghani, F., Alimardani, M., Rafigh, M., Hemmati, M., . . . Patrinos, G. P. (2023). Pharmacovariome scanning using whole pharmacogene resequencing coupled with deep computational analysis and machine learning for clinical pharmacogenomics. *Hum Genomics*, 17(1):62. https://doi.org/.10.1186/s40246-023-00508-1
89. Farmaki, A., Manolopoulos, E., Natsiavas, P. (2024). Will Precision Medicine Meet Digital Health? A Systematic Review of Pharmacogenomics Clinical Decision Support Systems Used in Clinical Practice. *Omics*, 28(9):442-460. https://doi.org/.10.1089/omi.2024.0131
90. Mishra, A., Majumder, A., Kommineni, D., Anna Joseph, C., Chowdhury, T., Anumula, S. K. (2025). Role of Generative Artificial Intelligence in Personalized Medicine: A Systematic Review. *Cureus*, 17(4):e82310. https://doi.org/.10.7759/cureus.82310
91. Elhaddad, M., Hamam, S. (2024). AI-Driven Clinical Decision Support Systems: An Ongoing Pursuit of Potential. *Cureus*, 16(4):e57728. https://doi.org/.10.7759/cureus.57728

CHAPTER 6

AI-Driven Structural Characterization of Orphan GPCRs: Predicting Protein Stability and Ligand Binding Pockets via AlphaFold and Deep Learning

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1. Introduction

G protein-coupled receptors (GPCRs) represent the largest family of membrane proteins in the human genome and play a central role in transmitting extracellular signals into the cell. These receptors regulate a wide range of physiological processes, including vision, olfaction, neurotransmission, and the immune response (1). From their clinical perspective, approximately 35% of modern drugs currently on the market directly or indirectly target GPCRs (2). This situation has made GPCRs a key focus of pharmacological research and the pharmaceutical industry.

Although the functional properties and binding molecules of most of the GPCR family are known, there are approximately 120 receptors called Orphan GPCRs, for which the endogenous ligand has not yet been identified (1, 2). These orphan receptors are considered an untapped "gold mine" for biomedical research, as many are associated with metabolic diseases, cancer, and central nervous system disorders (3).

However, structurally characterizing these receptors using experimental methods (such as X-ray crystallography or cryo-EM) is challenging due to technical limitations, including low expression levels and poor stability (4, 5). In recent years, the emergence of AI-based deep learning models such as AlphaFold has led to a paradigm shift in structural biology. In contrast to the years-long effort of traditional methods, AI models can predict protein structures with high accuracy in seconds (6). This technological leap has opened new horizons, particularly for mapping the binding pockets of Orphan GPCRs lacking structural data and for virtually screening drug candidate molecules.

2. AlphaFold and Protein Modeling

AlphaFold is a deep learning-based computational tool that can predict the three-dimensional structure of proteins from their amino acid sequences with atomic accuracy. The success of this system lies in its ability to integrate biological information within a complex neural network architecture. The Evoformer module, which forms the core of the algorithm, processes relationships between multiple sequence alignments (MSAs) and structural constraints simultaneously via a transformer architecture (6). This process enables the precise optimization of distance and orientation information between amino acid residues during protein folding (7). AlphaFold demonstrates superior performance compared to traditional homology modeling methods, particularly for proteins with seven transmembrane strands, such as GPCRs, which play critical roles in cellular signal transduction (8).

The structural complexity of GPCRs, particularly in the case of Orphan receptors, makes experimental structure prediction quite challenging. AlphaFold uses spatial patterns learned from existing structural data in the RCSB Protein Data Bank (RCSB PDB) to predict the conserved helical structure of these receptors within the lipid membrane (9). However, the accuracy of these models varies across different regions of the protein. To evaluate the reliability of the models, AlphaFold provides two key metrics: the Predicted Local Distance Difference Test (pLDDT) and the Predicted Aligned Error (PAE) (6). pLDDT scores the local structural confidence of each amino acid residue on a scale of 0 to 100. Scores of 90 and above indicate very high confidence, while scores between 70 and 90 are considered high confidence; the transmembrane strands of Orphan GPCRs generally fall within this high confidence range (7, 9). On the other hand, flexible loop regions found in both the extracellular and intracellular areas of GPCRs generally have lower pLDDT scores (6).

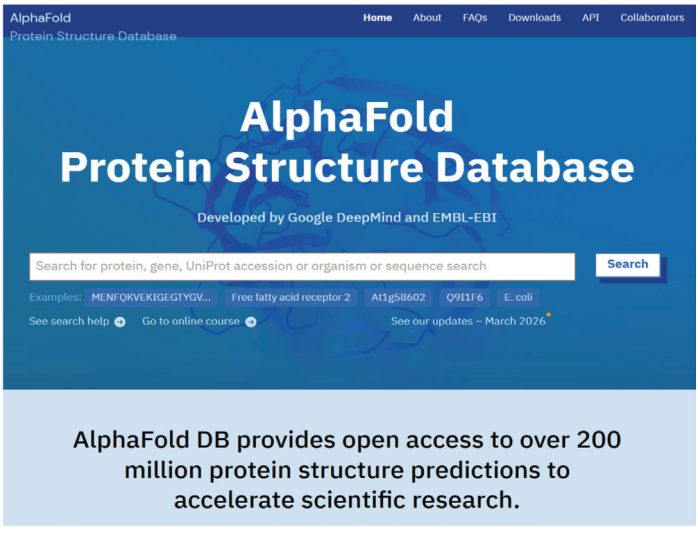


Figure 1. Screenshot from Alphafold Protein Structure Database Website, https://alphafold.ebi.ac.uk/

The PAE metric estimates the margin of error in the positioning of one region of the protein relative to another. This metric is particularly vital for understanding domain-to-domain relationships between G-proteins or arrestins that GPCRs interact with during signal transduction (10). While characterizing drug binding pockets of orphan receptors, PAE scores provide information on the geometric stability of the predicted pocket (11). The AlphaFold-Multimer version can further enable these analyses, allowing modeling of receptor dimerization tendencies or complex structures with helper proteins (12).

AlphaFold models, used in the de-orphanization of orphan GPCRs, provide a basic framework for structure-based drug discovery (SBDD) when experimental constructs are unavailable (13). These models can be incorporated into virtual screening protocols, enabling millions of small molecules to be tested in a computer environment for their receptor-binding potential (14). However, it should be noted that AlphaFold models represent a static moment in the protein's life cycle, whereas GPCRs are dynamic structures that transition between active and inactive conformations (15). Therefore, the confidence scores of these AI-generated models should be rigorously examined and supported by molecular dynamics simulations when necessary (13). In conclusion, AlphaFold technology bridges the gap in structural data in GPCR biochemistry, providing previously unattainable speed and accuracy for the development of next-generation therapeutics, as announced in the last version on May 2024, AlphaFold3 (6, 7, 16).

3. Structural Stability Analysis

The structural biology of GPCRs constitutes one of the most challenging frontiers of modern proteomic research due to the inherently dynamic nature of these proteins and their extreme sensitivity to environmental factors. The fundamental functional capacity of a receptor that is, its ability to detect signals from outside the cell and translate them into effector molecules inside the cell, such as G-proteins or arrestins relies entirely on its three-dimensional structural integrity and the thermodynamic stability of that structure (15). However, orphan GPCRs present a particular challenge for those working in structural biochemistry. The absence of an endogenous ligand (natural agonist or antagonist) in most of these receptors leaves the protein structurally unsupported and therefore thermodynamically unstable. During experimental studies, particularly in detergent-based purification processes, these orphan receptors tend to rapidly denature, misfold, or form insoluble aggregates (17). This structural fragility directly hinders the success of methods such as X-ray crystallography or high-resolution frozen electron microscopy (18). In this context, identifying the structural weaknesses of an orphan receptor using computational methods and stabilizing these regions through "smart mutagenesis" is a critical prerequisite for academic and industrial research before defining it as a drug target.

To understand the molecular basis of protein stability, it is first necessary to focus on the folding energy landscape of the protein. The stability of a protein is biophysically measured by the Gibbs free energy difference between the folded and unfolded states.

Artificial intelligence and deep learning models can predict with atomic precision how point mutations in the amino acid sequence shift this energy balance. For orphan GPCRs, this analysis allows us to filter out candidates with the highest potential for stabilization from billions of possible mutation combinations before proceeding to the experimental laboratory stage (19). For example, mutations that fill packing gaps between transmembrane helices or strengthen the internal interactions of the hydrophobic core significantly increase the receptor's melting temperature ™ (20). This type of thermal stabilization allows the receptor to be biochemically characterized and maintain its structural form in long-term analyses (18, 20).

Modern stability prediction systems currently rely on two main methodological approaches: physics-based energy functions and data-driven deep learning algorithms. Physics-based methods generate an energy score by calculating van der Waals interactions between atoms, electrostatic bonds, hydrogen bridges, and solvent-accessible surface areas using classical mechanics laws (20). However, because GPCRs are embedded in a heterogeneous lipid bilayer membrane rather than a liquid medium, these calculations require much more complex parameters than for standard soluble proteins. The atomic-resolution scaffold structures provided by AlphaFold allow these physical constraints to be combined with information learned by neural networks. The pLDDT on the model clearly reveals which regions of the protein are rigid and structurally stable, and which loops may lead to structural uncertainty due to high flexibility (16).

In the structural analysis of orphan GPCRs, it is a major misconception to treat stability as merely a static concept. GPCRs undergo continuous conformational change throughout the cell's signal transduction cycle; they switch between inactive, intermediate, and fully active forms within seconds (21). To elucidate the crystal structure of an orphan receptor, it is necessary to restrict this dynamic mobility and lock the protein into a specific conformational state. Deep learning-based stability analyses predict which residues can curb the protein's excessive flexibility by calculating conformational entropy changes (19). In this process, thermal stabilization mutations, in particular, help maximize structural resolution by stabilizing the receptor in a specific pharmacological state (19). This methodology has paved the way for high-resolution visualization and drug design applications for many orphan receptors previously labeled as unmodelable (14).

Protein-lipid interactions are another crucial, often overlooked, aspect in analyzing GPCR stability. Orphan GPCRs form highly specific and structurally supportive bonds with cholesterol molecules, phospholipids, and sphingolipids within the membrane. Advanced stability prediction algorithms can identify hydrophobic patches and potential annular/non-annular lipid-binding sites on the protein's outer surface (1). This bioinformatic data provides researchers with a roadmap for determining which detergents, such as n-Dodecyl-β-D-Maltoside, Lauryl Maltose Neopentyl Glycol, and Cholesteryl Hemisuccinate, should be used in experimental purification protocols, or which lipid nanodisk systems best preserve the receptor's natural structure (19). Simulating lipid-receptor interactions, in particular, is an indispensable data source for understanding the realistic and stable behavior of orphan receptors in the membrane environment.

Another dimension of computational stability analysis is the prediction of allosteric communication networks. In GPCRs, structural changes occurring in distant regions outside the orthosteric region, the main pocket where the ligand binds, can fundamentally disrupt the conformational stability and integrity of the entire protein (15). AI-assisted discovery of these cryptic/allosteric pockets in orphan receptors allows for the development of a new generation of allosteric drug candidates that can fine-tune the protein's function without compromising its overall stability (14). Artificial intelligence models how the structural signal propagates throughout the protein and which amino acid residues form a mechanistically interdependent network by plotting the stiffness of the protein. This holistic approach allows us to consider stability not just as a side effect of a local mutation, but as a collective property of the entire structural network of the protein.

Dynamic stability analyses should also be extended to include the protein's transient states. While static AlphaFold models capture the most likely protein conformation, the real-world stability of Orphan GPCRs is determined by fluctuations away from this static structure. Stability predictions, supported by molecular dynamics simulations, reveal which structural regions are most vulnerable to thermal fluctuations by analyzing the receptor's mobility over microseconds (16). These time-dependent analyses tell to the researchers not only how stable the protein is, but also how long and under what conditions it can maintain its structural integrity (19). For orphan receptors, this kind of information plays a vital role in the development of biosensors or the design of long-term biochemical assays.

In conclusion, structural stability prediction in Orphan GPCR research is not merely academic curiosity, but an operational and economic imperative of the modern drug discovery process. AlphaFold and advanced $\Delta\Delta G$ prediction tools identify the "stable skeletons" with the highest chance of success by screening millions of mutational variations in seconds—variations that are physically and financially impossible to test individually in a laboratory setting (19, 22). This intelligent design process provides a significant acceleration in elucidating the mysterious structures of orphan receptors and integrating these proteins into modern medical diagnostic and therapeutic protocols. An optimized orphan receptor serves as both a laboratory model for fundamental scientific discoveries and an unshakeable foundation for multi-billion dollar drug development projects (14, 15).

4. AI Analysis of Binding Regions

The most critical stage in the drug discovery process of orphan GPCRs is the highly accurate identification of binding pockets located on the surface or within the cavities of these receptors, where small molecule drug candidates can bind. In traditional structural biology, these pockets are defined through the interactions of known ligands with the protein; however, the absence of a natural ligand in orphan receptors causes these regions to remain invisible. At this point, AI and deep learning-based Pocket Discovery algorithms can predict potential binding sites without experimental data by analyzing the three-dimensional surface topology and physicochemical properties of the protein (21).

AI-based pocket discovery methods primarily focus on the geometric features, conservation, and energy potentials of proteins. One modern approach, Geometric Deep Learning, treats the protein surface as a cloud point or graph structure, mapping the volumetric and morphological properties of pockets in seconds. The algorithms used in this process analyze hotspot regions in the protein's amino acid sequence, determining which cavities are biologically more suitable for hosting a ligand. Considering the complex seven-transmembrane structure of orphan receptors, these algorithms have the potential to reveal not only the main orthosteric pocket but also previously unnoticed cryptic or allosteric pockets (23).

One of the most effective tools in this field, P2Rank, combines geometric features on the protein surface with machine learning models to score the points with the highest probability of drug binding. Instead of viewing the protein structure as a static object, P2Rank calculates the ligand binding score of each point on the surface (24). When P2Rank analysis is performed on orphan GPCRs, the gaps between the extracellular loops and transmembrane helices of the receptor generally receive the highest score. The integration of this data with static models developed by AlphaFold provides researchers with a precise coordinate system for conducting virtual screening (25).

Another innovative approach is tools that utilize convolutional neural networks, such as DeepSite. DeepSite views the protein structure as a box composed of 3D pixels (voxels) and analyzes properties such as hydrophobicity, hydrogen bonding capacity, and electrostatic charge distribution within this box. In simple terms, it views the structure as a spatial structure. Specific amino acid sequences in the transmembrane region of orphan GPCRs are compared with successful ligand-protein interaction patterns in datasets trained by DeepSite. This allows for preliminary predictions of how the receptor might exhibit an induced fit when a ligand binds (26).

DeepDrug3D is critical for accurately identifying and classifying binding sites in proteins, understanding the functions of hypothetical proteins, performing enzyme engineering, and developing new drugs. It uses computer vision to transform molecules into 3D voxels. Instead of RGB color channels in a classical image, this method uses channels representing the interaction energies of 14 different atomic types. This algorithm not only performs classification but also identifies which regions and interactions (such as hydrogen bonds, hydrophobic and aromatic contacts) on the protein are most distinctive and critical for classification using the Class Activation Mapping method (27).

In orphan receptors in particular, metrics such as pocket volume and pocket depth are key elements in determining the affinity of a drug candidate. AI models not only calculate the volume of these pockets but also model the dynamic structure of the pocket by considering the flexibility of the amino acids surrounding the pocket (8). This allows for the discovery of transient pockets that can close or open during the mobility of the protein in solution, as opposed to static models. This dynamic pocket analysis helps us focus on realistic ligand candidates by eliminating false positives in order to de-orphanize and deorphan a receptor (1, 7).

After identifying the potential drug binding sites of orphan receptors, the next step is to determine the functional validity and ligand selectivity of these pockets. Modern

artificial intelligence approaches are integrating into Virtual Screening protocols that go beyond simply finding a static gap, simulating how these pockets will interact with billions of different chemical structures. Given the structural flexibility of orphan GPCRs, the conformational fit of the ligand at the moment of pocket placement is the key factor determining drug efficacy (28). Deep learning tools, by considering the protein and ligand as a whole, predict a dynamic and interactive binding mechanism beyond the traditional lock-and-key model (17).

One of the key tools in this process is DiffDock, which uses a diffusion-based generative model to predict the most likely binding position and orientation of the ligand on the protein. Unlike traditional scoring functions, DiffDock models the binding event as a probability distribution, thus exhibiting much higher success rates in targets with limited structural data, such as Orphan GPCRs (29). Although the flexibility in the extracellular ECL2 loops of orphan receptors makes ligand entry into the binding pocket difficult, models like DiffDock can overcome these dynamic obstacles and find the point where the ligand is most stable in milliseconds (29). This technology dramatically reduces drug discovery costs by allowing researchers to focus only on candidate molecules with the highest binding energy, instead of conducting thousands of experiments (21).

Another critical point in binding pocket analysis is Allosteric Region Discovery. Many orphan receptors have secondary pockets besides the classic orthosteric pocket that can alter the stability or signal transduction speed of the protein. Artificial intelligence can detect these cryptic pockets, which communicate with the main pocket but are located on a different surface of the protein, by mapping the rigidity of the protein (23). Allosteric modulators generally offer a safer way to control the basal activity of orphan receptors than main ligands because these molecules fine-tune the receptor's natural signal rather than completely shutting it down. Deep learning models analyze the geometry of these hidden pockets, predicting with high accuracy which molecules can stabilize the receptor in an active or inactive form (8).

Successful case studies conducted in recent years have demonstrated the power of this AI-based approach. For example, after modeling the structures of some orphan GPCRs (such as GPR139 or GPR151) with AlphaFold, precursor compounds were discovered for the first time through virtual scans of pockets identified by tools such as P2Rank and DeepSite (30, 31). In this process, the druggability scores provided by AI models have clarified which orphan receptors are pharmacologically intervenable and which are structurally more challenging targets (32). In this process, the druggability scores provided by AI models have clarified which orphan receptors are pharmacologically intervenable and which are structurally more challenging targets.

Consequently, binding pocket discovery in orphan GPCRs is not just a gap finding process, but a process of understanding the entire biophysical network of the protein. Structure prediction, starting with AlphaFold, pocket discovery embodied by P2Rank, and ligand docking processes by DiffDock, create a holistic AI battleground that illuminates the mysterious world of orphan receptors. These digital systems have brought hundreds of receptors previously considered inaccessible into the scope of modern medicine

and next-generation therapeutics. In the future, expanding these models to include intracellular signaling pathways will enable the complete unraveling of the physiological roles of orphan receptors.

5. Drug Discovery and Virtual Screening Integration

The inclusion of orphan GPCRs in the drug discovery process has gained a new dimension thanks to the high-accuracy modeling of the atomic structures of these proteins by artificial intelligence (13). In traditional drug development processes, high-throughput screenings performed to find a ligand that binds to a receptor often fail due to the low stability and high production costs of orphan receptors (28). At this point, Virtual Screening technologies enable the identification of the most suitable candidates before physical testing by simulating the interaction of millions of small molecules with receptors in a computer environment (33). Artificial intelligence can simultaneously calculate not only the docking of molecules but also their binding free energies and pharmacokinetic properties (34).

The first step in the virtual screening process is to develop a Structure-Based Drug Design (SBDD) strategy that is appropriate to the dynamic properties of the ligand-binding pocket of the targeted orphan receptor (13). Orphan receptors typically possess narrow and highly specific hydrophobic pockets, necessitating high precision in the scoring functions used during virtual scanning (35). Deep learning algorithms analyze hydrogen bonds, aromatic stacking, and hydrophobic interactions (π-stacking) between proteins and ligands at the atomic level, capturing subtle details that traditional force fields might miss (33). This makes it possible to select high-affinity molecules specific to orphan receptors from ultra-large libraries containing billions of molecules (36).

Methods like Deep Docking exponentially increase the speed of virtual screening. Instead of trying each molecule in the library individually, this method trains a neural network on sub-samples of ligand-protein interactions, predicting the binding scores of the remaining molecules in seconds (33). This increased speed for orphan GPCRs allows for the simultaneous screening of thousands of different orphan receptors and the discovery of potential pan-GPCR modulators (28). Furthermore, AI models evaluate not only binding strength but also the molecule's ADMET parameters (Absorption, Distribution, Metabolism, Excretion, Toxicity) during the screening phase, filtering out molecules with a high probability of being rejected in the preclinical stage from the outset (34).

The performance of virtual screening on orphan GPCRs also depends on the correct selection of the receptor's active or inactive conformation (13). While searching for an agonist ligand, screening should be done through active form models generated by tools such as AlphaFold; however, when antagonism is targeted, inactive forms are used as the basis (35). Artificial intelligence also models the intermediate states between these two conformations, enabling the design of molecules with specific pharmacological profiles,

such as partial or biased agonists (36). This precise engineering is a vital tool for understanding the complex physiological roles of orphan receptors and developing treatments with low side effects (13).

After identifying the initial hit molecules in virtual screening processes, the next step is to optimize the selectivity and binding modes of these molecules on Orphan GPCRs (13). Traditional molecular docking methods attempt to fit the ligand into a static pocket, while next-generation AI-based methods account for ligand-induced fit mechanisms (37). In particular, machine learning-supported pharmacophore models can map the critical hydrogen bond donors, acceptors, and hydrophobic regions in an orphan receptor's binding pocket as a 3D map, eliminating millions of molecules that do not meet these geometric requirements in seconds (38). The CNN-scoring functions used in this process can predict experimental binding energies (Ki, Kd values) much more accurately than traditional mathematical models by processing the atomic interactions of the protein-ligand complex as a visual dataset (39).

One of the biggest obstacles encountered in drug discovery of orphan receptors is the risk of cross-reactivity with other GPCR families of similar structure. Artificial intelligence, using multi-target virtual screening protocols, simultaneously screens the affinity of a molecule not only to the target orphan receptor but also to other receptors that may lead to undesirable side effects, such as hERG channels or similar GPCR subtypes (40). This negative design strategy is one of the most important technological elements that reduces failure rates in clinical trials (41). Furthermore, generative AI models, instead of being limited to existing libraries, can propose completely new de novo designs that fit perfectly into the pocket of the orphan receptor, never before synthesized (42).

Another advanced aspect of virtual screening is the Protein Flexibility and Ensemble Docking approach. Screenings performed using a static AlphaFold model can sometimes yield unrealistic results because the receptor constantly vibrates and changes conformation within the cell (28).

Artificial intelligence, using different protein snapshots derived from molecular dynamics simulations, tests whether the ligand adapts to all motile states of the protein, not just a single main state (37, 39). This approach, in particular, enables the discovery of long-residence-time drug candidates, which is a critical parameter for the persistence of drug effect in the treatment of orphan receptors (13, 40).

In conclusion, the structural elucidation process, beginning with AlphaFold, combined with ultra-wide library screenings and deep learning-based ADMET filtering, has propelled Orphan GPCRs from the undruggable category to the forefront of modern medicine's most promising targets (13, 40). In the future, the integration of quantum computing and artificial intelligence will revolutionize the treatment of neurological and metabolic diseases associated with orphan receptors, making these screening processes real-time and error-free (41, 42). This technology offers an accelerated discovery cycle, resulting in bench-to-bedside synthesis of molecules designed digitally and their biological validation directly in the laboratory (42).

6. Future Perspectives and Constraints

The success of AI models in Orphan GPCR research is being taken to a new level by modeling proteins as conformational ensembles rather than static scaffold structures (43). The biggest limitation of older systems is that they freeze the receptor in a single static frame; whereas the Alphafold3 perspective focuses on four-dimensional modeling techniques that can simultaneously predict thousands of different movements of the protein within microseconds (16). This dynamic approach will allow us to predict not only the structural form of orphan receptors but also the specific signal transduction kinetics in different tissues (44). In particular, solving the concept of biased signaling with AI can open the door to ultra-selective drugs that trigger only a specific intracellular pathway with minimized side effects (43, 45).

New generation Few-Shot Learning and Self-Supervised Learning algorithms, developed to overcome dataset limitations, can make highly accurate predictions even for rare Orphan GPCRs with very little experimental data (46, 47). In the future, these models are expected to include not only the protein structure but also the effects of the membrane lipidome in which the protein is located in the equation (44). Membrane-sensitive AI systems will contribute to the creation of precision medicine by analyzing which lipids the receptor interacts with in which tissue (45). Furthermore, by integrating quantum bioinformatics tools, electron transfers and quantum tunneling effects in ligand-receptor interactions are simulated, aiming for zero error margin in drug discovery (42, 48).

The evolution of AI models in Orphan GPCR research is moving beyond simply predicting structural information and towards integrating this data in a hybrid manner with experimental validation processes. One of the most exciting developments in the future is hybrid approaches that combine quantum mechanics and classical machine learning methods. These systems can calculate the electron cloud density in ligand-binding pockets of orphan receptors and the energy transfers of non-covalent interactions much more accurately than traditional methods. In particular, this atomic-level accuracy will play a key role in deciphering the micro-interactions that determine the functional selectivity of orphan receptors (42, 48).

In the field of dynamic modeling, four-dimensional structure predictions fill the gap created by static AlphaFold models. This method can predict not just a single moment of the receptor's movement, but microsecond oscillations within the cell and the transient pockets that open and close during these oscillations (44, 49). The main reason many orphan GPCRs lack naturally occurring ligands is that these ligands bind only to specific protein conformations; 4D modeling techniques increase the success rate of virtual screening by digitally recreating these missing conformations (49).

Orphan receptors are not merely static structures consisting of amino acid sequences; cholesterol and phospholipid species within the membrane directly modulate the receptor's folding stability and signal transduction capacity. Lipid-aware AI systems will enable the development of tissue-specific drugs by predicting how an orphan receptor will take a structural form under different lipid compositions in different tissues (50).

7. Conclusions

In the mysterious world of GPCRs, artificial intelligence and deep learning technologies have led to a paradigm shift that is changing the course of biomedical research. As detailed in this study, algorithms like AlphaFold have become a force illuminating a previously obscure area, especially for protein families that are extremely difficult to characterize experimentally, such as Orphan receptors. This technological revolution has gone beyond simply predicting a static protein structure; it has created an integrated discovery pipeline ranging from structural stability analyses to the prediction of dynamic conformational assemblies and ultra-wide library screenings. Understanding the functional roles of Orphan GPCRs is opening up previously unimaginable treatment possibilities for neurodegenerative disorders, rare metabolic diseases, and specific types of cancer that modern medicine faces.

In conclusion, the data obtained show that AI-assisted structural biology has dramatically reduced the trial-and-error cost and time loss in the drug discovery process (51). Thanks to structural stability predictions, researchers can predict the risk of protein degradation in the laboratory and focus on the most stable variants . Mapping binding sites at atomic resolution has made it possible to design drugs not only for known active sites but also for hidden allosteric pockets. In the future, with the full integration of quantum computing and 4D modeling techniques into this process, the complexity of biological systems can be simulated digitally with near-zero error.

However, dataset bias and limitations of static modeling, which are constraints of this digital advancement, once again highlight the importance of collaboration between bioinformaticians and wet lab researchers. Artificial intelligence is not an alternative to experimental data; rather, it is an enhancer that amplifies, interprets, and optimizes this data for the next experiment. Micro-changes created by individual genetic variations in the structural pockets of orphan receptors can be analyzed by artificial intelligence to create personalized drug dosages and treatment protocols. With the inclusion of membrane-lipid interactions and post-translational modifications in the modeling, precision medicine applications will offer more personalized solutions with minimized side effects via orphan receptors. This vast, yet undiscovered biological reserve in the human body can be unearthed through the GPCRome de-orphanization process, made possible by artificial intelligence.

8. References

1. Hauser, A. S., Attwood, M. M., Rask-Andersen, M., Schiöth, H. B., & Gloriam, D. E. (2017). Trends in GPCR drug discovery: New agents, targets and indications. *Nature Reviews Drug Discovery, 16*(12), 829-842.
2. Sriram, K., & Insel, P. A. (2018). G protein-coupled receptors as targets for approved drugs: How many targets and how many drugs? *Molecular Pharmacology, 93*(4), 251-258.
3. Laschet, C., Dupuis, N., & Hanson, J. (2018). The G protein-coupled receptors deorphanization landscape. *Biochemical Pharmacology, 153*, 62-74.
4. Sakuma, T., Otani, Y., & Shimizu, H. (2026). Geometric-evolutionary deep learning decodes the human GPCR-metabolome interactome and enables systematic de-orphanization. *bioRxiv*. doi:10.1101/2026.02.21.707232

5. Insel, P. A., Sriram, K., Wiley, S. Z., Wilderman, A., Katakia, T., McCann, T., ... & Zhang, L. (2018). GPCRomics: GPCR expression in cancer cells and tumors identifies new, potential biomarkers and therapeutic targets. *Frontiers in Pharmacology, 9*, 431.
6. Jumper, J., Evans, R., Pritzel, B., Adler, T., Figurnov, M., Ronneberger, O., ... & Hassabis, D. (2021). Highly accurate protein structure prediction with AlphaFold. *Nature, 596*(7873), 583-589.
7. Akdel, M., Pires, D. E., Pardo, E. P., Jänes, J., Zalevsky, A. O., Mészáros, B., ... & Beltrao, P. (2022). A structural biology community assessment of AlphaFold2 applications. *Nature Structural & Molecular Biology, 29*(11), 1056-1067.
8. Alhumaid, N. K., & Tawfik, E. A. (2024). Reliability of AlphaFold2 models in virtual drug screening: A focus on selected Class A GPCRs. *International Journal of Molecular Sciences, 25*(18), 9854.
9. Varadi, M., Anyango, S., Deshpande, M., Nair, S., Natassia, C., Yushin, G., ... & Velankar, S. (2022). AlphaFold Protein Structure Database: Massively expanding the structural coverage of protein-sequence space with high-accuracy models. *Nucleic Acids Research, 50*(D1), D439-D444.
10. Elfmann, C., & Stülke, J. (2023). PAE viewer: A webserver for the interactive visualization of the predicted aligned error for multimer structure predictions and crosslinks. *Nucleic Acids Research, 51*(W1), W404-W410.
11. Senior, A. W., Evans, R., Jumper, J., Kirkpatrick, J., Sifre, L., Green, T., ... & Hassabis, D. (2020). Improved protein structure prediction using potentials from deep learning. *Nature, 577*(7792), 706-710.
12. Evans, R., O'Neill, M., Pritzel, A., Antropova, N., Senior, A., Potapenko, A., ... & Jumper, J. (2021). Protein complex prediction with AlphaFold-Multimer. *bioRxiv*. doi:10.1101/2021.10.04.463034
13. Lyu, J., Wang, S., Balius, T. E., Singh, I., Levit, A., Moroz, Y. S., ... & Shoichet, B. K. (2019). Ultra-large library docking for discovering new chemotypes. *Nature, 566*(7743), 224-229.
14. Meng, F., Zuo, C., Zheng, S., Wang, Z., Li, Y., & Xu, Y. (2022). An open-like conformation of the sigma-1 receptor reveals its ligand entry pathway. *Nature Communications, 13*(1), 1267.
15. Abramson, J., Adler, J., Dunger, J., Evans, R., Green, T., Pritzel, A., ... & Jumper, J. (2024). Accurate structure prediction of biomolecular interactions with AlphaFold 3. *Nature, 630*(8016), 493-500.
16. Jobe, A., & Vijayan, R. (2024). Orphan G protein-coupled receptors: The ongoing search for a home. *Frontiers in Pharmacology, 15*, 1373510.
17. Yang, D., Zhou, Q., Labroska, V., Qin, S., Darbalaei, S., Wu, Y., ... & Wang, M. W. (2021). G protein-coupled receptors: Structure- and function-based drug discovery. *Signal Transduction and Targeted Therapy, 6*(1), 7.
18. Lee, H., Kim, J., & Choi, S. (2026). Protein folding stability estimation with explicit consideration of unfolded states. *Nature Communications, 17*(1), 1883.
19. Worth, C. L., Kreuchwig, A., Tiemann, J. K., Kleinau, G., Krause, G., & Schöneberg, T. (2017). GPCR-SSFE 2.0—a fragment-based molecular modeling web tool for Class A G-protein coupled receptors. *Nucleic Acids Research, 45*(W1), W408-W415.
20. Zhang, M., Cao, J., & Guo, Z. (2024). G protein-coupled receptors (GPCRs): Advances in structures, mechanisms and drug discovery. *Signal Transduction and Targeted Therapy, 9*(1), 88.
21. Chakravarty, D., Schafer, N. P., Chen, M., & Wolynes, P. G. (2024). AlphaFold predictions of fold-switched conformations are driven by structure memorization. *Nature Communications, 15*(1), 7296.
22. Nussinov, R., Zhang, M., Liu, Y., & Jang, H. (2023). AlphaFold, allosteric, and orthosteric drug discovery: Ways forward. *Drug Discovery Today, 28*(6), 103551.
23. Krivák, R., & Hoksza, D. (2018). P2Rank: Machine learning based tool for rapid and accurate prediction of ligand binding sites from protein structure. *Journal of Cheminformatics, 10*(1), 39.
24. Liu, F., Wu, H., & Qin, J. (2024). GPCR-BSD: A database of binding sites of human G-protein coupled receptors under diverse states. *BMC Bioinformatics, 25*(1), 343.
25. Jiménez, J., Doerr, S., Martínez-Rosell, G., Rose, A. S., & De Fabritiis, G. (2017). DeepSite: Protein-binding site predictor using 3D-convolutional neural networks. *Bioinformatics, 33*(19), 3036-3042.
26. Pu, L., Govindaraj, R. G., Lemoine, J. M., Brylinski, M., & Jaggi, B. (2019). DeepDrug3D: Classification of ligand-binding pockets in proteins with a convolutional neural network. *PLoS Computational Biology, 15*(2), e1006718.
27. Sadybekov, A. V., & Katritch, V. (2023). Computational approaches streamlining drug discovery. *Nature, 616*(7958), 673-685.
28. Corso, G., Stärk, H., Jing, B., Barzilay, R., & Jaakkola, T. (2023). DiffDock: Diffusion steps, twists, and turns for molecular docking. *arXiv preprint arXiv:2210.01776*.
29. DePasquale, O., Smith, R., & Jones, A. B. (2025). The orphan receptor GPR151: Discovery, expression, and emerging biological significance. *ACS Chemical Neuroscience, 16*(9), 1639-1646.
30. Mao, J., Liu, X., Wang, Y., Zhang, L., & Chen, H. (2023). Design and synthesis of novel GPR139 agonists with therapeutic effects in mouse models of social interaction and cognitive impairment. *Journal of Medicinal Chemistry, 66*(20), 14011-14028.
31. Wong, F., Krishnan, A., Zheng, E. J., Stärk, H., Manson, A. L., Earl, A. M., ... & Collins, J. J. (2022). Benchmarking AlphaFold-enabled molecular docking predictions for antibiotic discovery. *Molecular Systems Biology, 18*(9), e11081.
32. Gentile, F., Agrawal, V., Hsing, M., Ton, A. T., Ban, F., Norinder, U., ... & Cherkasov, A. (2020). Deep Docking: A deep learning platform for augmentation of structure based drug discovery. *ACS Central Science, 6*(6), 939-949.
33. Askr, H., El-Sappagh, S., Hemdan, A., & El-Rashidy, N. (2023). Deep learning in drug discovery: An integrative review and future challenges. *Artificial Intelligence Review, 56*(7), 5975-6037.

34. Lee, S., Kim, H., & Shin, J. (2023). Evaluating GPCR modeling and docking strategies in the era of deep learning-based protein structure prediction. *Computational and Structural Biotechnology Journal, 21*, 158-167.
35. Gorgulla, C., Boeszoermenyi, A., Panzi, L., Musso, G., Ye, K., Singh, I., ... & Arthanari, H. (2020). An open-source drug discovery platform enables ultra-large virtual screens. *Nature, 580*(7805), 663-668.
36. Vamathevan, J., Clark, D., Czodrowski, P., Dunham, I., Ferran, E., Pinheiro, G., ... & Zhao, S. (2019). Applications of machine learning in drug discovery and development. *Nature Reviews Drug Discovery, 18*(6), 463-477.
37. Schneider, G. (2019). Mind and machine in drug design. *Nature Machine Intelligence, 1*(3), 128-130.
38. Hollingsworth, S. A., & Dror, R. O. (2018). Molecular dynamics simulation for all. *Neuron, 99*(6), 1129-1143.
39. Stevens, R. C., Cherezov, V., Katritch, V., Abagyan, R., Kuhn, P., Rosen, H., & Wüthrich, K. (2013). The GPCR Network: A large-scale collaboration to determine human GPCR structure and function. *Nature Reviews Drug Discovery, 12*(1), 25-34.
40. Gutiérrez-Mondragón, M. A., König, C., & Vellido, A. (2022). A deep learning-based method for uncovering GPCR ligand-induced conformational states using interpretability techniques. In *Bioinformatics and Biomedical Engineering* (pp. 450-462). Cham: Springer International Publishing.
41. Zhou, Y., Zhang, Q., & Li, W. (2026). Quantum-machine-assisted drug discovery. *npj Drug Discovery, 3*(1), 1.
42. Cui, X., Liu, Y., & Wang, S. (2025). Beyond static structures: Protein dynamic conformations modeling in the post-AlphaFold era. *Briefings in Bioinformatics, 26*(4).
43. Hedger, G., Lyman, E., & Rouse, S. L. (2026). Ligand-like lipid interactions with membrane proteins: Simulations and machine learning. *Current Opinion in Structural Biology, 97*, 103226.
44. Estau, D., & Li, Z. (2026). Future directions in GPCR biased signaling and ligand pharmacology. *Handbook of Experimental Pharmacology, 290*, 343-350.
45. Yi, J., Chen, L., & Wu, X. (2025). Pushing the boundaries of few-shot learning for low-data drug discovery with a Bayesian meta-learning hypernetwork framework. *Briefings in Bioinformatics, 26*.
46. Lin, Z., Akin, H., Rao, R., Hie, B., Zhu, Z., Ng, W., ... & Rives, A. (2023). Evolutionary-scale prediction of atomic-level protein structure with a language model. *Science, 379*(6637), 1123-1130.
47. Li, W., Yang, M., & Zhang, J. (2024). A hybrid quantum computing pipeline for real world drug discovery. *Scientific Reports, 14*(1), 16942.
48. Cheng, K., Wei, L., & Zhao, H. (2025). 4D diffusion for dynamic protein structure prediction with reference and motion guidance. *Proceedings of the AAAI Conference on Artificial Intelligence, 39*, 93-101.
49. Fourel, C., Martin, A., & Leroy, G. (2025). Allosteric coupling between a lipid bilayer and a membrane protein. *Biophysical Journal, 124*(16), 2613-2626.
50. Ocana, A., Perez, J., & Martinez, R. (2025). Integrating artificial intelligence in drug discovery and early drug development: A transformative approach. *Biomarker Research, 13*(1), 45.

CHAPTER 7

The Power of Deep Learning in Histological and Embryological Sections: The Third Eye in the Microscope

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1. Introduction

Histology and embryology have developed as fundamental disciplines based on the visual evaluation of biological tissues and cellular structures at the microscopic level throughout history. The traditional approach involves preparing tissue samples on glass slides and examining them by a histologist using an optical microscope. However, this manual evaluation process, based on human observation and experience, has several limitations due to its high labor requirements, time constraints, and susceptibility to differences among observers. Advances in imaging technologies and the integration of artificial intelligence methods have led to a significant change in the field of histology and embryology. One of the key elements of this change is Whole SlideImaging (WSI) technology, whichmakes it possible to transfer glass slides to a digital environment via high-resolution scanners (1).

The combination of artificial intelligence and digital pathology has emerged as a transformative force in healthcare and biomedical research. Komura et al., focusing on developments since 2018, present a comprehensive analysis of machine learning applications in histopathological imageanalysis. They have studied significant advances that expand the technical capabilities and practical applications of computational pathology; progress made in addressing key challenges in the field; gigapixel WSI processing, undersigned data, multidimensional analysis, inter-agency field shifts, and the interpretability of machine learning models. Overall, the researchers highlight the potential of machine learning to enhance both routine pathological analysis and scientific discovery in pathology. Thanks to WSI technology, tissue sections are transformed into gigapixel-level digital images that preserve subcellular details, and histological data are converted into large-scale data sets suitable for computational analysis (2). This digitalization has enabled the storage, remote access, and processing of images with advanced image

analysis algorithms by transferring microscopic examination to the computer screen. In analyzing the large volume of data resulting from digitalization, traditional machine learning approaches have been replaced by deep learning algorithms inspired by the workings of the human brain. While traditional methods depend on expert-defined features such as cell shape or tissue structure, deep learning models can directly learn complex and abstract features from raw image data. In particular, Convolutional Neural Networks (CNNs) can perform tasks such as cell segmentation, tissue classification, and developmental stage prediction with high accuracy by analyzing pixel-level patterns in histological images (3).

These AI-powered systems, which function as a "third eye" in histology and embryology practice, reveal morphological details and complex relationships that are too fine for the human eye to distinguish. For example, it is now possible to mapcell proliferation in three dimensions in whole embryos imaged with light sheet fluorescence microscopy or to automatically count hundreds of thousands of cells in histological sections (4).

Especially in critical decisions such as evaluating embryo quality in IVF laboratories, manual morphological grading systems can remain subjective and lead to disagreements among experts. With the introduction of time-lapse imaging systems in clinical embryology, embryo development can be monitored continuously and dynamically without removing it from the incubator. Instead of static observations, these systems record the developmental kinetics of embryos, producing video data reflecting time-dependent developmental processes and providing a rich analytical infrastructure for artificial intelligence models (5).

In this section, we will discuss the fundamental dynamics of the transition from optical microscopy to digital approaches, the artificial intelligence terminology used in histology and embryology, and how these technologies have transformed a descriptive scientific field into a more quantitative and predictive discipline.

2. Digital Imaging Technologies in Histology and Embryology

The journey of computer-assisted analysis of histological data first took root in the 1960s with the digitization of cell and chromosome images. However, the real turning point in this field occurred in the 1990s with the invention of whole-slide scanners, and this technology formed the back bone of digital pathology (6).

After the 2000s, with increasing computing power and artificial intelligence algorithms, digital imaging began to be used not only for archiving purposes but also for diagnostic support, education, and research.

2.1. WholeSlideImaging (WSI)

WSI technology enables the conversion of classic glass preparations into high-definition data via advanced optical scanners, creating massive digital maps on a giga pixel scale.

The images obtained using this method, with their functions such as magnification, reduction, and panning, completely transfer the observation experience offered by traditional light microscopy to the digital environment, while also allowing simultaneous accessby multiple experts. These massive images are then divided into smaller, processable parts, often called "patches" or "tiles," for processing by artificial intelligence algorithms (7).

Although WSI technology has brought about a significant transformation in histological analysis, the resulting large file size splace a serious burden on data storage and computational infrastructures. Inaddition, differences in staining protocols and calibration of scanner systems that vary between laboratories can lead to significant color variations in digital images. Since such variations can negatively affect the generalizability of AI models, color normalization, noise reduction, and texture-back ground separation approaches have become a critical preprocessing step in WSI-based analyses (1).

2.2. Accelerated (Time-Lapse) Microscopy in Embryology

One of the most significant technological advances in clinical embryology, going beyond static imaging approaches, is time-lapse imaging (TLI) systems, which allow continuous monitoring of embryo development without removing it from the incubator. While in traditional practices embryos are removed from the incubator at specific times for developmental assessment, TLI systems capture images at regular intervals without disrupting culture conditions.These systems present the entire developmental process of the embryo, from the zygote stage to the blastocyst stage, in a video format. This makes it possible to accurately measure morphokinetic parameters and cell division timings that cannot be captured by static observation. Furthermore, the complete automation of embryo scoring meansless manual evaluation and eliminates deviations caused by inter-observer and intra-observer variation. TLI uses algorithms that evaluate critical growth mile stones by continuously monitoring embryo development and reveals that developmental kinetics (temporal data) in culture can correlate with embryo quality. Deep learning algorithms are used to predict fetal heart beat or implantation success using this video data (5). Furthermore, thanks to these systems, the potential of embryos to reach the blastocyst stage can be predicted through kinetic patterns that are imperceptible to the human eye (8, 9).

2.3. Virtual Staining

Traditional histochemical staining methods are labor-intensive and time-consuming, and require irreversible procedures on the tissue. Virtual staining is a deep learning-based process that transforms images obtained with label-free microscopy methods into a format that containssufficient information for clinical diagnosis and is interpretable, by mimicking the morphological features revealed by various histochemical staining styles (e.g., H&E). In this method, generative artificial intelligence models such as CycleGAN learn the visual transformation between label-free images and standard

histological images (10, 11). Thus, histological details are revealed without chemical staining, solely based on the auto fluorescence or light scattering properties of the tissue. Forexample, images obtained with UV-photoacoustic microscopy or reflection confocal microscopy can be transformed into virtual histological images that preserve the morphology of the cell nucleus and cytoplasm using artificial intelligence models. This approach offers significant advantages, particularly in situations where preserving embryos or delicate tissue samples is critical, by reducing tissue preparation time to the level of minutes (2, 12). Furthermore, virtual staining techniques increase data efficiency by allowing the digital derivation of multiple staining types from a single tissue section. Inaddition to the advantages of reducingstainingcostsandpreservingvaluablesamples, thistechnologyensuresconsistency in histological evaluations by mitigating field shifts caused by staining variability.

2.4. LightPlateMicroscopyand 3D Imaging

Although biological tissues are inherently three-dimensional structures, traditional histology examines these structures by reducing them to two-dimensional thin sections, which can leadto a loss of spatial integrity of the tissue. Light Sheet Fluorescence Microscopy (LSFM), developed to over come this limitation, allows for three-dimensional imaging of the entire embryo by making it optically transparent, especially in developmental biology. This method creates high-resolution optical sections of cellular structures with in the tissue without the needfor physical sectioning (13). For example, tracking organogenesis processes and volumetric analyses in mouse or Xenopus embryos are possible with this technique. However, 3D imaging generates enormous amounts of data, and manual analysis of this data is almostimpossible. This is where deep learning models come into play, automatically segmenting tubular structures or cell populations in 3D volumes, allowing researchers to quantitatively evaluate complex phenotypes (14).

In light of current technological developments, new generation deep learning platforms enable three-dimensional histological mapping of the entire organ using serial cross-sectional images taken from the tissue block surface. The most distinctive feature of these systems is that they provide a volumetric data set while preserving the physical integrity of the tissue (15). Figure 1 illustrates the 3D volumetric rendering and 3D visualization of the anatomical features of a mouse brain, liver, and kidney. Here, a 3D histological image of the entire mouse brain, reconstructed using hundreds of serial virtual H&E-stained histological images; virtual H&E images of coronal sections at different depths of the mouse brain; 3D features of the mouse brain extracted from different perspectives; a reconstructed 3D histological image of a mouse liver block; a representative 2D virtual H&E image of the displayed liver block; serial zoomed-in images of the white box region; and vascular networks of the liver block extracted using image thresholding are shown. A reconstructed 3D histological image of a mouse kidney is also presented. Two virtual H&E-stained images of the cortex and papillary structures at different depths of the kidney are shown.

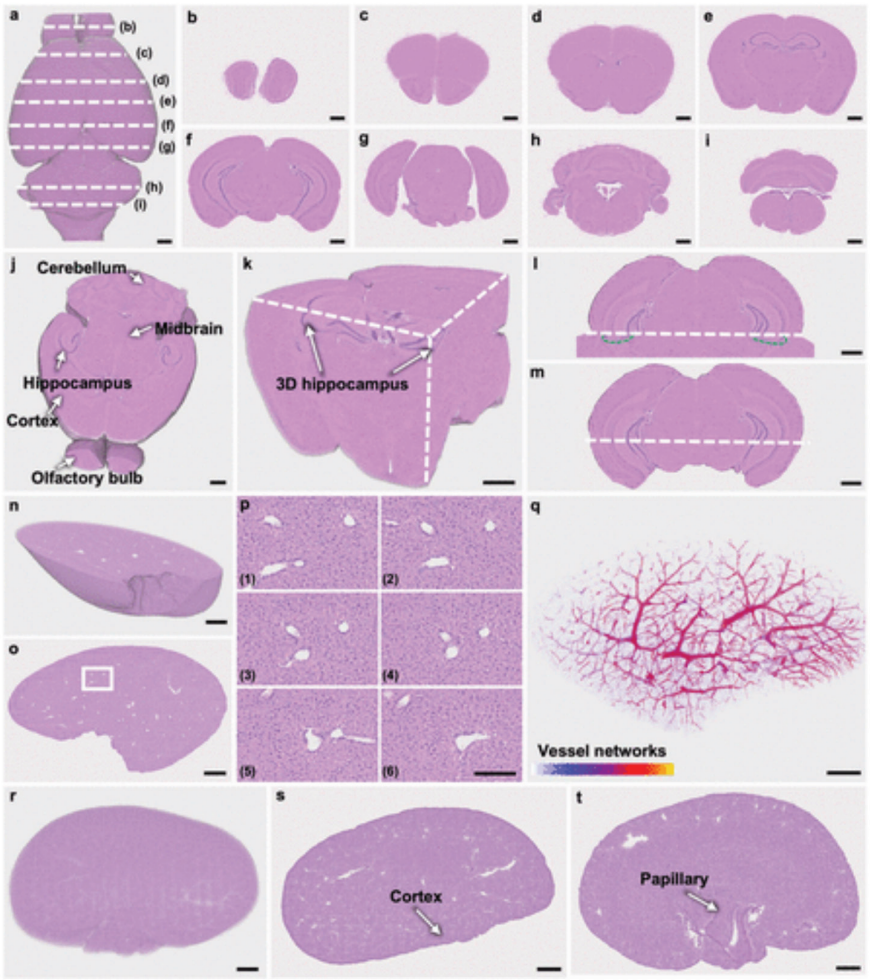


Figure 1. 3D volumetric rendering and 3D visualization of anatomical features of a mousebrain, liver, and kidney. (a) 3D histological image of the whole mouse brain reconstructed with hundreds of serialvirtual H&E stained histological images. (b–i) Virtual H&E images of coronal sections at different depths of the mouse brain. (j–m) Extracted 3D features of the mouse brain with different perspectives. (n) A reconstructed 3D histological image of a mouse liver block. (o) A representative 2D virtual H&E image of the imaged liver block in (n). (p) Serial zoomed-in images of the white box region in (o). (q) Vessel networks of the liver block in (n) extracted by image thresholding. (r) A reconstructed 3D histological image of a mouse kidney. (s, t) Two virtual H&E images at different depths of the kidney, showing cortex and papillary structures, respectively. Scale bars: 1 mm (a–o, q–t) and 50 μm (p) (15).

3. Fundamentals of Deep Learning in Histology and Embryology

Obtaining digital images in histological and embryological studies constitutes only the initial stage; the real added value arises from extracting meaningful biological information from these images. In this process, artificial intelligence approaches that mimic human in-

telligence, machine learning methods that focus on learning patterns from data, and deep learning models that work with multi-layered architectures play a fundamental role. This section provides an in-depth theoretical perspective that will enable medical professionals to master the working principles of these digital tools, correctly evaluate their application potential, and be aware of existing limitations.

Machine Learning: Refers to approaches that enable algorithms to learn patterns in histological data without explicitly defining rules. Traditional machine learning methods (e.g., Support Vector Machine, Random Forest) have been used in histological analysis for many years, and these approaches are generally based on the principle of extracting and processing "hand-selected" features (e.g., nuclear shape, tissue architecture, orangularity of glands) determined by the histologist based on field knowledge (6). For example, in assessing embryo quality, predefined features such as zona pellucida thickness or blastomere symmetry are presented to the algorithm (16). However, this approach may be insufficient to fully reflect the multidimensional complexity of biological processes, as it is limited tofeatures that the human eye can distinguish and clearly define (6).

Deep Learning: A more advanced subfield of machine learning that uses Artificial Neural Networks (ANN) inspired by the working principles of neurons in the human brain. Machine learning (ML) and deep learning (DL) based imaging methods have demonstrated the capacity to process extremely high-dimensional data for a range of computer vision tasks. While these approaches have been applied to numerous data types, this capacity is particularly useful in histopathological images that capture cellular and structural features with high resolution and microscopic perspectives. These methods have shown promising performance in various applications such as disease classification, cancer grading, structure and cellular localizations, and prognostic predictions. There are a wide variety of pathologies requiring histopathological evaluation in gastroenterology and hepatology, making these disciplines highly target able for the integration of these technologies. Gastroenterologists are also ready to consider the impact of these algorithms, as the development of real-time endoscopic video analysis software has been an active and popular area of research (17).

The fundamental characteristic that distinguishes deep learning from classical approaches is its complete automation of the process by eliminating manual intervention in thefeature extraction phase. In this architecture, the algorithm performs a hierarchical learning process directly from raw pixel data. While shallow layers of the network recognize basic visual features such as edge and color transitions present in all images; deeper layers combine these simple structures to reach a levelwhere they can detect cellular components and complex morphological structures specific to the data set (18).

This ability allows the discovery of morphological patterns and textural relationships so fine that the human eye can not perceive them, in histological sections or time-lapse embryo images.

3.1. Learning Models

The performance of artificial intelligence models is shaped by the learning paradigm, which is the method of extracting information from data, rather than the chosen archi-

tecture. In histopathological and embryological analyses, the scale and annotation status of the data set play a critical role in determining the training methodology to be applied.

3.1.1. Reference (GroundTruth) Assisted Learning

This is the most commonly used approach in histology and embryology and relies on labeled data set screated by experts. In this method, the model learns the relationship between the input data and the corresponding label (18). For example, to differentiate the trophectoderm and iner cell mass regions of a blastocyst, the model is trained on a large number of samples pre-labeled by experts (19). This approach is considered standard in tasks requiring high accuracy, such as embryo grading, cell counting, and histological tissue classification (1, 9). However, the main limitation of this method is the high demand for high-quality and reliable labeled data sets requiring expert labor.

3.1.2. Unlabeled Learning Paradigm

In scenarios where expert-approved labeled data sets are limited, unsupervised learning strategies play a critical role. In this approach, the model independently discovers structural similarities and patterns in the data without a predefined target. The algorithm groups similar samples into the same clusters by tracking statistical projections between data (20). For example, autoencoder-based models can learn the basic visual features of an image without requiring labels (17). The most striking reflection of this approach in the medical world is virtual staining technology. Generative models such as CycleGAN learn to transform unstained tissue images into a standard histological staining appearance without paired training data (11).

3.1.3. WeaklySupervised Learning fromDetailtoWhole

In histology, it is practically impossible to labele very single cell of all gigapixel-sized slide images at the pixel level. Weakly supervised learning offers a solution to this problem by using only slide or patient-level global labels instead of detailed regional annotations. In this approach, the model is presented with a single global label for the entire image (e.g., the clinical success status of the embryo). Attention-based learning approaches such as CLAM (Clustering-constrained Attention Multiple Instance Learning) automatically identify the micro-regions that are most influential on the decision, instead of evaluating the entire image with equal weight, and make these are as visible through attention maps. Thus, the model focuses on biologically meaningful patterns while also providing visual explain ability to the decision-making process (21).

3.1.4. Semi-Supervised Learning

This approach leverages the advantages of bothworldsbycombining a small amount of labeled data with a large amount of unlabeled data. It is particularly preferred for the detection of rare anomalies or in cases where labeling is very expensive. In histopathological

tissue segmentation, it enables the processing of large data sets with a limited number of expert drawings. Interactive systems such as ELEPHANT (Efficient Learning using Efficient Projection Human Annotations for Nuclear Tracking) increase efficiency in practical applications by offering semi-supervised processes where the user starts with a small number of sample annotations and the model gradually improves its predictions (22).

3.1.5. Self-Supervised Learning and Foundation Models

This approach, a major break through in recent years, enables the use of massive data sets without the need for labeling by deriving learning signals from the data itself. In this approach, instead of relying directly on external labels, the model develops visual representations through auxiliary tasks such as reconstructing image integrity or approximating similar samples. Thus, distinctive and generalizable features can be learned from histological and embryological images without human intervention.

Foundation Models (e.g., FEMI) trained with millions of histology and embryo images can be adapted to specific tasks (transfer learning) with very little data after learning general tissue characteristics. The FEMI (Foundational Embryology Model forImaging) model, trained on time-lapse embryo imagery, has achieved high success in tasks such as ploidy prediction and blastocyst quality scoring (23).

These models, by leveraging large pools of unlabeled data, provide a strong foundation for specific histological analyses with limited data.

3.2. FundamentalTasks in Deep Learning

Tasks such as recognizing tissue type (classification), finding a specific cell (detection), or drawing cellular boundaries (segmentation), which a histologist or embryologist does when looking under a microscope, requiredifferentmathematicalgoalsand architectures for artificial intelligence models. This section will detail the most frequently used basic deep learning tasks in histology and embryology practice and their application areas.

Classification is the most fundamental application area of the deep learning ecosystem, and it is the process of assigning a unique identifier to the whole of an image or to its microscopic sub-parts (patches). Based on the features it extracts from the image, the model generates a probability value for each class and determines the most appropriate category.

Defining the over all structure of a tissue section (e.g., differentiating liver, kidney, or lung tissue) or classifying specific regions within the tissue (e.g., stroma vs. epithelium) falls into this category. In histological analyses, entire slide images are divided into small pieces, each region is assigned to specific tissue categories, and tissue distribution is mapped (17).

In embryology, classifying embryo images according to quality is a fundamental application supporting the clinical decision-making process (24).

Object detection not only identifies the identity of a structure but also determines its location in the visual plane. The model classifies the object and defines its coordinates by placing bounding boxes around the target structures.

In embryology, determining the location of an embryo or blastocyst in the microscopic field allows the image to focus on the relevant region, speeding up the analysis process and reducing the data processing load.

In histology, critical structures such as cells in mitosis or specific cell populations can be automatically marked in large areas. This method enables the extraction of cell population break downs, especially in large areas where manual counting is impossible.

Although it does not offer detailed boundary delineation at the pixel level, it provide shigh efficiency in work flows requiring rapid scanning and quantitative counting of large data sets.

Segmentation forms the basis of morphometric analyses (area, perimeter, and geometric form measurements) conducted in histology and embryology studies. In this approach, the image is segmented in detail by determining the structure to which each pixel belongs, thus revealing structural boundaries with high precision. Segmentation is generally divided into two types: semantic and sample segmentation.

Semantic segmentation labels all objects of the same type as a single class. Forexample, separating the zona pellucida, trophectoderm, and iner cell mass regions in a blastocyst image is one of the are as where semantic segmentation is most successful. Segmentation-oriented networks (e.g., U-Net and SSS-Net) isolate embryonic structures from the back ground by classifying them at the pixel level, there by automating area, volumetric equivalent, or ratio analyses of the relevant regions (25).

Sample segmentation, on the other hand, distinguishes objects belong ingto the same class and in contact with eachother (e.g., neighboring cell nuclei) as independent samples. This method is necessary for the individual separation of thousands of nuclei in histological sections and the analysis of morphological features such as nuclear pleomorphism.

While classification systems categorize data into categories such as "present/absent" or "stage 1/stage 2," regression models generate continuous numerical values and probability scores. This approach plays a significant role, particularly in the analysis of dynamic developmental processes in embryology and quantitative parameters in histology. Deep learning models can predict out comes such as implantation probability or developmental potential as numerical scores from static images or time-lapse data (5, 26). Similarly, biological parameters such as the number of cells in a tissue section, the mean intercellular distance, or the time it takes for an embryo to reach a specific developmental stage can be quantitatively calculated directly from the image (22). This approach allows for the acquisition of objective and measurable biomarkers instead of subjective grading.

3.3. From Image to Data: Computational Transformation Process

In a digitized histology or embryology laboratory, a microscopic image is no longer treated merely as a visual "picture," but as a digital pixel matrix (tensor) that can be processed by a computer. When a biological tissue section is digitized, each pixel that makes up the image is converted into numerical values representing the light intensity, color components, and textural features at that point. This numerical representation makes it possibleto process

visual morphology in a way suitable for computational analysis and artificial intelligence models. For example, a standard RGB (Red-Green-Blue) histology image is represented by a computer as a three-dimensional matrix (height × width × 3 color channels). In this structure, each pixel is numerically encoded with intensity values corresponding to the red, green, and blue channels, typically ranging from 0 to 255. Thanks to this transformation, the dark purple color of a cell nucleus or the pinkish color of the cytoplasm cease to be merely aesthetic features and become concrete data points on whichthe model can perform mathematical operations.

Artificial intelligence models take these numerical matrices as input, analyze the statistical relationships between pixels, and identify biological structures recognized by the human eye (e.g., a blastocyst) through numerical representations.

Instead of memorizing the image as a whole pattern, deep learning models systematically analyze local regions. In this process, the model detects edge, texture, and structural patterns in each region by sliding small scanning windows (filters or nuclei) over the image. Thus, the image is hierarchically analyzed, starting from simple pixel-level features to more complex morphological representations. During this process, mathematical operations are performed between the pixel matrix and the filters, capturing local morphological patterns in specific regions of the image (e.g., the curvature of a cell membrane or the texture of the nucleus). This process allows the image to be separated from its raw pixel values and transformed into "feature maps" showingthelocation of edge, texture, and structural patterns. Thus, the algorithm begins to learn the content of the image not pixel by pixel, but through the meaningful local structures formed by these pixels (3).

One of the most powerful features of deep learning networks is their ability to organize there presentations they learn in a hierarchicalstructure; this approach offers a numerical modeling similar to how the human brain processes visual information in a layered manner.

The initial layers of the network detects impleedges, colortransitions, andcorners in theimage. As thelayersdeepen, these simple features combine to form cellular structures (e.g., nuclear shape or mitotic figures). In the deepest layers of the network, the model can encode more complex organizations formed by the aggregation of cellular structures (e.g., glandular organization or embryonic developmental stages) into more abstract and holistic representations. This hierarchical feature learning allows the model to automatically learn structural relationships ranging from visual details at the cellular level to larger-scale tissue organization.

The "learning" process of an artificial intelligence model is actually a continuous cycle of prediction and correction. The model makes a prediction for an image presented to it (e.g., "this embryo is of good quality") and compares this prediction to the actual result (expert label or pregnancy outcome). By calculating the difference (error) between the prediction it produces and the actual result, the model aims to minimize this difference and, for this purpose, gradually updates its internal parameters (weights).

During the training process, this feed backloop is repeated thousands of times; each time, the model updates its parameters by reducing its error and learns to produce predictions closer to the correct result. This iterative optimization process allows the model to spontaneously discover mathematical structures from the data that best represent bio-

logical variations. The most important indicator of success in medical AI applications is themodel's ability to produce reliable and accurate results not only on training data but also on new data it has not encountered before; in otherwords, the generalizability of the model. If the model "memorizes" (overfits) the specific details and random noise of the training data instead of learning the patterns in that data, it may fail on new images obtained from different centers, even though its training performance may appear high. This indicates that the generalizability of the model is limited (6, 27)

Technical factors such as staining differences, slice thickness, and scanner characteristics create large variations in histological images. For the model to be resilient to these variations, it is essential that the training data includes diverse samples from different laboratories and instruments.

Model strained with carefully cleaned and selected data set sunder laboratory conditions may show performance degradation when faced with more complex and noisy images encountered in clinical practice (e.g., artifact-containing or out-of-focus recordings). Therefore, the diversity of training sets to reflectreal-world conditions is vitalfor the reliability of artificial intelligence.

3.4. Basic Network Architectures in Histology and Embryology Applications

Deep learningapproaches do not consist of a single standard structure; different model architectures are preferred depending on thetype of biological problem addressed (e.g., classification, segmentation, or time seriesanalysis). The basic architectures commonly used in histology and embryology applications and considered virtually standard within the field, along with their main areas of application, are summarized below.

3.4.1. Image Analysis with Convolutional Neural Networks (CNNs)

Convolutional Neural Networks (CNNs), the most widely used deep learning architecture in histology and embryology, are the fundamental structure that enables the automatic analysis of cellular and textural information from microscopic sections. In histology, CNN-based methods allow for the automatic determination of cell nuclei, cytoplasm, and tissue boundaries, enabling a more objective assessment of tissue organization. Unlike classical methods, CNNs do not require expertstopre-define the visual features to be analyzed. Instead, the model learns the intrinsic patterns of the image directly from the data and represents them in a multilayered structure. Examining large histological and embryological sections by dividing them into small image segments allows CNNs to correlate local cellular features with the overall tissue organization. In embryology research, CNNs support the systematic examination of cellular differentiation patterns and morphogenetic structures in early developmental stages (14, 18).

CNN architectures operate through three fundamental components that transform images into meaningful representations:

a. **Convolutionlayers:** Forming the first stage of analysis, these layers automatically learn the spatial hierarchy in theimage by detecting low-level features such as edges,

textures, and shapes through filters that traverse the input image (e.g., an H&E section).

b. **Pooling Layers:** Feature maps obtained after convolution are processed by these layers, reducing their spatial dimensions; this process both reduces the computation alload and ensures that the model gains invariance against small shifts ordistortions in the tissue sample, thus keeping over fittin gunder control.

c. **FullyConnectedLayers:** Located at the end of the network, these layers take all the abstracted features extracted and compressed in the previous stages as a flattened vector and integrate this information to produce the final classification decision (e.g., cell type, tissue status, or embryo qualitye stimation).

3.4.2. U-Net anditsVariations (3D U-Net, V-Net)

U-Net is a CNN-based architecture developed for biomedical image segmentation and is considered a de facto standard in the fields of histology and embryology. Its name is based on the "U" conditions, which include the characteristics of the encoder and decoder parameters (28, 29). This architecture provides precise pixel-level segmentation while preserving detailed layered details when processing structures in a multilayered representation space in the image (3). Its three-dimensional variations (3D U-Net, V-Net) play a significant role in volumetric segmentation of structures such as the kidney, brain, and vascular systems in model organs (13, 14). It is widely used in histology and embryology for the fragmentation of blastocyst components (inner cell cells, trophectoderm, zona pellucida) and for determining the boundaries of cells in histological sections (4, 19, 25).

3.4.3. HoVer-Net (Horizontal-Vertical Net)

HoVer-Net is a specialized architecture developed for both segmentation and classification of cell nuclei in histological images. It offers high accuracy in the sample segmentation area, especially by enabling the separate identification of nuclei that are in contact with each other or densely clustered. This approach provides a significant advantage in quantitative analyses such as counting dense cell populations and determining cellular

3.4.4. ResNet (Residual Networks)

ResNet is an architecture with residual connection structure that enables more stable training of deep networks (31). In histological sections, it shows high performance in tissue classification and cellular phenotype analysis. In embryology, it is preferred especially in studies such as blastocyst grading, ploidy prediction and implantation success prediction (23).

3.4.5. Inception (GoogLeNet)

The Inception (GoogLeNet) architecture is notable for its modular structure capable of feature extraction at different scales. This feature allows for the simultaneous evaluation of

both fine morphological details at the cellular level and broader tissue organization (32). Inception-based models have been used in systems such as STORK, developed for blastocyst quality assessment, providing more objective analyzes that reduce inter-embryologist variability (33). Hybrid approaches combined with U-Net increase spatial accuracy in the segmentation of embryological structures (3). The trophectoderm (TE) is one of the main components of the 5-day-old human embryo (blastocyst) that is related to embryo quality. Precise segmentation of the TE is a crucial step in achieving automated human embryo quality assessment based on morphological image features. Automated segmentation of the TE is a challenging task, and previous studies on this topic are quite limited. Rad et al. (2020) proposed four fully convolutional deep learning models for accurate segmentation of the TE in microscopic images of human blastocysts. In addition, a multiscale ensemble method was proposed that combines five models trained at various scales and balances the quantity and quality of spatial information. Furthermore, synthetic embryo images were generated for the first time to address the lack of data in training deep learning models. These synthetically generated images have proven effective in filling the generalization gap in deep learning when limited data is available for training. In particular, the proposed Inceptioned U-Net model outperforms the most advanced methods by 10.3% in Accuracy, 9.3% in Dice Coefficient, and 13.7% in Jaccard Index. Further experiments were conducted to highlight the effectiveness of the proposed models compared with some new deep learning-based segmentation methods. This multiscale representational power contributes to a more holistic modeling of tissue heterogeneity (3).

3.4.6. RecurrentNeural Networks (RNN) andLongShort-Term Memory (LSTM)

RNN and LSTM architectures are structures that can analyze the time dimension beyond static images. They play an important role, especially in embryology, in the evaluation of time-lapse imaging data. Long Short-Term Memory (LSTM) networks can provide predictions about implantation potential or developmental outcomes by learning successive changes in the developmental process of the embryo (9). These models enable quantitative analysis of dynamic processes such as cleavage timings and morphokinetic patterns.

4. Clinical and Research Applications of Virtual Histology

Deep learning algorithms have not only improved image quality in histology laboratories but have also introduced new standards that preserve tissue integrity, enable multiple staining, and allow three-dimensional analyses. This section will discuss the innovative solutions that these technologies bring to basic histology and tissue analysis.

4.1. Preserving Tissue Integrity and Rapid Analysis with Virtual Histology

Traditional histochemical staining methods involve tissue tracking and chemical processing steps; these processes can lead to irreversible changes in the physical structure

of the tissue. In contrast, deep learning-based virtual histology approaches allow for the preservation of tissue integrity by converting label-free images into H&E-like representations via digital algorithms without exposing the tissue to chemical staining processes (12). Raw images obtained by UV-photoacoustic microscopy or autofluorescence imaging are converted into virtual H&E images via generative models such as CycleGAN or E-CUT (11). Images obtained with this method show a high degree of morphological similarity and diagnostic suitability with sections prepared by traditional methods. Since the virtual staining approach does not require chemical fixation or traditional staining processes on the tissue, it allows the same sample to be used in an intact form for DNA/RNA extraction or other molecular analyses after imaging (12). In this way, researchers can both perform morphological evaluation and preserve the tissue for genetic and molecular investigations from a single biological sample. In evaluating complex tissue organizations, serial sections are often required to visualize different components individually, such as collagen fibers or basal membranes. Deep learning-based virtual staining approaches can digitally generate different histological staining styles, such as H&E, Masson Trichrome, or silver stain (Jones stain), from a single label-free image. This method allows for multidimensional and comprehensive structural analyses to be performed on limited quantities of valuable tissue samples (e.g., rare biopsies or embryonic tissues) without tissue loss (2).

4.2. QuantitativeModeling of Cellular Phenotypes

Artificial intelligence is not limited to optimizing histological images visually, but can also convert cellular and textural features that the human eye has difficulty distinguishing into numerical parameters. This transformation moves histology from a predominantly descriptive field to an analytical discipline that produces quantitative and measurable data. Advanced architectures such as HoVer-Net can separate nuclei that are in contact or overlapping in tissue sections individually using the "instance segmentation" method (30). General-purpose segmentation algorithms such as Cellpose can automatically distinguish the cytoplasm and nucleus of cells in different types of microscopy without requiring additional retraining; thus, they can calculate morphometric parameters such as cell area, perimeter length, etc. (34). These quantitative data allow for the objective evaluation of organizational features such as cell density or nucleus/cytoplasm ratio in tissue development and regeneration studies.

In histological analysis of organs with tubular structures such as the kidney or testis, morphometric parameters such as lumen opening and tubule diameter can be measured with high precision through U-Net-based models. In particular, the automatic separation and three-dimensional visualization of proximal and distal tubules in kidney tissue provides quantitative and comparable data on the integrity of tissue architecture (14). In addition, deep learning models allow for morphometric analysis by segmenting the vascular networks (intersegmental vessels) of model organisms such as zebrafish in developmental studies in 3D (13).

4.3. Three-Dimensional Organ Mapping and Volumetric Histological Analysis

Since the traditional histological approach evaluates three-dimensional organ structures through two-dimensional thin sections, the spatial context of the tissue can be partially lost. In contrast, next-generation deep learning applications integrate serial images to create three-dimensional reconstructions, thus enabling the development of a new analysis paradigm defined as "volumetric histology". The HistoTRUST platform creates a 3D histological map of the entire organ by serially imaging and virtually staining the surface of fresh tissue blocks cut with a vibratome using deep learning. This technology makes it possible to seamlessly track the vascular networks and anatomical structures (e.g., hippocampus or glomeruli) of organs such as the brain, heart, liver, and kidney in a 3D environment. In addition, this method eliminates the workload of traditional serial sectioning and staining processes, which can take weeks, reducing the process to hours or days (15). Time series volumetric data obtained by light-sheet microscopy can be analyzed using deep learning-based tools such as ELEPHANT, and cell migration and proliferation processes can be monitored in four dimensions (3D + time) (22). For example, mesenchymal cell proliferation in mouse embryos can be segmented with 3D U-Net models; thus, morphogenetic movements and volumetric changes in the organogenesis process can be mapped in detail (4).

Deep learning and digitalization processes are transforming not only research and clinical applications but also the methodological framework of histology education. The traditional education model based on the use of physical microscopes is increasingly being replaced by Virtual Microscopy applications; this allows students to more easily access digital tissue preparations and work interactively with images. Virtual microscopy ensures that rare or technically difficult-to-prepare histological specimens (WSI) are presented to all students with equal and high image quality. Students can examine tissue details by navigating and magnifying digital slides, and this process is found to be more user-friendly compared to using an optical microscope. Digitized slides can be shared via cloud-based platforms, allowing students to work simultaneously on the same image, annotate, and create shared notes. Various studies have shown that virtual microscopy applications improve students' success in recognizing histological structures and strengthen the learning process by providing access outside the lab (35).

5. AI-BasedApproaches in Clinical Embryology

One of the most crucial stages in assisted reproductive techniques is selecting and transferring the embryo with the highest probability of pregnancy. Traditional morphological evaluation systems (e.g., Gardner classification) are largely subjective, relying on the embryologist's experience and leading to evaluation differences of up to 83% among observers (18).

Deep learning-based approaches aim to reduce this subjective variation, transforming embryo selection into a more standardized and repeatable process. These algorithms aim

to predict implantation potential more objectively by analyzing complex patterns that the human eye has difficulty distinguishing (e.g., fine tissue texture or cytoplasmic dynamics). Single (static) images obtained with traditional microscopy are the most common data source for deep learning models (especially CNNs). Instead of mimicking the manual grading done by embryologists, these systems focus on directly predicting the embryo's live birth potential. Deep learning frameworks such as STORK, trained with thousands of embryo images, have achieved an accuracy rate of over 98% (AUC > 0.98) in classifying blastocysts as "good" or "poor" quality. These models can automatically score inner cell mass and trophectoderm quality by analyzing embryo images at the pixel level and show a high degree of agreement with embryologists' decisions (33).

Traditional morphological grading systems may not always reliably predict pregnancy outcome. In contrast, AI-based systems such as Life Whisperer have been trained not only on morphological quality but also on the "fetal heartbeat" result, a direct indicator of live pregnancy. These systems have reported 24.7% higher accuracy in predicting embryo viability compared to embryologists using standard optical microscope images (26). Deep learning models (e.g., 3D-CNN or LSTM networks) can automatically label the transition times of the embryo from the 2-cell stage to the blastocyst stage (t2, t3, t5, tB) by analyzing time-lapse videos (5, 18).

Systems such as iDAScore (Intelligent Data Analysis Score) can rank embryos according to their implantation potential based on raw video data without human intervention, speeding up the process tenfold compared to manual evaluation (36).

Recently developed models such as BELA (Blastocyst Evaluation Learning Algorithm) and FEMI (Foundational Embryology Model for Imaging) attempt to predict chromosomal abnormalities (aneuploidy) by focusing not just on a single image, but on the embryo's developmental video (especially between 96-112 hours) (23). Artificial intelligence tools such as ERICA (Embryo Ranking Intelligent Classification Algorithm) can predict the probability of an embryo being euploid (having normal chromosomes) by analyzing a single blastocyst image. These models can distinguish aneuploid embryos with 70% accuracy and help select the healthiest embryo without biopsy (37, 38). Figure 2 shows examples of blastocyst photomicrographs before and after preprocessing and segmentation enhancement, along with actual segmentation data.

Including not only the image but also maternal age and clinical data in the model (multimodal approach) increases the success of ploidy prediction. For example, models such as STORK-A or FEMI can achieve high success in distinguishing complex aneuploidies by combining embryo image with maternal age (23). U-Net-based models can distinguish the inner cell mass and trophectoderm regions in blastocyst images with high accuracy. Customized approaches such as SSS-Net reliably segment these structures, allowing for more objective evaluation of parameters such as the degree of embryo expansion and cellular density (19, 25). In this way, embryo quality can be expressed not only based on visual interpretations but also through measurable and comparable quantitative data. Artificial intelligence applications are also used in evaluating the suitability of the embryo for biopsy or freezing (vitrification) procedures. For

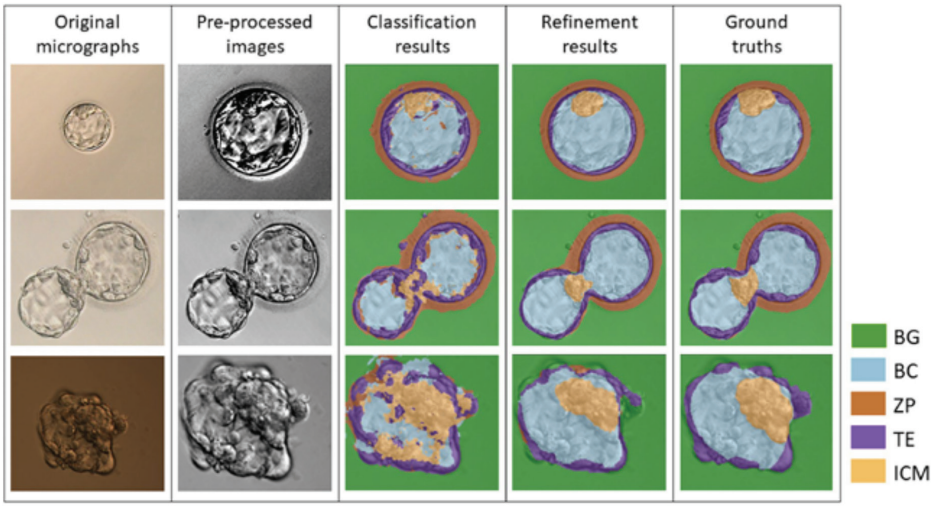


Figure 2. Examples of the original blastocyst micrographs, the images after pre-processing, before and after the segmentation refinement, and the ground truth. Please note that these images might have been stretched, shrunk, or cropped for aesthetic purposes, but the pixel values remained unaltered (38).

example, models have been developed that can determine the most suitable region on the zona pellucida for laser application during assisted budding with high accuracy (8). In IVF laboratories, mixing up embryos or transferring them to the wrong patient is one of the most feared mistakes. Artificial intelligence minimizes this risk by recognizing embryos like a "face recognition" system. Each embryo has its own unique developmental process and morphological characteristics. AI-based systems (e.g., FEMI or CNN-based approaches) can determine with high accuracy whether images of the embryo obtained at different time points belong to the same embryo by comparing them (23). This technology offers a reliable "digital verification" mechanism based on the embryo's own biological characteristics, in addition to RFID chips (Radio Frequency Identification) or manual control processes (8). Thus, laboratory safety is increased and the risk of sample mix-ups is reduced.

6. Transparency and Trust in Medical Deep Learning Models

Despite the high analytical and predictive success of deep learning algorithms in histology and embryology laboratories, one of the biggest obstacles to integrating these systems into routine laboratory workflows is the black box problem. The complex and multi-layered structure of deep neural networks, consisting of millions of parameters, makes it difficult for researchers to understand how the model arrives at a specific morphological classification or embryo quality score (1, 9). High accuracy rates alone are not sufficient for experts to trust the system and ensure the reliability of the results in laboratory decision-making

processes; it is a scientific necessity that the decision made by artificial intelligence be transparent, explainable, and demonstrably based on biological principles (1, 2).

6.1. From Black Box toTransparency: Explainable AI

To address this trust issue, Explainable AI (XAI) approaches have been developed in the literature (1). XAI methods aim to transform the complex computations occurring in the inner layers of deep learning models into visual evidence that histologists and embryologists can interpret in a biological context (1, 9).

Heat Maps and Class Activation Mapping (CAM): One of the most commonly used XAI methods, Class Activation Maps (CAM, Grad-CAM), shows which microscopic regions of the image the model focuses on when making its prediction via a heat map (1, 39). For example, when evaluating the quality of an embryo or classifying a complex tissue architecture, the cellular structures that most influence the model's decision are highlighted with warm colors (red/yellow) on the map, providing the expert with a direct morphological justification (21, 23).

Attention Mechanisms contribute to making the decision-making process more understandable in whole histological slide images (WSI) that can reach gigapixel dimensions. Attention-based models such as CLAM automatically identify the most diagnostically distinctive sub-regions within the whole slide, making it visible which areas the model focuses on (21).

• Thanks to this approach, experts can monitor which specific cell groups (e.g., a particular epithelial area or trophectoderm cells) the algorithm relies on in the tissue section and check whether this assessment is consistent with underlying histological information (21, 23).

6.2. Uncertainty Measurement and Clinical Decision Support

Another important dimension of transparency is that the model not only produces a result but also can numerically determine how accurate or inaccurate that prediction is at any given time. (40). Artificial intelligence models encounter two basic types of uncertainty in the analysis process: "aleatoric uncertainty" arising from image quality, laboratory conditions, or biological variability, and "epistemic (model) uncertainty" arising from the model's inability to represent all biological variations due to the limitations of its training data (7, 40). By using appropriate uncertainty estimation methods, the confidence level regarding the outputs produced by the model can be quantitatively expressed, thus increasing the interpretability of the decision-making process (1, 40). If the model has a high uncertainty (low confidence) score for the analysis of an image (e.g., an out-of-focus scanned section or an embryo showing atypical cell division), the AI excludes this sample from the system instead of forcing it to produce an erroneous result. This uncertain image, excluded from the decision-making process, is referred directly to an expert histologist or embryologist for manual and more detailed morphological examination, thus preventing laboratory errors (1).

6.3. Ethical Approaches, Bias, and Human-Machine Collaboration

The standardization and widespread application of artificial intelligence models in laboratory settings is not only a technical issue but also a data-driven ethical matter. For algorithms to produce fair and unbiased decisions, training data should not be based on a single center or a homogeneous patient group (9, 41). Including data from populations with different demographic characteristics, various microscopy systems, and variable histological staining protocols in the training process is a fundamental requirement in reducing algorithmic bias (17). This diversity allows models to adapt not only to a specific data distribution but also to real clinical conditions, increasing their generalizability. Artificial intelligence systems should be positioned not as autonomous decision-makers replacing human judgment in basic sciences and laboratory practice, but as decision support tools supporting researchers and clinicians (2, 17). Using artificial intelligence models developed within the framework of transparency and reliability principles, together with the supervision of experts in the field (human-in-the-loop), will increase analytical accuracy and contribute to the development of a safer and more standardized evaluation approach in histology and embryology workflows (21, 22, 41).

7. Results and Potential Areas for Development

WSI and time-lapse imaging systems, which form the basis of digital pathology, have transformed this field into a quantitative and data-driven discipline by enabling the conversion of histological and embryological data into large-scale numerical datasets. This has made it possible to quantitatively analyze high-dimensional morphological patterns and dynamic cellular changes in histological and embryological images through deep learning algorithms. In the field of basic histology, revolutionary innovations have been achieved thanks to deep learning models, such as quantitative phenotyping of cells and three-dimensional (3D) volumetric mapping of organs with virtual staining applications that preserve tissue integrity without the need for chemical treatments. Simultaneously, in clinical embryology, AI-assisted systems have minimized inter-observer variability, leading to a more standardized and reproducible approach. AI-assisted analyses are transforming embryo selection from subjective morphological evaluation into a data-driven and reproducible clinical decision-making process. However, the full integration of AI into laboratory routines cannot be achieved solely through high accuracy rates. It is emerging as a critical requirement that the results produced by deep learning architectures be transparent, biologically based, and explainable. In the histology and embryology laboratories of the future, AI models that can provide visual explanations of algorithmic decisions through Class Activation Maps (CAMs) and also numerically express the level of uncertainty regarding their predictions are expected to become standard analytical tools. In addition, the development of models trained with large and heterogeneous datasets obtained from different imaging devices and various demographic populations, and free from algorithmic bias effects, will continue to be one of the fundamental research priorities of the coming period in terms of the reliability, generalizability, and clinical applicability of these systems. In summary, deep learning algorithms should be positioned in histology

and embryology research, clinical studies, and education not as autonomous systems that replace human expertise, but as advanced analytical tools that establish relationships between complex data sets, standardize evaluation processes, and support researchers' decisions with a human-in-the-loop approach. The synergistic combination of technological advancements and biological expertise will both expand analytical boundaries in histology and embryology and contribute to the creation of new standards in future laboratory workflows. In this context, artificial intelligence-based systems can be considered a powerful "third eye," accelerating microscopic evaluation processes, providing more objective and repeatable analyses, and enabling a more systematic presentation of morphological details.

8. References

1. Abdelsamea, M. M., Zidan, U., Senousy, Z., Gaber, M. M., Rakha, E., &Ilyas, M. (2022). A survey on artificial intelligence in histopathology image analysis. WIREs Data Miningand Knowledge Discovery, 12(6), e1474. https://doi.org/10.1002/widm.1474
2. Komura, D., Ochi, M., &Ishikawa, S. (2025). Current status and future perspectives of artificial intelligence in pathology: A comprehensive review of the literature from 2018 to 2024. ComputationalandStructuralBiotechnologyJournal, 27, 383–400. https://doi.org/10.1016/j.csbj.2024.12.033
3. Rad, R. M., Saeedi, P., Au, J., &Havelock, J. (2020). Trophectoderm segmentation in human embryo images via inceptioned U-Net. Medical Image Analysis, 62, 101612. https://doi.org/10.1016/j.media.2019.101612
4. LoVercio, L. D., Green, R. M., Robertson, S., Guo, S., Dauter, A., Marchini, M., Vidal-García, M., Zhao, X., Mahika, A., Marcucio, R. S., Hallgrímsson, B., &Forkert, N. D. (2022). Segmentation of tissues and proliferating cells in light-sheet microscopy images of mouse embryos using convolutional neural networks. IEEE Access, 10, 105084–105100. https://doi.org/10.1109/access.2022.3210542
5. Berntsen, J., Rimestad, J., Lassen, J. T., Tran, D., &Kragh, M. F. (2022). Robust and generalizable embryo selection based on artificial intelligence and time-lapse image sequences. PLOS ONE, 17(2), e0262661. https://doi.org/10.1371/journal.pone.0262661
6. Shafi, S., &Parwani, A. V. (2023). Artificial intelligence in diagnostic pathology. DiagnosticPathology, 18, 109.
7. Khened, M., Kori, A., Rajkumar, H. et al. (2021). A generalized deeplearning framework forwhole-slide image segmentation and analysis. SciRep 11, 11579. https://doi.org/10.1038/s41598-021-90444-8
8. Jiang, V. S., &Bormann, C. L. (2023). Artificial intelligence in the in vitro fertilization laboratory: A review of advancements over the last decade. FertilityandSterility, 120(1), 17–23. https://doi.org/10.1016/j.fertnstert.2023.05.149
9. AlSaad, R., Abusarhan, L., Odeh, N., Abd-alrazaq, A., Choucair, F., Zegour, R., Ahmed, A., Aziz, S., &Sheikh, J. (2025). Deep learning applications for human embryo assessment using time-lapseimaging: Scoping review. Frontiers in Reproductive-Health, 7, 1549642. https://doi.org/10.3389/frph.2025.1549642
10. Zhu, J. Y. et al. Unpaired image-to-image translation using cycle-consistent adversarial networks. In: Proceedings of the 2017 IEEE International Conference on ComputerVision, 2223–2232. Venice, Italy: IEEE, 2017.
11. Yoon, C., Park, E., Misra, S. et al. (2024). Deeplearning-basedvirtualstaining, segmentation, andclassification in label-free-photoacoustichistology of humanspecimens. LightSciAppl 13, 226. https://doi.org/10.1038/s41377-024-01554-7
12. Martell, M.T., Haven, N.J.M., Cikaluk, B.D. et al. (2023). Deeplearning-enabledrealisticvirtualhistologywithultravioletphotoacousticremotesensingmicroscopy. NatCommun 14, 5967. https://doi.org/10.1038/s41467-023-41574-2
13. Yin J, Yang G, Qin X, Li H, and Wang L (2022) Optimized U-Net model for 3D light-sheetimagesegmentation of zebra fishtrunkvessels, Biomed. Opt. Express 13, 2896-2908.
14. Naert, T., Çiçek, Ö., Ogar, P., Bürgi, M., Shaidani, N.-I., Kaminski, M. M., Xu, Y., Grand, K., Vujanovic, M., Prata, D., Hildebrandt, F., Brox, T., Ronneberger, O., Voigt, F. F., Helmchen, F., Loffing, J., Horb, M. E., Willsey, H. R., &Lienkamp, S. S. (2021). Deeplearning is widelyapplicabletophenotypingembryonicdevelopmentanddisease. Development, 148(21), dev199664. https://doi.org/10.1242/dev.199664
15. Kang L, Yu W, Zhang Y, Chen Z, andWong T.T.W. (2023). Deep Learning EnablesRapidWhole-Organ HistologicalImaging-withUltraviolet-ExcitedSectioningTomography. ACS Photonics, 10 (10), 3541-3550. DOI: 10.1021/acsphotonics.3c00536
16. Bormann, C. L., Thirumalaraju, P., Kanakasabapathy, M. K., Kandula, H., Souter, I., Dimitriadis, I., Gupta, R., Pooniwala, R., &Shafiee, H. (2020). Performance of a deeplearningbasedneural network in theselection of humanblastocystsforimplantationeLife9:e55301 https://doi.org/10.7554/eLife.55301
17. Kobayashi, S., Saltz, J. H., Yang, V. W. (2021). State of machineanddeeplearning in histopathologicalapplications in digestivediseases. World J Gastroenterol. 28;27(20):2545-2575. doi: 10.3748/wjg.v27.i20.2545. PMID: 34092975; PMCID: PMC8160628.

18. Mapstone, C., Plusa, B. (2025). Machine learningapproachesforimageclassification in developmentalbiologyandclinicalembryology. Development, 152 (4): DEV202066. doi: https://doi.org/10.1242/dev.202066
19. Harun, M. Y., Huang, T., &Ohta, A. T. (2019). Inner cellmassandtrophectodermsegmentation in humanblastocystimagesusingdeepneuralnetwork. In2019 IEEE 13th International Conference on Nano/MolecularMedicineandEngineering (NANOMED) (pp. 214–219). IEEE.
20. Ali, M., Benfante, V., Basirinia, G., Alongi, P., Sperandeo, A., Quattrocchi, A., Giannone, A. G., Cabibi, D., Yezzi, A., DiRaimondo, D., Tuttolomondo, A., &Comelli, A. (2025). Applications of artificialintelligence, deeplearning, andmachinelearningtosupporttheanalysis of microscopicimages of cellsandtissues. Journal of Imaging, 11(2), 59. https://doi.org/10.3390/jimaging11020059
21. Lu, M. Y., Williamson, D. F. K., Chen, T. Y., Chen, R. J., Barbieri, M., &Mahmood, F. (2021). Data-efficient and weakly supervised computational pathology on whole-slideimages. Nature Biomedical Engineering, 5(6), 555–570. https://doi.org/10.1038/s41551-020-00682-w
22. Sugawara, K., Çevrim, Ç., &Averof, M. (2022). Trackingcelllineages in 3D byincrementaldeeplearning. eLife, 11, e69380. https://doi.org/10.7554/eLife.69380
23. Rajendran, S., Rehani, E., Phu, W. et al. (2025). A foundational model for in vitro fertilizationtrained on 18 million timelapse images. Nat Commun 16, 6235. https://doi.org/10.1038/s41467-025-61116-2
24. Chen, K., Zuo, J., Han, W., &Guo, J. (2025). Intelligent assisted reproduction: Innovativeapplications of artificial intelligence in embryo health assessment. LabMed Discovery, 2, 100075. https://doi.org/10.1016/j.lmd.2025.100075
25. Arsalan, M., Haider, A., Choi, J., & Park, K. R. (2022). Detecting blastocyst components by artificial intelligence for human embryological analysis toimprovesuccess rate of in vitro fertilization. Journal of Personalized Medicine, 12(2), 124. https://doi.org/10.3390/jpm12020124VE
26. VerMilyea, M., Hall, J. M. M., Diakiw, S. M., Johnston, A., Nguyen, T., Perugini, D., Miller, A., Picou, A., Murphy, A. P., &Perugini, M. (2020). Development of an artificial intelligence-based assessment model forprediction of embryo viability using static images captured by optical light microscopy during IVF. Human Reproduction, 35(4), 770–784. https://doi.org/10.1093/humrep/deaa013
27. Isensee, F., Jaeger, P. F., Kohl, S. A. A., Petersen, J., &Maier-Hein, K. H. (2021). nnU-Net: a self-configuring method for deep learning-based biomedical image segmentation. Nature Methods, 18(2), 203–211. https://doi.org/10.1038/s41592-020-01008-z
28. Ronneberger, O., Fischer, P. &Brox, T. (2015). U-Net: Convolutional Networks for Biomedical Image Segmentation. Preprint at arXiv 1505.04597.
29. https://lmb.informatik.uni-freiburg.de/people/ronneber/u-net/
30. Graham, S., Vu, Q. D., Raza, S. E. A., Azam, A., Tsang, Y. W., Kwak, J. T., &Rajpoot, N. (2019). Hover-Net: Simultaneous segmentation and classification of nuclei in multi-tissue histology images. Medical Image Analysis, 58, 101563. https://doi.org/10.1016/j.media.2019.101563
31. He, K., Zhang, X., Ren, S., & Sun, J. (2016). Deep residual learning for image recognition. InProceedings of the IEEE conference on computervisionandpatternrecognition (pp. 770-778).
32. Szegedy, C., Liu, W., Jia, Y. Q., Sermanet, P., Reed, S., Anguelov, D., et al. (2015). Going deeper with convolutions. Proc-CvprIeee. (2015):1–9. doi: 10.48550/arXiv.1409.4842
33. Khosravi, P., Kazemi, E., Zhan, Q., Malmsten, J. E., Toschi, M., Zisimopoulos, P., Sigaras, A., Lavery, S., Cooper, L. A. D., Hickman, C., Meseguer, M., Rosenwaks, Z., Elemento, O., Zaninovic, N., &Hajirasouliha, I. (2019). Deep learning enables robust assessment and selection of human blastocysts after in vitro fertilization. npjDigitalMedicine, 2, 21. https://doi.org/10.1038/s41746-019-0096-y
34. Stringer, C., Wang, T., Michaelos, M., &Pachitariu, M. (2021). Cellpose: A generalist algorithm for cellular segmentation. Nature Methods, 18(1), 100–106. https://doi.org/10.1038/s41592-020-01018-x
35. Magnani, F., Demaria, E., Ambrosi, F., Sala, C., Pasquinelli, G., Fiorentino, M., & Gri, G. (2025). The positive impact of virtual microscopy on histopathology education: A comparative, student-centered study. Advances in PhysiologyEducation, 49, 136–146. https://doi.org/10.1152/advan.00110.2024
36. Illingworth, P. J., Venetis, C., Gardner, D. K., Nelson, S. M., Berntsen, J., Larman, M. G., Agresta, F., Ahitan, S., Ahlström, A., Cattrall, F., Cooke, S., Demmers, K., Gabrielsen, A., Hindkjær, J., Kelley, R. L., Knight, C., Lee, L., Lahoud, R., Mangat, M., ... Hardarson, T. (2024). Deep learning versus manual morphology-based embryo selection in IVF: A randomized, double-blind non inferiorityтrial. Nature Medicine. https://doi.org/10.1038/s41591-024-03166-5
37. Chavez-Badiola, A., Flores-Saiffe-Farías, A., Mendizabal-Ruiz, G., Drakeley, A. J., Cohen, J. (2020). Embryo Ranking Intelligent Classification Algorithm (ERICA): artificial intelligence clinical assistant predicting embryo ploidyandimplantation. ReprodBiomed Online.41(4):585-593. doi: 10.1016/j.rbmo.2020.07.003. Epub 2020 Jul 5. PMID: 32843306.
38. Farias, A. F., Chavez-Badiola. A., Mendizabal-Ruiz, G., Valencia-Murillo, R., Drakeley, A., Cohen, J., Cardenas-Esparza, E. (2023). Automated identification of blastocystregions at differentdevelopmentstages. SciRep. 2;13(1):15. doi: 10.1038/s41598-022-26386-6. PMID: 36593239; PMCID: PMC9807603.
39. Selvaraju, R. R., Cogswell, M., Das, A., Vedantam, R., Parikh, D., &Batra, D. (2019). Grad-cam: Visual explanationsfromdeep Networks viagradient-basedlocalization. International Journal of ComputerVision, 128(2), 336–359. https://doi.org/10.1007/s11263-019-01228-7)41)41)
40. Gudhe, N.R., Kosma, VM., Behravan, H. et al. (2023). Nuclei instance segmentation from histopathology images using Bayesi andropout based deeplearning. BMC MedImaging 23, 162 (2023). https://doi.org/10.1186/s12880-023-01121-3
41. Ma, Y., Jamdade, S., Konduri, L. et al. (2025). AI in Histopathology Explorer for comprehensive analysis of the evolving AI land scape in histopathology. npjDigit. Med. 8, 156.https://doi.org/10.1038/s41746-025-01524-2

CHAPTER 8

From Physiological Mechanisms to Computational Models: Artificial Intelligence in Physiology

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1. Introduction

Physiology is a fundamental biomedical science that examines how normal functions arise in living organisms at the cellular, tissue-specific, and systemic levels. This discipline aims to explain multiscale processes ranging from ion channels to organ systems in accordance with experimental observations and physical principles. In the classical physiological approach, knowledge production is based on controlled experiments, measurable variables, and the identification of causal relationships among these variables (1-3).

At the center of traditional physiological research are mechanistic models aimed at explaining the functioning of biological systems. These models attempt to represent the processes underlying a specific physiological output (for example, cardiac output, neural firing pattern, or gas exchange) through mathematical or conceptual frameworks. The strongest aspect of mechanistic models is their explanatory nature and their presentation of physiological knowledge within a causal context. However, this approach has limitations in terms of scalability and generalizability, particularly in situations where multiple organ systems interact simultaneously or where high-dimensional data generation is involved (4).

Artificial intelligence (AI) is an interdisciplinary field of research that examines the theoretical foundations and applications of artificial "agents" that process inputs perceived from their environment and generate actions directed toward specific goals within that environment (5). In this context, AI provides a conceptual framework for approaches that aim to abstract the information processing, adaptation, and decision-making characteristics of biological systems and transform them into computational models. In the current policy and standards literature, AI systems are defined as machine-based systems that, in line with explicit or implicit objectives, infer from the data they receive to generate

outputs such as predictions, classifications, decisions, or recommendations; that can influence physical or virtual environments through these outputs; and that can exhibit certain levels of autonomy and post-deployment adaptability (6).

Machine learning (ML), one of the core subfields of AI, is based on the principle that a computer program's performance on a specific task improves in a measurable manner through experience or data; this approach is classically formulated within the framework of the relationship between task, experience, and performance measure (7). When considered in the context of physiology, ML methods offer powerful tools for modeling the computational counterparts of biological mechanisms such as neural networks, homeostatic regulation, feedback loops, and adaptive responses, for extracting meaningful patterns from large-scale physiological data, and for analyzing multilevel biological processes in an integrated manner.

In recent years, in parallel with advances in biomedical technologies, the amount and diversity of data generated in the field of physiology have increased markedly. Continuous physiological monitoring systems, high-resolution biosignals, and electronic health records have led researchers to work with large-scale datasets that are now difficult to handle using traditional analytical methods. In this context, AI and ML methods have emerged as data-driven approaches focused on extracting patterns from these complex data structures (8).

AI-based methods have the capacity to model statistical relationships in data without relying on a predefined mechanistic assumption regarding physiological systems. In particular, deep learning approaches have been extensively investigated because of their ability to capture short- and long-term dependencies in physiological signals with time-series characteristics. Nevertheless, even when many of these methods achieve high accuracy, the outputs they generate often remain limited in terms of interpretability and causal explanation. In the literature, this situation is described as the "black box" nature of AI models and is considered a significant methodological issue in the production of physiological knowledge (9).

At this point, evaluating the relationship between physiology and AI solely within the framework of a "new analytical tool" is insufficient. The core discussion concerns how data-driven models can be integrated with physiological knowledge, under which conditions they can provide meaningful physiological inferences, and in which situations they remain limited to correlation-based predictions. The existing literature indicates that, rather than replacing mechanistic physiological knowledge, AI methods can assume a complementary role to this knowledge when used appropriately (10).

The purpose of this section is to clarify the relationship between mechanistic explanations used in physiology and computational and data-driven models, and to present- in light of current and verifiable literature- how AI methods contribute to the production of physiological knowledge, what limitations they have, and under which conditions they can generate scientifically meaningful results. Within this framework, application areas ranging from physiological signals to clinical datasets, as well as methodological requirements and conceptual boundaries, will be addressed with a cautious perspective.

2. Mechanistic Models and Computational Approaches in Physiology

2.1. Definition of the Mechanistic Model: "Modeling the System" and the Goal of Causality

Mechanistic physiological models aim to explain the behavior of biological systems through mathematical or formal representations of known physical and chemical processes and their interactions with one another. This approach is positioned along the line of "modelling the system," in the terminology of Carson & Cobelli. The objective is to represent the physiological mechanisms underlying the observed input-output behavior under explicit assumptions (4).

Guyton & Hall and Ağar et al. consider physiology as a discipline that seeks to understand the cell-, tissue-, and organ-level mechanisms that generate measured outputs, rather than focusing solely on the outputs themselves, and they particularly emphasize the goal of explaining physiological principles in the language of molecular and physical sciences. This emphasis explains why mechanistic models constitute a persistent methodological backbone in physiology. The explanatory goal requires not only a good "fit," but also an interpretable and testable structural representation (1, 2).

In this context, typical forms of mechanistic models include:

- Representation of dynamic processes using differential equations (e.g., flow-pressure relationships, feedback dynamics) (3),
- Tracking of substance/energy flows using compartmental models (e.g., metabolism, endocrine system) (2),
- Representation of spatial heterogeneity using distributed-parameter models. Carson & Cobelli systematically frame that physiological systems can be modeled using classifications such as linear/nonlinear; deterministic/stochastic; time-varying/time-invariant; lumped/distributed (4).

2.2. Why "Mechanistic Models" are Challenging: Complexity, Scalability, and Measurement Constraints

Physiological systems are multiscale and hierarchical structures. Feedback and control mechanisms exist across molecular, cellular, organ, and organism levels. Carson & Cobelli emphasize that physiological complexity (nonlinearity, stochasticity, time variation, etc.) and measurement limitations give rise to the "need for models"; in many cases, quantities that cannot be measured directly require inference through models based on indirect measurements (4).

This situation produces three fundamental methodological problems in practice:
Parameterization and identifiability: The parameters of a model may not be uniquely identifiable from data, even under ideal conditions. For this reason, Carson & Cobelli's treatment of a priori (structural) identifiability as a "necessary prerequisite for parameter

estimation" is critical (4). This issue is also discussed in the modern systems biology literature in terms of the notion that "if parameters cannot be uniquely identified, some parts of the model are more ambitious than what the data allow" (11).

Model validation and the "garbage paradigm": Carson & Cobelli discuss model validation through steps such as comparing system behavior with model output, examining residuals, and evaluating the "reasonableness" of parameters that have physiological counterparts. They also particularly emphasize that even a perfect model will produce poor results when fed with poor data (the "garbage paradigm") (4, 12).

Generalizability and context dependence (domain of validity): The same physiological process may exhibit different dominant mechanisms at different time scales or hierarchical levels. For this reason, Carson & Cobelli suggest that, rather than relying on "a single model," it may sometimes be more appropriate to think in terms of "sets of models," each with its own domain of validity (4, 12).

This illustrates that mechanistic modeling in physiology is not about "fitting everything into a single set of equations," but about selecting an appropriate level of abstraction according to the purpose and scale of interest.

2.3. Why "Mechanistic Models" are Challenging: Complexity, Scalability, and Measurement Constraints

ML approaches often fall on the side of "modelling the data," in the terminology of Carson & Cobelli. Quantitative descriptions are derived from input-output data, while the connection to the underlying physiological mechanism often remains implicit (4).

This does not mean that these methods are without value. On the contrary, Carson & Cobelli state that data-driven models may be particularly appropriate in situations where mechanistic knowledge is insufficient or only the overall input-output dynamics of the system are of interest (4).

The critical methodological distinction here is the following: is the aim of a model to explain or to predict? This distinction has been explicitly discussed in the statistical literature. In explanatory models, causal and theoretical structure is emphasized, whereas in predictive models, error minimization on new data and generalization performance are prioritized (13).

In physiology, "mechanistic models" are most often positioned along the axis of explanation, whereas "data-driven AI" is most often positioned along the axis of prediction. This duality forms the basis of the question "which model family should be used for which question?" in the remainder of this section.

2.4. When is a Claim of "Causality" Meaningful?

A relationship learned from data alone does not constitute causality. For a causal claim, intervention and counterfactual thinking, as well as structural assumptions, are required-at least in a formal sense. The modern literature on causal theory delineates this explicitly (14).

Therefore, when a data-driven model identifies a strong relationship between two variables, additional experimental design, interventional data, or strong structural assumptions are required to convert this into "evidence of a mechanism." Clarifying this point is important in order to avoid convenient but scientifically risky statements such as "AI discovers mechanisms" in a book chapter.

2.5. Interpretability and Clinical/Physiological Trust: The Problem of the "Explained Black Box"

In the context of physiology and medicine, it is important not only that models make accurate predictions, but also that it is understood why they make correct predictions (especially in the context of high-risk decisions). In this regard, Rudin discusses the problems associated with the "post hoc explanation" of black-box models in high-risk applications and argues that, where possible, inherently interpretable models should be preferred (15).

This discussion can be translated into physiology as follows: mechanistic models are often inherently interpretable (the variables carry physiological meaning), whereas data-driven models operate through high-dimensional representations, making "interpretability" a separate design objective.

2.6. Complementarity: Mechanistic + Data-Driven = The Logic of a "Hybrid/Integrative" Approach

The main conclusion of this section is as follows: rather than replacing one another, mechanistic and data-driven models serve different purposes. Carson & Cobelli's distinction between "modelling the data" and "modelling the system" already provides the methodological origin of this complementarity (4).

Mechanistic models: They are strong for hypothesis testing, checking physiological consistency, meaningful interpretation of parameters, and controlled inference. The historical and scientific importance of this approach within physiology has been discussed elsewhere (16).

Data-driven models: They can offer practical advantages such as pattern extraction from high-dimensional data, better prediction in certain cases, and automatic feature extraction. However, causality and interpretability require separate evaluation (4, 13).

For this reason, instead of asking "which approach is better?", the following question is more scientific and functional: "Does the research question seek explanation, prediction, or both?" (13). In addition, the following should be considered: Can the model's parameters be reliably identified from the data (identifiability)? What is the model's domain of validity? Do data quality and measurement design support the model's claims? (11).

3. Data Infrastructure for Artificial Intelligence in Physiology

AI-based physiological modeling largely relies on high-quality, well-documented, and reusable datasets. Given the dynamic and multiscale nature of physiological systems, data

infrastructure must be sufficient not only in terms of volume, but also with respect to measurement accuracy, temporal resolution, label reliability, and contextual information. These requirements are among the fundamental factors determining the success of AI applications in physiology.

In this context, one of the most important open science initiatives in the field of physiological signal and clinical data sharing is PhysioNet. PhysioNet provides researchers with access to a wide range of physiological datasets-such as electrocardiography (ECG), electroencephalography (EEG), respiration, hemodynamic, and autonomic nervous system signals-accompanied by detailed documentation and standardized formats. The seminal work by Goldberger and colleagues characterizes PhysioNet not merely as a data repository, but also as a methodological ecosystem for physiological signal analysis (17-19). This ecosystem has played a critical role in reproducibility in physiological AI research by enabling the comparison of different algorithms on the same data.

An important feature of PhysioNet datasets is that, in addition to raw signals, they include time-stamped annotations and clinical contextual information. This has made it possible for AI-based pattern recognition studies on physiological signals to focus not only on classification performance but also on physiological interpretability. Nevertheless, the literature also emphasizes that these datasets often pertain to specific patient groups or controlled conditions, and therefore caution is required regarding the generalizability of the results (17).

From the perspective of intensive care physiology, the most commonly used data sources in AI research are the Medical information mart for intensive care (MIMIC)-III and MIMIC-IV databases. MIMIC-III is a large-scale, freely accessible electronic health record (EHR) database that includes vital signs, laboratory results, medication administrations, and clinical notes of patients admitted to intensive care units (20). MIMIC-IV, as a more recent version of this infrastructure, incorporates improvements related to data standardization and long-term patient follow-up (21).

These databases have enabled the investigation, using AI methods, of relationships between physiological time series and clinical outcomes (such as mortality, length of stay in the intensive care unit, and complications). Particularly in the intensive care setting, continuously measured physiological parameters provide a rich research domain for time-series modeling and early warning systems. Nevertheless, the literature clearly states that such EHR-based datasets are fundamentally observational in nature and do not substitute for randomized experimental designs (20).

At this point, the limitations of the data infrastructure for AI in physiology are as important as the opportunities it provides. First, missing data, irregularities in measurement frequency, and sensor-related artifacts are common in intensive care and EHR data. Second, the fact that clinical labels (such as diagnoses or outcome variables) are often created for secondary purposes can lead to label uncertainty in AI models. These issues have been discussed in detail in the EHR-based ML literature, with emphasis on the fact that they may inflate apparent model performance and limit clinical applicability (22).

In addition, the fact that physiological datasets are specific to particular institutions or patient populations makes the requirement for external validation of AI models even more important. The literature provides strong evidence that models trained on single-center data may not exhibit similar performance in different clinical settings (22). For this reason, in AI applications in physiology, data infrastructure is recognized as a critical element not only for model training, but also for the assessment of generalizability and reliability.

In conclusion, the scientific value of AI applications in physiology is closely related not so much to the algorithms used as to the quality of the data infrastructure that feeds these algorithms. Although open and well-documented data resources such as PhysioNet and MIMIC have made significant contributions to the field, the observational nature and structural limitations of these data necessitate a cautious interpretation of the results in physiological and clinical contexts. This discussion of data infrastructure provides a fundamental basis for understanding why the modeling approaches addressed in subsequent sections require specific methodological precautions.

4. Deep Learning Approaches in Physiological Time Series

A substantial portion of physiological signals consists of measurements that vary over time and therefore exhibit a time-series structure. Physiological measurements such as heart rate intervals, blood pressure fluctuations, respiratory patterns, and EEG signals gain meaning not only from their instantaneous values, but also from their temporal dependencies and dynamics. This characteristic has made methods capable of modeling sequential dependencies particularly important in the analysis of physiological data.

In this context, recurrent neural networks (RNNs) and their derivatives-Long Short-Term Memory (LSTM) networks and Gated Recurrent Units (GRUs)-have been widely used in the modeling of physiological time series. The LSTM architecture was developed to mitigate the vanishing gradient problem observed in classical RNNs, thereby enabling the learning of long-term dependencies (23). GRUs, on the other hand, aim to achieve similar objectives with a more streamlined architecture by employing fewer parameters (24). The primary reason these models are attractive for physiological signals is their ability to learn temporal patterns in data without requiring a predefined physiological model.

From the perspective of applications specific to physiology, the review by Mao and colleagues systematically summarizes how RNN-based models have been used in time series related to cardiovascular, respiratory, and metabolic physiology (25). Such reviews are useful for revealing the diversity of architectures and evaluation approaches employed across different physiological domains. Nevertheless, the literature also notes that most of these studies are application-oriented and that linking model outputs to underlying physiological mechanisms often remains a secondary consideration.

One of the fundamental methodological distinctions regarding the use of deep learning time-series approaches in physiology is the balance between predictive performance

and physiological interpretability. The peer-reviewed literature emphasizes that, although high-capacity black-box models can produce successful predictions, their internal representations often do not carry direct physiological meaning. Especially in high-risk applications, understanding why model outputs are generated has been identified as critical from both clinical and scientific perspectives (15). This has raised the question of whether producing accurate predictions alone is sufficient in the physiological context.

This discussion becomes particularly pronounced in the intensive care setting. Physiological time series generated in intensive care units are directly linked to clinical decisions, and therefore the interpretability of model outputs is of great importance. Deng et al., demonstrated, in their explainable time-series deep learning models developed to predict mortality, prolonged length of stay, and readmission risk in Intensive Care Unit (ICU) patients, which time points and variables the model focused on through attention mechanisms (26). This study shows that deep learning models do not have to be entirely "uninterpretable," but that additional methodological design choices are required to obtain outputs that are meaningful from physiological and clinical perspectives.

Nevertheless, the literature also emphasizes that the insights provided by interpretability methods should not be conflated with causal explanation. The fact that a time-series model assigns high weight to a particular signal segment does not mean that this segment is physiologically causal; it merely indicates that the model finds that information useful for prediction. This distinction is directly related to the prediction-explanation dichotomy discussed in earlier sections and is important for clarifying the limits of deep learning use in physiological time series (13).

In conclusion, deep learning-based time-series models offer powerful tools for capturing the complex temporal structure of physiological signals. However, the scientific value of these models in the field of physiology should be evaluated not solely on the basis of performance metrics, but also in conjunction with criteria such as interpretability, contextual validity, and physiological consistency. This perspective forms the methodological framework for the specific physiological applications to be discussed in subsequent sections.

5. Cardiovascular Physiology: ECG-Based Artificial Intelligence Applications

Cardiovascular physiology is one of the physiological domains in which AI and ML applications have been adopted earliest and investigated most extensively. One of the primary reasons for this is that ECG signals have high temporal resolution, relatively standardized measurement procedures, and a long-established framework for clinical interpretation. Because ECG provides direct and continuous information on the electrical activity of the heart, it offers a suitable foundation for AI-based pattern recognition among physiological signals (27).

A substantial proportion of ECG-based AI studies has focused on the detection and classification of arrhythmias. In this context, the study by Hannun et al., demonstrated

that multi-class arrhythmia classification can be performed from single-lead ambulatory ECG recordings using deep neural networks, and that the model's performance on a specific test set reached a level comparable to that of experienced cardiologists (28). This study has been regarded as a milestone in the literature, as it showed that clinically meaningful outputs can be generated directly from raw physiological signals.

Nevertheless, it is also clearly stated in the same literature that the results presented by Hannun and colleagues are limited to a specific dataset and evaluation framework. The data used in the study belong to a particular device ecosystem and patient population. Therefore, the direct generalizability of the results to different clinical settings may be limited. This situation is considered a general methodological issue of ECG-based deep learning studies (29).

Systematic reviews examining deep learning applications in ECG signals reveal the fundamental limitations in the field from a broader perspective. The review by Xiao and colleagues shows that issues such as dataset dependency, lack of external validation, and heterogeneity of reporting standards are common in many studies (29). In particular, the fact that most models are trained based on single-center or single data sources gives rise to uncertainties regarding how performance changes on independent datasets.

Another important methodological issue is the physiological interpretability of ECG-based deep learning models. Although deep neural networks can perform classification by emphasizing certain segments of the signal or frequency components, what the physiological counterpart of this focus is often remains unclear. In the literature, it is emphasized that a model's sensitivity to a particular QRS complex morphology or rhythm pattern does not mean that this is biologically causal (30). This distinction is of critical importance for the use of ECG-based AI outputs in clinical decision support.

In recent years, the need for external validation, prospective evaluation, and testing in a clinical context has been increasingly emphasized in ECG-based AI applications. In the context of cardiovascular physiology, the scientific and clinical value of AI models should be evaluated not only by performance metrics such as classification accuracy, but also together with criteria such as consistency across different patient groups, integration into clinical workflow, and physiological meaningfulness (31).

In conclusion, although ECG-based AI applications offer great potential in cardiovascular physiology, issues such as data diversity, external validation, and physiological interpretability must be addressed meticulously in order for this potential to be realized reliably. These considerations also provide common methodological lessons for AI applications targeting other physiological systems, which will be discussed in the following sections.

6. Neural Physiology: The Example of EEG and Epilepsy

EEG is a fundamental physiological measurement method that reflects the electrical activity of the brain over time. Due to the low signal-to-noise ratio of EEG signals, their high

sensitivity to artifacts (muscle activity, eye movements, motion), and pronounced inter-individual variability, they constitute a challenging type of data for AI methods. Despite these challenges, the fact that epilepsy is a disorder that physiologically involves paroxysmal and temporal patterns has made EEG-based analyses particularly attractive for seizure detection and, to a more limited extent, seizure prediction.

A large proportion of EEG-based AI studies in the literature focus on the problem of seizure detection (ictal-interictal discrimination). Comprehensive reviews in recent years show that convolutional neural networks (CNNs) and RNN/LSTM have been used on both raw EEG and time-frequency representations, and that higher classification performances compared to traditional methods have been reported on certain datasets (32, 33). However, it is particularly emphasized that these performance gains are mostly obtained in patient-dependent evaluations or assessments conducted within the same data source.

Patient-independent (cross-patient) modeling in EEG-based studies emerges as a fundamental methodological challenge due to the heterogeneity of epilepsy physiology. Factors such as the anatomical location of epileptic foci, underlying etiology, medication use, and age lead to substantial differences in EEG patterns between individuals. Recent reviews report that the performance of patient-independent models generally decreases markedly, and therefore clinical reliability remains limited (32, 34). This situation demonstrates that physiological heterogeneity constitutes a structural barrier for AI-based EEG analyses.

Seizure prediction (detection of pre-ictal periods) is a more ambitious and physiologically more complex target compared to the detection problem. The aim of prediction studies is to capture the physiological changes that emerge in the EEG before seizure onset. However, the literature indicates that the definition of the pre-ictal state is not consistent across datasets, that time windows can be selected arbitrarily, and that results are strongly dataset-dependent (35). Therefore, although deep learning models offer promising results for seizure prediction, there is a general consensus that caution is required regarding the translation of these results into clinical practice.

Another important issue in EEG-based deep learning studies is physiological interpretability. The fact that deep models show sensitivity to certain frequency bands or time segments does not mean that these features are physiologically causal. Many reviews note that the relationship between the patterns attended to by the model and epileptic pathophysiology often cannot be clearly established (32, 33). This situation highlights the need for additional validation and physiological justification for the use of EEG-based AI models as clinical decision support.

In conclusion, the field of EEG and epilepsy is one of the examples that simultaneously make visible both the potential and the limitations of AI in physiology. Although deep learning methods can provide high-performance seizure detection under certain conditions, inter-individual heterogeneity, patient-independent generalizability, and physiological interpretability remain fundamental challenges that still need to be resolved. This example clearly demonstrates why data, models, and biological context must be considered together in physiological AI applications.

7. Intensive Care Physiology and Artificial Intelligence

ICUs are among the clinical environments with the highest level of physiological complexity due to simultaneous monitoring of multiple organ systems, rapid physiological changes, and high intervention intensity. Interactions among the cardiovascular, respiratory, renal, and neurological systems are often shaped by nonlinear and time-dependent feedback mechanisms. Therefore, the ICU environment provides a context in which physiological time series are both rich and difficult to interpret.

AI models developed in this context have primarily focused on mortality prediction, early warning systems (e.g., clinical deterioration, sepsis risk), and clinical decision support applications. Vital signs continuously measured in the ICU, laboratory values, and therapeutic interventions theoretically provide a favorable data infrastructure for AI-based time series modeling. However, this theoretical suitability encounters many methodological and physiological limitations in practice.

Systematic reviews reveal that the number of AI applications in the ICU has increased rapidly in recent years; however, the majority of studies are retrospective, single-center, and have limited external validation (10). The same reviews draw attention to widespread issues such as heterogeneity in performance reporting, lack of appropriate comparison groups, and evaluation metrics that are disconnected from the clinical context. This situation makes the direct translation of AI models into clinical use difficult in a high-risk environment such as the ICU.

One of the fundamental problems specific to ICU physiology is that most observed physiological variables are influenced not only by the disease process but also by clinical interventions. For example, a patient's blood pressure or oxygen saturation reflects not only the underlying pathophysiology but also vasopressor use, ventilator settings, or fluid therapy. This situation raises the question of whether the relationships learned by AI models are causal or merely intervention-mediated correlations. In the ICU literature, such "treatment-outcome entanglement" is particularly emphasized as an important source of bias for AI models (36).

Another critical issue is the interpretability of AI models in the ICU. Intensive care decisions are often time-constrained and high-risk. Therefore, understanding why model outputs are generated is of great importance for clinicians. Recent reviews indicate that explainability methods are increasingly used in ICU AI studies, but that most of these methods are post hoc in nature and should not be confused with physiological causality (37). This situation shows that the explanation-prediction distinction discussed in previous sections becomes even more critical in the ICU context.

Issues of bias and generalizability also prominently emerge in ICU AI applications. The demographic characteristics of patient populations, hospital protocols, and measurement practices can vary substantially across institutions. Therefore, it is uncertain whether a model developed in one center and reported to have high performance will produce similar results in another center. In the ICU literature, it is emphasized that multicenter data, external validation, and prospective clinical studies are essential to address such generalizability problems (10).

Finally, prospective evaluation and clinical impact analysis are required for the transition of AI models into clinical practice in the ICU. A model performing well retrospectively does not mean that it will improve clinical decisions. Recent studies demonstrate that how AI-supported decision systems behave when integrated into real clinical workflows can only be understood through prospective and controlled evaluations (37).

In conclusion, intensive care physiology is one of the fields in which AI applications combine the highest potential with the highest risk. In the ICU context, the scientific and clinical value of AI should be evaluated not only by predictive accuracy, but also together with criteria such as physiological consistency, interpretability, bias control, and prospective clinical impact. This approach is essential for accurately defining the limits and realistic potential of AI use in the ICU.

8. Digital Twins and Hybrid Models

In recent years, the concept of the "digital twin" has increasingly gained prominence in the biomedical literature with the aim of creating personalized, dynamic, and time-updatable representations of physiological systems. Although the digital twin approach originates from virtual replicas of physical systems in the field of engineering, it has a more complex and not yet fully standardized framework in the context of health and physiology. The main reason for this complexity is that biological systems exhibit multiscale, heterogeneous, and time-dependent structures (38).

Digital twin approaches in healthcare mostly aim to combine mechanistic physiology models with data-driven AI methods. Such hybrid models seek, on the one hand, to preserve known biophysical and physiological constraints, while on the other hand to update the model using parameters learned from individual-specific data. The current literature describes this approach as an effort to strike a balance between physiological consistency and personalization compared to purely mechanistic or purely data-driven models (38, 39).

One of the main promises of applying the digital twin concept to physiology is the ability to predict physiological responses through personalized simulations. For example, in cardiovascular or respiratory systems, integrating individual anatomical and functional characteristics into the model aims to allow the potential effects of a specific intervention (such as medication, ventilator settings, or fluid management) to be evaluated in a virtual environment. However, comprehensive reviews clearly state that such applications largely remain at the level of conceptual frameworks, prototype systems, or limited case studies, and that clinical effectiveness has not yet been strongly demonstrated (38).

From a methodological perspective, one of the most important challenges facing digital twins is model updating, validation, and uncertainty management. For a digital twin to represent the real physiological system, measurement errors, missing data, and inter-individual variability must be explicitly addressed. In the current literature, it is criticized that in a significant portion of digital twin studies these uncertainties are not sufficiently quantified and that model outputs are often presented in a deterministic manner (38, 39).

For this reason, digital twins should currently be regarded not as a proven clinical standard, but as an emerging research framework that aims to integrate physiological modeling with AI. A commonly emphasized view in the literature is that, for digital twins to transition into clinical application, clear use-case definitions, multicenter validation studies, and methodological standards centered on physiological interpretability need to be developed (38).

In conclusion, digital twins and hybrid models offer a promising direction that represents the long-term goals of AI in physiology. However, the ability of this direction to produce scientifically and clinically meaningful outcomes depends not so much on technological advancement as on the combined application of physiology-informed modeling, methodological rigor, and evidence-based evaluation principles. Therefore, at the current stage, digital twins should be considered not as a "solution" but as a research program that must be carefully structured.

9. Conclusion

AI applications in physiology offer significant opportunities for extracting patterns from large and complex datasets, generating short- and long-term predictions, and quantitatively addressing high-dimensional physiological processes. In particular, in contexts such as time-series physiological data, electronic health records, and simultaneous monitoring of multiple organ systems, they have contributed to the development of methods that go beyond traditional analytical approaches. However, the literature discussed in this section clearly demonstrates that AI-based models should not be regarded as an unlimited or automatic solution for physiological knowledge generation.

Nevertheless, in recent years, AI- and ML-based studies focusing on anthropometric and musculoskeletal physiological parameters have also attracted attention. In this regard, the studies conducted on elite athletes by Osmanoğlu et al., Örücü et al., and Işık et al., published in 2025, can be cited as examples of the meticulous integration of AI and ML methods into the field (40-43). Although current studies process instantaneous states of structural physiological characteristics using AI and ML methods, the processing of dynamic musculoskeletal physiological characteristics in future studies and their incorporation into the literature remain gray areas that still await full clarification.

Current studies show that data-driven AI models are predictive in nature in most cases, but do not directly provide causal explanations of physiological mechanisms. Mechanistic physiology models continue to play an indispensable role in explaining the functioning of biological systems and in hypothesis testing (1, 4). Therefore, AI methods should be regarded not as approaches that replace mechanistic explanations, but as complementary tools that address specific questions. In the literature, there is strong evidence that AI models developed in a manner detached from the physiological context have serious limitations in terms of generalizability, interpretability, and clinical reliability (10, 22).

The examples presented in this book chapter-ECG-based cardiovascular applications, EEG, musculoskeletal anthropometric studies and epilepsy research, intensive care physiology, and digital twin approaches-concretely demonstrate both the potential and the

limitations of AI in physiology. In particular, physiological heterogeneity, observational data sources, and the entanglement of interventions with data make careful interpretation of AI model outputs imperative. In this context, methodological requirements such as interpretability, external validation, and prospective evaluation emerge as fundamental elements that determine the physiological and clinical value of AI applications (15, 37).

In conclusion, the future of AI in physiology depends on a careful, disciplined, and cautious integration of data-driven models with knowledge of physiological mechanisms. This integration should aim not only to achieve higher predictive performance, but also to develop models that preserve physiological consistency, have clearly defined boundaries, and are scientifically defensible. Moreover, it is evident that AI and ML methods, beyond their ability to instantaneously reflect potential changes in physiological mechanisms, need to be designed and developed in a way that captures the multiple and continuous interactions of the organism together with its multiple organ systems and the dynamic outcomes of these interactions. From this perspective, it can be stated that digitally supported applications such as AI and ML cannot be independent of the "human" factor. As long as this approach is adopted, AI can make meaningful contributions in the field of physiology not by weakening mechanistic understanding, but by complementing and deepening it.

10. References

1. Hall, J. E. (2016). Guyton and Hall textbook of medical physiology (13th ed.). Elsevier.
2. Ağar, E. (2021). İnsan Fizyolojisi (Human Physiology). Ed.; Ağar E. İstanbul Tıp Kitabevleri, 1st ed., İstanbul, Turkey. (In Turkish).
3. Rhoades, R., & Bell, D. R. (2012). Medical physiology: principles for clinical medicine. Lippincott Williams & Wilkins.
4. Carson, E., & Cobelli, C. (2001). Modelling methodology for physiology and medicine. Academic Press.
5. Norvig, P. & Russel, S. (2021). Artificial Intelligence: A Modern Approach, Global Edition (4th Edt.). Pearson
6. OECD. (2024) Explanatory memorandum on the updated OECD definition of an AI system. OECD Artificial Intelligence Papers, 8, OECD Publishing, Paris, https://doi.org/10.1787/623da898-en
7. Mitchell, T.M. (1997). Machine Learning (1st Edt.). McGraw-Hill Education
8. Esteva, A., Robicquet, A., Ramsundar, B., Kuleshov, V., DePristo, M., Chou, K., … Dean, J. (2019). A guide to deep learning in healthcare. Nature medicine, 25(1), 24-29. https://doi.org/10.1038/s41591-018-0316-z
9. Samek, W., Wiegand, T., & Müller, K.R. (2017). Explaınable Artıfıcıal Intellıgence: Understandıng, Vısualızıng And Interpretıng Deep Learnıng Models. ITU Journal: ICT Discoveries, 1 (13), 39-48.
10. van de Sande, D., van Genderen, M. E., Huiskens, J., Gommers, D., & van Bommel, J. (2021). Moving from bytes to bedside: a systematic review on the use of artificial intelligence in the intensive care unit. Intensive care medicine, 47(7), 750-760. https://doi.org/10.1007/s00134-021-06446-7
11. Raue, A., Karlsson, J., Saccomani, M. P., Jirstrand, M., & Timmer, J. (2014). Comparison of approaches for parameter identifiability analysis of biological systems. Bioinformatics (Oxford, England), 30(10), 1440-1448. https://doi.org/10.1093/bioinformatics/btu006
12. Ralyté, J., Koutsopoulos, G. & Stirna, J. (2025). Verification, validation, and evaluation of modeling methods: experiences and recommendations. Softw Syst Model. https://doi.org/10.1007/s10270-025-01304-2
13. Shmueli. (2010). To Explain or to Predict? Statist. Sci., 25(3), 289-310. https://doi.org/10.1214/10-STS330
14. Pearl, J. (2013). Causality: Models, reasoning, and inference (2nd ed.). Cambridge University Press.
15. Rudin C. (2019). Stop Explaining Black Box Machine Learning Models for High Stakes Decisions and Use Interpretable Models Instead. Nature machine intelligence, 1(5), 206-215. https://doi.org/10.1038/s42256-019-0048-x
16. Noble D. (2002). The rise of computational biology. Nature reviews. Molecular cell biology, 3(6), 459-463. https://doi.org/10.1038/nrm810
17. Goldberger, A. L., Amaral, L. A., Glass, L., Hausdorff, J. M., Ivanov, P. C., Mark, R. G., … Stanley, H. E. (2000). PhysioBank, PhysioToolkit, and PhysioNet: components of a new research resource for complex physiologic signals. Circulation, 101(23), E215-E220. https://doi.org/10.1161/01.cir.101.23.e215
18. Jiang, H., Mutahira, H., Wei, S., & Muhammad, M. S. (2025). ECG-Mamba: Cardiac Abnormality Classification With Non-Uniform-Mix Augmentation on 12-Lead ECGs. IEEE journal of translational engineering in health and medicine, 13, 461-470. https://doi.org/10.1109/JTEHM.2025.3613609

19. Erlebach, R., Pale, U., Beck, T., Markovic, S., Seric, M., David, S., & Keller, E. (2025). Limitations of SpO2 / FiO2-ratio for classification and monitoring of acute respiratory distress syndrome-an observational cohort study. Critical care (London, England), 29(1), 82. https://doi.org/10.1186/s13054-025-05317-7
20. Johnson, A. E., Pollard, T. J., Shen, L., Lehman, L. W., Feng, M., Ghassemi, M., …& Mark, R. G. (2016). MIMIC-III, a freely accessible critical care database. Scientific data, 3, 160035. https://doi.org/10.1038/sdata.2016.35
21. Johnson, A. E. W., Bulgarelli, L., Shen, L., Gayles, A., Shammout, A., Horng, S., … Mark, R. G. (2023). MIMIC-IV, a freely accessible electronic health record dataset. Scientific data, 10(1), 1. https://doi.org/10.1038/s41597-022-01899-x
22. Beam, A. L., & Kohane, I. S. (2018). Big Data and Machine Learning in Health Care. JAMA, 319(13), 1317-1318. https://doi.org/10.1001/jama.2017.18391
23. Hochreiter, S., Schmidhuber, J. (1997). Long Short-Term Memory. Neural Comput, 9(8), 1735-1780. doi: https://doi.org/10.1162/neco.1997.9.8.1735
24. Cho, K., van Merriënboer, B., Gulcehre, C., Bahdanau, D., Bougares,F., Schwenk, H., & Bengio, Y. 2014. Learning Phrase Representations using RNN Encoder-Decoder for Statistical Machine Translation. In Proceedings of the 2014 Conference on Empirical Methods in Natural Language Processing (EMNLP), pages 1724-1734, Doha, Qatar. Association for Computational Linguistics
25. Mao, S., & Sejdic, E. (2023). A Review of Recurrent Neural Network-Based Methods in Computational Physiology. IEEE transactions on neural networks and learning systems, 34(10), 6983-7003. https://doi.org/10.1109/TNNLS.2022.3145365
26. Deng, Y., Liu, S., Wang, Z., Wang, Y., Jiang, Y., & Liu, B. (2022). Explainable time-series deep learning models for the prediction of mortality, prolonged length of stay and 30-day readmission in intensive care patients. Frontiers in medicine, 9, 933037. https://doi.org/10.3389/fmed.2022.933037
27. Azuaje, F., Clifford, G.,& McSharry, P. (2006). Advanced Methods and Tools for ECG Data Analysis. Artech, 2006.
28. Hannun, A. Y., Rajpurkar, P., Haghpanahi, M., Tison, G. H., Bourn, C., Turakhia, M. P., & Ng, A. Y. (2019). Cardiologist-level arrhythmia detection and classification in ambulatory electrocardiograms using a deep neural network. Nature medicine, 25(1), 65-69. https://doi.org/10.1038/s41591-018-0268-3
29. Xiao, Q., Lee, K., Mokhtar, S. A., Ismail, I., Pauzi, A. L. b. M., Zhang, Q., & Lim, P. Y. (2023). Deep Learning-Based ECG Arrhythmia Classification: A Systematic Review. Applied Sciences, 13(8), 4964. https://doi.org/10.3390/app13084964
30. Clifford, G. D., Behar, J., Li, Q., & Rezek, I. (2012). Signal quality indices and data fusion for determining clinical acceptability of electrocardiograms. Physiological measurement, 33(9), 1419-1433. https://doi.org/10.1088/0967-3334/33/9/1419
31. Shen, D., Wu, G., & Sulk, H-I. (2017). Deep Learning in Medical Image Analysis. Annual Review Biomedical Engineering. 19,221-248. https://doi.org/10.1146/annurev-bioeng-071516-044442
32. Zhang, X., Zhang, X., Huang, Q., & Chen, F. (2024). A review of epilepsy detection and prediction methods based on EEG signal processing and deep learning. Frontiers in neuroscience, 18, 1468967. https://doi.org/10.3389/fnins.2024.1468967
33. Shoeibi, A., Khodatars, M., Ghassemi, N., Jafari, M., Moridian, P., Alizadehsani, R., … Acharya, U. R. (2021). Epileptic Seizures Detection Using Deep Learning Techniques: A Review. International journal of environmental research and public health, 18(11), 5780. https://doi.org/10.3390/ijerph18115780
34. Xu, J., An, K., Deng, Z., Yang, Y., Liu, J-X., Wang, J., & Yuan, S. (2024). EEG-based epileptic seizure detection using deep learning techniques: A survey. Neurocomputing, 610, 128644. https://doi.org/10.1016/j.neucom.2024.128644
35. Kuhlmann, L., Lehnertz, K., Richardson, M. P., Schelter, B., & Zaveri, H. P. (2018). Seizure prediction - ready for a new era. Nature reviews. Neurology, 14(10), 618-630. https://doi.org/10.1038/s41582-018-0055-2
36. Komorowski, M., Celi, L. A., Badawi, O., Gordon, A. C., & Faisal, A. A. (2018). The Artificial Intelligence Clinician learns optimal treatment strategies for sepsis in intensive care. Nature medicine, 24(11), 1716-1720. https://doi.org/10.1038/s41591-018-0213-5
37. Hadweh, P., Niset, A., Salvagno, M., Al Barajraji, M., El Hadwe, S., Taccone, F. S., & Barrit, S. (2025). Machine Learning and Artificial Intelligence in Intensive Care Medicine: Critical Recalibrations from Rule-Based Systems to Frontier Models. Journal of Clinical Medicine, 14(12), 4026. https://doi.org/10.3390/jcm14124026
38. Zhang, K., Zhou, H. Y., Baptista-Hon, D. T., Gao, Y., Liu, X., Oermann, E., …& International Consortium of Digital Twins in Medicine (2024). Concepts and applications of digital twins in healthcare and medicine. Patterns (New York, N.Y.), 5(8), 101028. https://doi.org/10.1016/j.patter.2024.101028
39. Viceconti, M., Hunter, P., & Hose, R. (2015). Big data, big knowledge: big data for personalized healthcare. IEEE journal of biomedical and health informatics, 19(4), 1209-1215. https://doi.org/10.1109/JBHI.2015.2406883
40. Osmanoğlu, U.Ö., Erdağı, K., Işik, B., Örücü, S., & Özbay, E. (2025). Comparative analysis of Microsoft Kinect Azure and manual measurement methods in the sit and reach test among elite female weightlifters. Scientific reports, 15(1), 24636. https://doi.org/10.1038/s41598-025-09754-w
41. Örücü, S., Erdağı, K., Işık, B., Özbay, E., & Osmanoğlu, U.Ö. (2025). Azure Kinect for joint range of motion analysis: A validity and reliability evaluation in elite female weightlifters. PloS one, 20(11), e0334890. https://doi.org/10.1371/journal.pone.0334890
42. Örücü, S., Işık, B., Erdağı, K., Osmanoğlu, U. Ö., & Özbay, E. (2025). Kinect-based anthropometric measurements: a comparative analysis of traditional methods in youth female weightlifters. BMC sports science, medicine & rehabilitation, 17(1), 75. https://doi.org/10.1186/s13102-025-01129-y
43. Işik, B., Erdağı, K., Örücü, S., Osmanoğlu, U.Ö., & Özbay, E. (2025). Analysis of anthropometric measurements in U-15 female weightlifters using a Kinect camera and comparison with traditional methods. Medical & biological engineering & computing, 63(10), 3003–3018. https://doi.org/10.1007/s11517-025-03373-3

CHAPTER 9

AI-Driven Anatomical Segmentation: Bridging Medical Imaging, Anatomy, and Clinical Research

MD. Ismail Sivri

1. Introduction

Human anatomy, a pivotal component of health sciences education, has been traditionally imparted through three interlinked modalities involving structured pedagogical approaches primarily focused on multidimensional illustrations, traditional cadaver dissection and digital imaging-based dissection. Digital tools to teach and visualize anatomy (2D/3D imaging and AR/VR) have expanded considerably over the years especially with COVID-19 but dissections remain an essential means to appreciate layered complexity when learning human anatomy. However, cadaveric dissection is highly limited by practical and legal issues in many countries so supplementary teaching modalities are often required (1).

This restriction has increased reliance on radiology-based and virtual tools. Incorporating the structured depths of radiological resources with interactive 3D post-processing software, postmortem CT (PMCT), and cadaver-available CT datasets in this manner augments diagnostic reasoning, visual-spatial competence, clinical contextualisation, and learner confidence. Yet, despite these validated benefits, radiology remains largely embedded as an adjunct to gross anatomy curricula rather than serving as the centerpiece of pedagogical innovation (2).

Radiology education is critical for anatomical competence and clinical preparedness, yet it remains widely underintegrated into undergraduate medical curricula. What with, a comprehensive review of 52 studies spanning the years 2000-2025 shows that the inclusion of radiology teaching, along with anatomical teaching, significantly improves objective learning outcomes over traditional teaching alone. Although ultrasound is the most used modality in these settings, CT, MRI, and plain radiography are under-represented despite their high clinical impact. The widening gaps in imaging reading proficiency

among incoming residents, combined with the increasing prominence of image-based measures used to assess knowledge on licensure examinations, underscore an urgent need for earlier implementation of radiology infusion within the preclinical curriculum (3). These findings suggest that radiology should no longer be viewed merely as a supplement to cadaveric or atlas-based learning. Rather, it should be reconceived as a key, multimodal, and clinically contextualized element of medical education that really integrates basic sciences and clinical practice.

As Artificial Intelligence (AI) moves from a supportive assistant to an integral part of the foundation on which clinical practice rests, with machines analyzing massive corpora of evidence-based data and patient histories, the nature of medicine may change forever. Its applications in an era of high-precision predictive modeling span areas as diverse as diagnostic assistance in radiology and dermatology, real-time risk stratification for major adverse cardiovascular events, and electrocardiogram interpretation in cardiology, and intraoperative hemodynamic optimization via clinical decision support during anesthesia. Beyond clinical practice, AI will improve surgical procedures through computer vision and robotics; enable oncological prognosis through multi-omics integration; and increase institutional efficiency through the standardization of complex medical administration and documentation (4).

Medical image segmentation is an essential process that partitions digital images into disease-specific, distinct anatomical areas (e.g., organs and lesions). Classic methods such as thresholding and edge-based approaches are computationally inexpensive but fail in the presence of noise or complex image boundaries. While traditional methods rely on human-driven feature extraction, deep learning architectures (Convolutional Neural Networks (CNNs), U-Net, Generative Adversarial Networks (GANs)) enable automatic feature extraction with pixel-level accuracy. Since deep learning is highly effective but also computationally expensive and requires large datasets for training, hybrid models that combine the stability of traditional rules with the flexibility of neural networks have emerged (5).

In this chapter, we investigate that AI domain-specific segmentation is far beyond a computational tool; it is the translation bridge between anatomy and clinical research.

2. From Imaging Physics to Quantitative Anatomy

2.1. Computed Tomography (CT) and Hounsfield Unit

An example of quantitative anatomical information representation in radiology with a strong classical basis is the isotropic measure of tissue radiodensity from CT known as Hounsfield unit (HU). HU units are a linear transformation of the X-ray attenuation coefficient noted by the CT equipment and given an arbitrary baseline; distilled water is assigned 0 HU whilst air has a value of −1000 HU[21]. Dense tissues show positive values, up to around +1000 HU in bone and beyond +3000 HU in metals, whereas less dense tissues are darker (negative values). Devised by Sir Godfrey Hounsfield, this scale converts many of the physical properties of tissue into perceptible grayscale images (6).

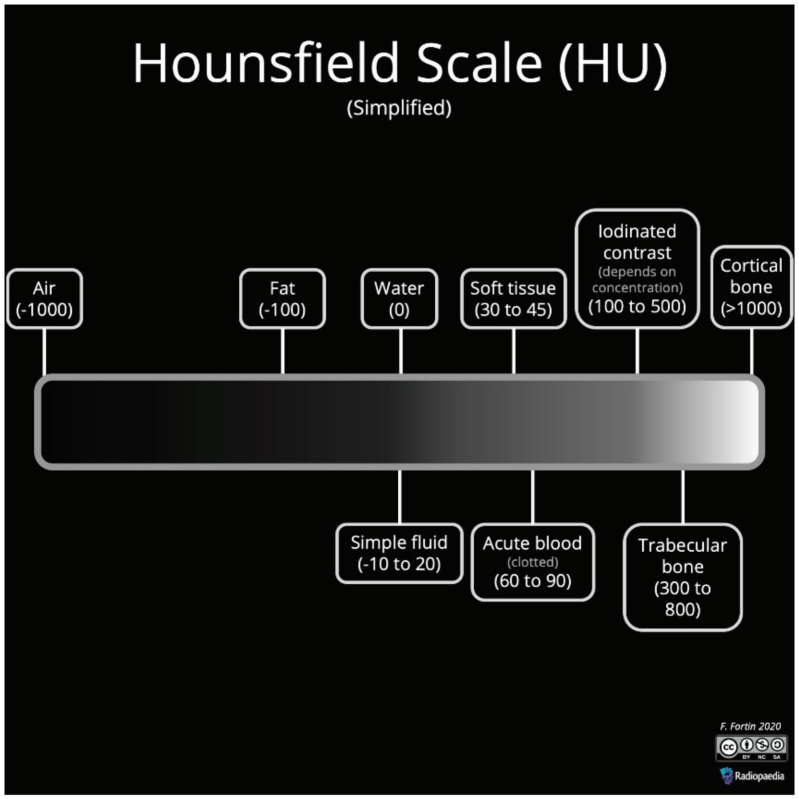


Figure 1. Simplified depiction of the Hounsfield scale illustrating representative attenuation values for selected anatomical structures (7)

2.2. Magnetic Resonance Imaging (MRI) and Signal Intensity

Signal intensity—which represents the amplitude of radiofrequency signals released by hydrogen protons within various tissues—determines tissue contrast in MRI. Higher signal intensity structures appear brighter (hyperintense), while lower signal intensity structures appear darker (hypointense). Unlike CT, where grayscale values depend primarily on X-ray attenuation, MRI signal intensity is influenced by intrinsic tissue properties such as proton density and T1- and T2-relaxation times. Tissues rich in mobile hydrogen protons—such as fluid-containing structures—typically demonstrate high signal on T2-weighted images, while fat, owing to its short T1 relaxation time, appears bright on T1-weighted images. In contrast, cortical bone and air, which contain very few mobile protons, consistently demonstrate low signal intensity and appear black. Thus, MRI signal characteristics translate microstructural and biochemical tissue properties into distinct grayscale patterns, providing anatomically and clinically meaningful differentiation between normal structures and pathology (8).

Voxel dimensions constitute a fundamental determinant of image quality in cross-sectional imaging. A voxel is the three-dimensional counterpart of a pixel and is defined by the in-plane pixel dimensions and the slice thickness. In-plane pixel size is calculated by dividing the field of view (FOV) by the acquisition matrix, which typically ranges from 128×128 to 512×512, yielding pixel dimensions of 0.5-1.5 mm (9).

2.3. Partial Volume Effect and Quantitative Measurement Bias

The partial-volume effect, or PVE, is a common phenomenon in medical imaging where the measured signal in a scan does not perfectly match the true distribution of a tracer or tissue. This discrepancy primarily arises because imaging systems have physical limits on their ability to resolve small details. There are two main reasons for this: limited spatial resolution and the way images are divided into 3D pixels called voxels. When a system has limited spatial resolution, the signal from a specific point effectively blurs into the surrounding areas, a process known as spillover. As a result, tiny lesions or structures appear larger than they actually are, and their internal intensity appears weaker than it actually is. Simultaneously, a single voxel frequently contains a mixture of various tissue types because images are reconstructed on a grid. Instead of a precise measurement of a single tissue, the resulting value for that voxel is just an average of everything inside it. When a lesion is very small—that is, smaller than roughly three times the system's resolution limit—these effects become significant. In these situations, the tumor's edges become warped, and its recorded activity is greatly underestimated. While PVE does not actually destroy the signal, it redistributes it in a way that makes it difficult to accurately measure tumor characteristics or plan precise treatments (10).

3. Fundamentals of Segmentation

Segmentation means separating related groups from their environment (11). Segmenting images into distinct, identifiable segments is referred to as Image Segmentation. The purpose of the segmentation process is to break down the overall image representation into its most meaningful components, so that the segments produced are clear and easily identifiable. The process to achieve a segmented image consists of four general steps: acquiring an image, preprocessing it (resizing, augmenting, rescaling, cropping), extracting the features of the image and segmenting it into separate segments. The last stage of processing an image is to produce a segmented output (12).

3.1. Manual and Automatic Segmentation

Segmentation methods are generally categorized according to the degree of human involvement. Manual segmentation refers to the slice-by-slice delineation of anatomical structures directly by an expert, relying entirely on hand-crafted annotations. Semi-automated segmentation uses predefined computational algorithms to generate an initial

segmentation, which the user then reviews and refines. Fully automated segmentation employs machine-learning–based models to perform segmentation with minimal or no human intervention, aiming to optimize efficiency and reproducibility (13).

Manual segmentation is currently the gold standard for identifying critical structures; it remains a time-consuming and labor-intensive process. This traditional approach requires a high level of anatomical expertise and demands a significant amount of time to complete (14).

While manual segmentation remains the gold standard, atlas-based automated methods have significantly improved the efficiency of anatomical segmentation. This approach relies on registering target images to predefined templates to propagate anatomical labels (15). Traditional approaches, including thresholding, region-based methods, and edge detection, rely on classical image processing and mathematical principles; although computationally efficient, they often lack precision in capturing fine structural details (16).

3.2. Tools for Medical Image Segmentation

ITK-SNAP is an open-source software application developed to facilitate medical image segmentation in clinical and research settings. It was designed to make advanced active contour and level set–based segmentation techniques accessible to users without requiring extensive mathematical or programming expertise. The software provides an interactive interface that allows users to perform both manual slice-by-slice delineation and semi-automatic segmentation within a three-dimensional visualization environment (17).

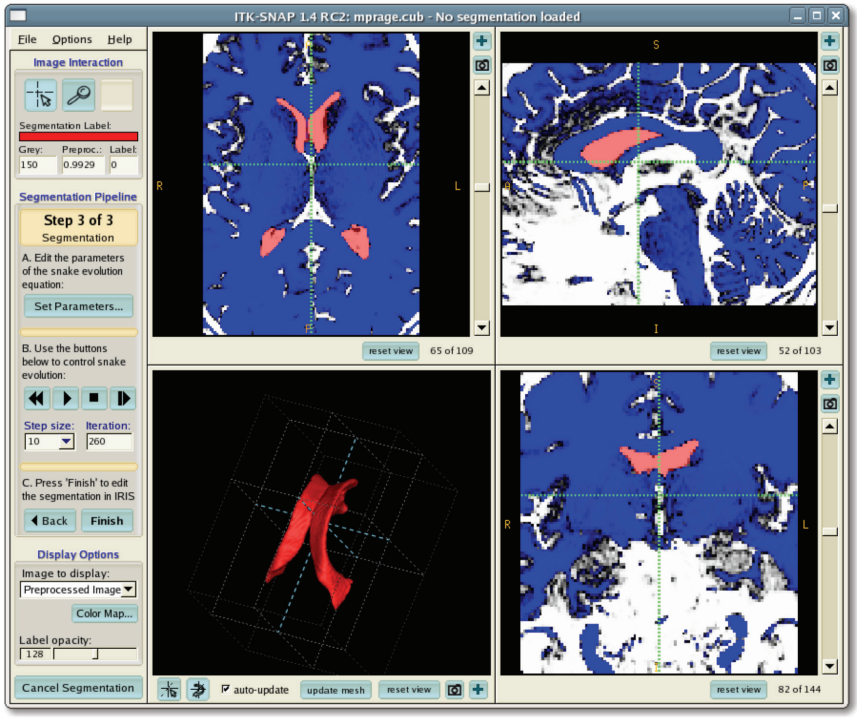


Figure 2. The lateral ventricle segmentation with Active Contours by ITK-SNAP (18)

The field of automated neuroanatomical segmentation has seen significant advances, evolving from traditional atlas-based methods to high-speed deep-learning frameworks. A widely used software suite, such as FreeSurfer, that uses surface-based and volumetric atlases for detailed cortical and subcortical labeling (19). FreeSurfer requires local installation, and on widely used platforms such as Windows it typically runs in a virtual machine or the Windows Subsystem for Linux. In addition, the segmentation process is computationally intensive and time-consuming, and its effective use generally requires a moderate level of proficiency with the command line. Furthermore, cloud-based platforms such as MRICloud and volBrain have refined these techniques through multi-atlas fusion strategies, enabling high-throughput, objective analysis across diverse clinical datasets (20,21). Since VolBrain and MRICloud operate as web-based services, they do not require any local software installation and can be used easily through a standard web browser. More recently, deep-learning–driven frameworks such as OpenMAP-T1 have been introduced to address the computational burden and morphological limitations of atlas-based and multi-atlas label-fusion approaches. OpenMAP-T1 performs rapid whole-brain parcellation of T1-weighted MRI using a multi-stage convolutional neural network pipeline, segmenting the brain into 280 anatomical structures while maintaining robustness across scanner type, magnetic field strength, and image preprocessing conditions. By reducing processing time from several hours to under 90 seconds without compromising segmentation accuracy, it offers a scalable, clinically adaptable alternative to traditional atlas-dependent methods (22). Default installation of the OpenMAP-T1 requires installing Python, PyTorch, additional dependencies, and executing command-line instructions. However, the same parcellation workflow can also be accessed through the MRICloud web interface, allowing users to perform the analysis without running commands or installing software locally.

The field of medical image segmentation has witnessed tremendous improvements with the advent of deep learning technologies, such as CNNs, which can automatically extract features from raw data rather than laboriously hand-coding them into machine learning models (12). Access to open-source platforms and self-configuring frameworks that connect sophisticated algorithms with clinical research have enabled the practical application of these deep learning breakthroughs. nnU-Net is a new, universal framework that automatically configures itself architecture and hyperparameters to any given medical dataset that has repeatedly outperformed model trained with expert knowledge (24). TotalSegmentator leverages this framework to deliver high reliability in performing more than 100 automated segmentations of anatomical structures across CT and MRI images (25). Advanced models are being coalesced into user-friendly software to facilitate efficient modelling and administration of ongoing clinical workflows, such as 3D Slicer which offers a real-time space for series refinement manually or through AI (26). TotalSegmentator can be used either through a Python-based environment or via the free 3D Slicer extension. However, because the pipeline relies on NVIDIA CUDA for GPU acceleration, efficient operation generally requires a system equipped with a mid- to high-level NVIDIA graphics card with compatible CUDA drivers.

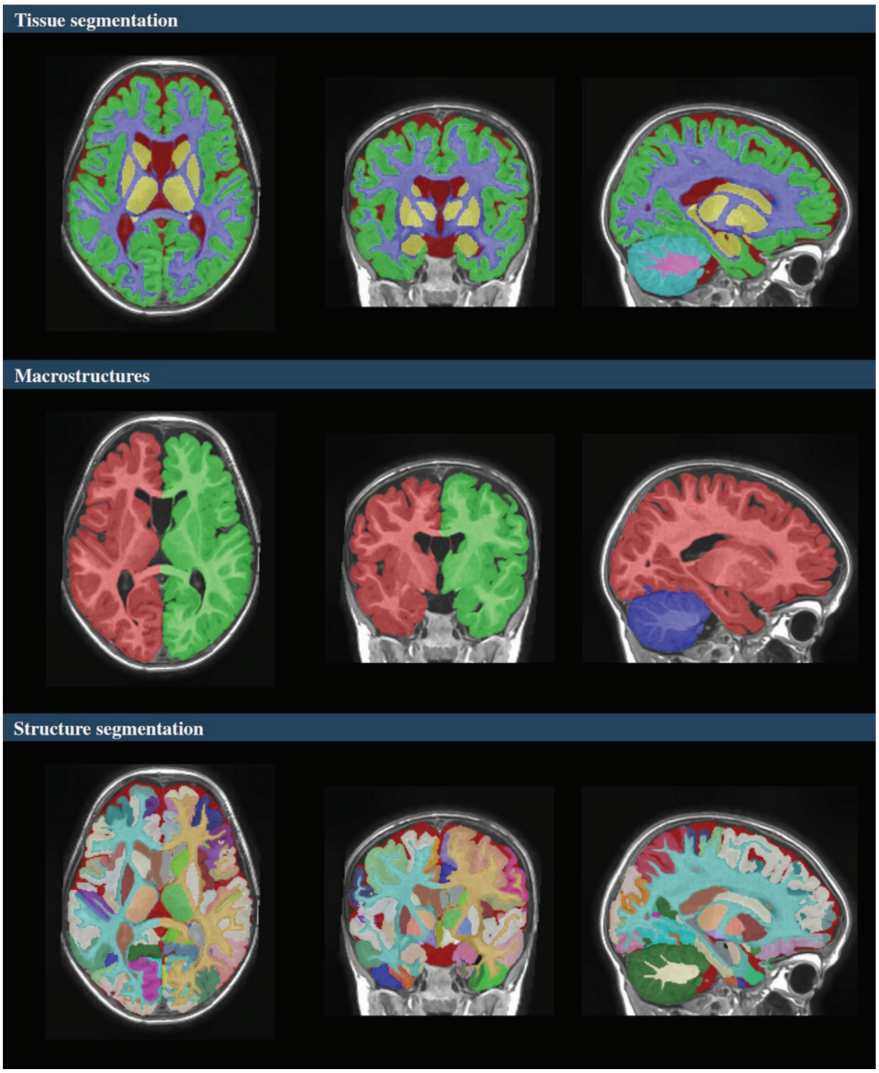


Figure 3. A segmentation example with VolBrain (23)

Whole-body imaging, in some instances, provides substantial advantages compared to regionally focused imaging relevant for anatomical assessments with a systemic orientation. CT and MRI are standard imaging techniques for multi-regional structures such as large muscle groups and fat layers, although Positron Emission Tomography (PET) image segmentation has become a powerful method to perform these calculations. MOOSE (Multiple-Organ Objective Segmentation) is a software designed for high-throughput systemic investigations to probe the human body using whole-body PET/CT images. It

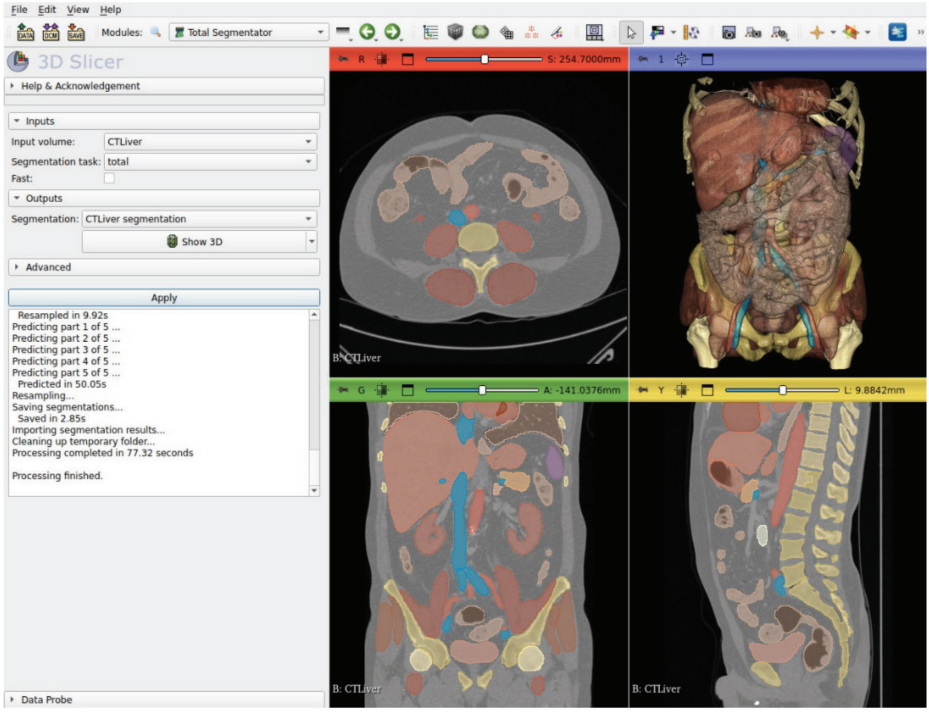


Figure 4. A segmentation example with 3D Slicer and TotalSegmentator plug-in (25,27)

employs data-centric AI principles to create subject-directed, automatic segmentations of multiple anatomical structures (28). Nonetheless, it does not cater to nontechnical people — its functionality relies on a knowledge of both coding and command-line interfaces. This dependence on programming expertise poses a major obstacle to its widespread clinical implementation and use, faced by non-computationally literate users.

3.3. Reliability

Medical image segmentation algorithms are typically evaluated against manual expert annotations, treated as ground-truth references. Segmentation output quality is evaluated incrementally using pixel- and element-wise metrics. Dice and Jaccard indices measure the degree of spatial overlap between predicted and reference segmentations, with higher values indicating greater similarity. Segmentation accuracy is the ratio of correctly classified pixels to the ground-truth area. Oversegmentation and undersegmentation rates quantify false-positive and false-negative pixel classifications, respectively. Furthermore, the Hausdorff distance quantifies contour agreement by computing the maximum spatial distance between the predicted and ground-truth silhouettes, thereby also capturing edge misalignments. Together, these indices are commonly employed to confirm the strength, consistency and quantitative reliability of segmentation algorithms (16).

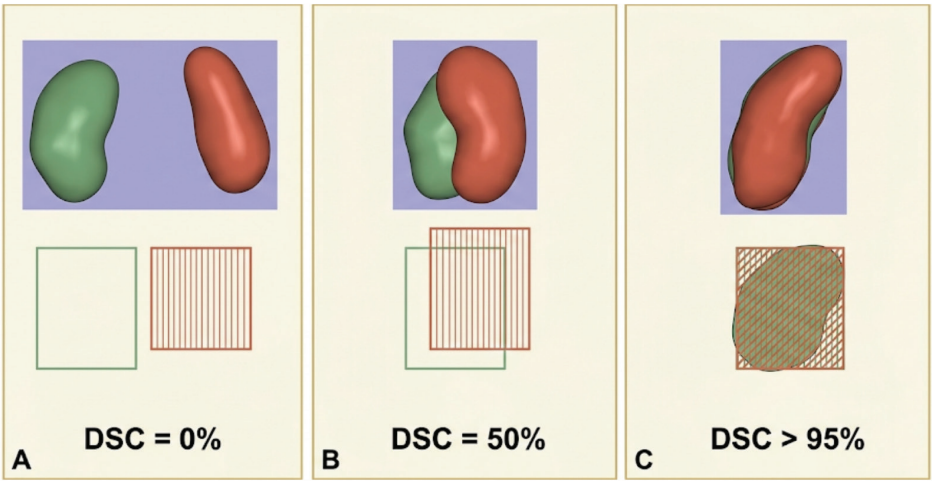


Figure 5. This figure shows the segmentation quality measured with the Dice Similarity Coefficient (DSC) for both ground-truth anatomy (brown) and predicted segmentation (green). The panels display the increment from no overlap (DSC=0%) to partial alignment (DSC=50%) and almost perfect overlap (DSC > 95%)

In comparison, and specifically in subcortical structures (excluding lateral ventricles), the mean Dice coefficients were higher for VolBrain than those for FreeSurfer (0.7327) or FIRST (0.7706), with peak values recorded in hippocampal regions (0.9533±0.0092) and thalamic structures (0.9476±0.0196). Alternatively, for small structures like the accumbens (0.8362±0.0576), dice variability was still relatively high.

OpenMAP-T1 achieved consistently higher (DSC) and lower Hausdorff Distance (HD) compared to 3D U-Net (nnU-Net), particularly in cortical and white matter regions across all age groups. The most pronounced differences were observed in younger subjects (8–19 years), where OpenMAP-T1 achieved significantly improved boundary accuracy with markedly reduced HD values (22).

The 1.5-mm TotalSegmentator model achieved a Dice coefficient of 0.943 and a Normalized Surface Dice (NSD) of 0.966, whereas the 3-mm model showed a lower Dice (0.840) with similar NSD performance. On the Beyond the Cranial Vault (BTCV) dataset, the model reached a Dice of 0.849 and NSD of 0.932, outperforming an nnU-Net trained on the same dataset (Dice 0.839; NSD 0.915; $p<0.001$). Typical failure cases included partial omission of small vascular or bowel structures and confusion between adjacent vertebrae and ribs (25).

Although MOOSE achieved high reliability for most abdominal and skeletal structures, segmentation performance was suboptimal for certain anatomically complex or variable organs, including the adrenal glands, pancreas, bladder, and selected small bone structures, which showed lower median DSC values and greater variability (28).

3.4. Clinical Problems with Segmentation

The principal challenges encountered in the clinical analysis and segmentation of medical images include several interrelated factors.

First, the limited availability of labeled data constitutes a major obstacle, as manually annotating medical images is an extremely time-consuming, labor-intensive, and costly process that requires expert physicians to mark structures individually; consequently, there are often insufficient numbers of high-quality, ground-truth–annotated examples to adequately train robust models.

Second, domain shift is an inverse model of contrast degradation, and a key challenge in the field. This "domain shift" occurs as a result of differences in imaging devices, acquisition parameters, and patient populations between hospitals that create image characteristics divergence across systems, resulting in an AI model performing well in one institution but poorly on data from another.

Third, boundary ambiguity is a largely internal challenge that arises from limited visibility of physical objects, in particular the margins of organs (e.g., the prostate) or tumors, which are not demarcated sharply along their edges and are therefore difficult to delineate.

Fourth, inter-modality heterogeneity makes various segmentation tasks even more complex, as the same patient and the same tissue will often look completely different depending on which imaging modality (e.g., MRI, CT, or PET) is used, leading to decreased interoperability of systems across modalities and poor cross-modality consistency. Fifth, the dimensional complexity poses an additional burden in both methodological and computational terms, because medical imaging data do not comprise only two-dimensional pictures; they also involve three-dimensional volumes composed of hundreds of slices or even four-dimensional datasets integrating temporal information (i.e., functional MRI), which are much harder to process.

Finally, data privacy concerns, including patient confidentiality and regulatory security requirements, restrict the free sharing of medical data between institutions, directly limiting algorithm development, validation, and large-scale testing (29).

4. Results

AI integration in anatomical segmentation workflows have already shown tremendous efficiency improvements. Fully automated, deep learning–based frameworks allowed for fast, large-scale segmentation of complex anatomical datasets; processing times decreased from hours to minutes as high overlap metrics were achieved consistent with expert annotation. Automated segmentation methods showed high overall spatial agreement as well as strong cross-dataset generalization across a wide array of anatomical regions and imaging conditions. However, the scarcity of subsection datasets with gold-standard, manually segmented ground truths that are used for testing reliability poses a major concern in this domain. The preparation of high-quality reference annotations is labor intensive and requires advanced anatomical expertise that limits the size and diversity of training and validation cohorts. Broader access to standardized, expert-validated segmentation datasets should stimulate methodological refinement and improve the robustness of generalizability and performance evaluation.

Despite these measurable improvements in speed and computational performance, anatomical & pathological correctness remains nuanced and paramount. Segmentation outputs are vulnerable to domain shift, boundary ambiguity, partial-volume effects, and inter-modality heterogeneity, which may lead to subtle but clinically relevant mistakes. Lower performance was observed in small, anatomically complex, or highly heterogeneous structures when boundary imprecision and segmentation inconsistencies persisted. Existing fully automated AI systems, if used in the absence of an expert and without the supervision of a clinician, risk leading to downstream analyses and therapeutic planning to propagate misclassifications or boundary inaccuracies. Although AI-driven segmentation is indeed a disruptive innovation, its outputs must still be understood in the light of expert validation and close observation regarding their anatomical and pathological fidelity is crucial to guarantee safe clinical application.

In addition to clinical applications, segmentation technologies may also contribute to anatomy education by converting two-dimensional radiological datasets—where multiple organs appear intermingled—into interpretable three-dimensional anatomical models, facilitating a clearer understanding of spatial relationships.

5. References

1. Massalou D, Bronsard N, Hekayem L, Baqué P, Camuzard O. Modern and synchronized clinical anatomy teaching based on the BDIE method (board–digital dissection–imaging–evaluation). Surg Radiol Anat. 2022;44:803–808. doi: 10.1007/s00276-022-02943-6.
2. Nakamatsu NA, Aytaç G, Mikami B, Thompson JD, Davis M, Rettenmeier C, Maziero D, Andrew Stenger V, Labrash S, Lenze S, et al. Case-based radiological anatomy instruction using cadaveric MRI imaging and delivered with extended reality web technology. European Journal of Radiology. 2022;146:110043. doi: 10.1016/j.ejrad.2021.110043.
3. Alexander M, Montalbano MJ, Loukas M. Learning Anatomy With Radiology: A Systematic Review. Clinical Anatomy. 2025;ca.70048. doi: 10.1002/ca.70048.
4. Wiśniewski KP, Witkowski P, Bachurski P, Chmiel G, Pierzga E, Międlar M, Muda M, Pacek S, Zarański B, Kalinowski P. The Role of Artificial Intelligence and Machine Learning in Modern Medicine: A Literature Review. Qual Sport. 2026;51:68548. doi: 10.12775/QS.2026.51.68548.
5. Xu Y, Quan R, Xu W, Huang Y, Chen X, Liu F. Advances in Medical Image Segmentation: A Comprehensive Review of Traditional, Deep Learning and Hybrid Approaches. Bioengineering. 2024;11:1034. doi: 10.3390/bioengineering11101034.
6. DenOtter TD, Schubert J. Hounsfield Unit. StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 [cited 2026 Feb 17]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK547721/.
7. Fortin F. Hounsfield scale (diagram). Radiopaedia.org [Internet]. Radiopaedia.org; 2020 [cited 2026 Feb 17]. Available from: https://radiopaedia.org/cases/77397.
8. Weinreb JC, Redman HC. SOURCES OF CONTRAST AND PULSE SEQUENCES. Magnetic Resonance Imaging of the Body [Internet]. Elsevier; 1987 [cited 2026 Feb 17]. p. 12–16. Available from: https://linkinghub.elsevier.com/retrieve/pii/B9780721620596500073.
9. Drew Z, Campos A, Bell D. Voxel size. Radiopaedia.org [Internet]. Radiopaedia.org; 2018 [cited 2026 Feb 23]. Available from: https://radiopaedia.org/articles/62838.
10. Soret M, Bacharach SL, Buvat I. Partial-Volume Effect in PET Tumor Imaging. Journal of Nuclear Medicine. 2007;48:932–945. doi: 10.2967/jnumed.106.035774.
11. Khaizi ASA, Rosidi RAM, Gan H-S, Sayuti KA. A mini review on the design of interactive tool for medical image segmentation. 2017 International Conference on Engineering Technology and Technopreneurship (ICE2T) [Internet]. Kuala Lumpur: IEEE; 2017 [cited 2026 Feb 11]. p. 1–5. Available from: http://ieeexplore.ieee.org/document/8215985/.
12. Rayed MdE, Islam SMS, Niha SI, Jim JR, Kabir MM, Mridha MF. Deep learning for medical image segmentation: State-of-the-art advancements and challenges. Informatics in Medicine Unlocked. 2024;47:101504. doi: 10.1016/j.imu.2024.101504.
13. Jain R, Lee F, Luo N, Hyare H, Pandit AS. A Practical Guide to Manual and Semi-Automated Neurosurgical Brain Lesion Segmentation. NeuroSci. 2024;5:265–275. doi: 10.3390/neurosci5030021.
14. Powell KA, Liang T, Hittle B, Stredney D, Kerwin T, Wiet GJ. Atlas-Based Segmentation of Temporal Bone Anatomy. Int J CARS. 2017;12:1937–1944. doi: 10.1007/s11548-017-1658-6.

15. Cabezas M, Oliver A, Lladó X, Freixenet J, Bach Cuadra M. A review of atlas-based segmentation for magnetic resonance brain images. Computer Methods and Programs in Biomedicine. 2011;104:e158–e177. doi: 10.1016/j.cmpb.2011.07.015.
16. Liu X, Song L, Liu S, Zhang Y. A Review of Deep-Learning-Based Medical Image Segmentation Methods. Sustainability. 2021;13:1224. doi: 10.3390/su13031224.
17. Yushkevich PA, Piven J, Hazlett HC, Smith RG, Ho S, Gee JC, Gerig G. User-guided 3D active contour segmentation of anatomical structures: Significantly improved efficiency and reliability. NeuroImage. 2006;31:1116–1128. doi: 10.1016/j.neuroimage.2006.01.015.
18. ITK-SNAP Screenshots [Internet]. [cited 2026 Feb 23]. Available from: https://www.itksnap.org/pmwiki/pmwiki.php?n=Screenshots.Screenshots.
19. Fischl B, Salat DH, Busa E, Albert M, Dieterich M, Haselgrove C, Van Der Kouwe A, Killiany R, Kennedy D, Klaveness S, et al. Whole Brain Segmentation. Neuron. 2002;33:341–355. doi: 10.1016/S0896-6273(02)00569-X.
20. Mori S, Wu D, Ceritoglu C, Li Y, Kolasny A, Vaillant MA, Faria AV, Oishi K, Miller MI. MRICloud: Delivering High-Throughput MRI Neuroinformatics as Cloud-Based Software as a Service. Comput Sci Eng. 2016;18:21–35. doi: 10.1109/MCSE.2016.93.
21. Manjón JV, Coupé P. volBrain: An Online MRI Brain Volumetry System. Front Neuroinform [Internet]. 2016 [cited 2025 Jan 14];10. doi: 10.3389/fninf.2016.00030.
22. Nishimaki K, Onda K, Ikuta K, Chotiyanonta J, Uchida Y, Mori S, Iyatomi H, Oishi K, Alzheimer's Disease Neuroimaging Initiative, Australian Imaging Biomarkers and Lifestyle Flagship Study of Ageing. OPENMAP - T1 : A Rapid Deep-Learning Approach to Parcellate 280 Anatomical Regions to Cover the Whole Brain. Human Brain Mapping. 2024;45:e70063. doi: 10.1002/hbm.70063.
23. Esmaeel TEZ, Abdelghany HS, Mounir SM, Rasekh AI, Mahmoud HAA, Allam MFAB. The utility of volumetric MRI in assessment of volume changes in ventral diencephalon in autistic children. Egypt J Radiol Nucl Med. 2023;54:173. doi: 10.1186/s43055-023-01118-6.
24. Isensee F, Jaeger PF, Kohl SAA, Petersen J, Maier-Hein KH. nnU-Net: a self-configuring method for deep learning-based biomedical image segmentation. Nat Methods. 2021;18:203–211. doi: 10.1038/s41592-020-01008-z.
25. Wasserthal J, Breit H-C, Meyer MT, Pradella M, Hinck D, Sauter AW, Heye T, Boll DT, Cyriac J, Yang S, et al. TotalSegmentator: Robust Segmentation of 104 Anatomic Structures in CT Images. Radiology: Artificial Intelligence. 2023;5:e230024. doi: 10.1148/ryai.230024.
26. Fedorov A, Beichel R, Kalpathy-Cramer J, Finet J, Fillion-Robin J-C, Pujol S, Bauer C, Jennings D, Fennessy F, Sonka M, et al. 3D Slicer as an image computing platform for the Quantitative Imaging Network. Magn Reson Imaging. 2012;30:1323–1341. doi: 10.1016/j.mri.2012.05.001.
27. GitHub - lassoan/SlicerTotalSegmentator: Fully automatic total body segmentation in 3D Slicer using "TotalSegmentator" AI model [Internet]. [cited 2026 Feb 19]. Available from: https://github.com/lassoan/SlicerTotalSegmentator?tab=readme-ov-file.
28. Sundar LKS, Yu J, Muzik O, Kulterer OC, Fueger B, Kifjak D, Nakuz T, Shin HM, Sima AK, Kitzmantl D, et al. Fully Automated, Semantic Segmentation of Whole-Body18 F-FDG PET/CT Images Based on Data-Centric Artificial Intelligence. J Nucl Med. 2022;63:1941–1948. doi: 10.2967/jnumed.122.264063.
29. Guan H, Liu M. Domain Adaptation for Medical Image Analysis: A Survey. IEEE Trans Biomed Eng. 2022;69:1173–1185. doi: 10.1109/TBME.2021.3117407.

CHAPTER 10

Metabolic Profiling and Machine Learning in Complex Disease: A Clinical Biochemistry Perspective

Prof. Dr. Tugba Raika Kiran
Assoc. Prof. Dr. Feyza Inceoglu

1. Introduction

Complex diseases such as metabolic syndrome, type 2 diabetes, cardiovascular disorders, and neurodegenerative conditions are characterized by pronounced biological heterogeneity and multifactorial pathophysiology (1, 2). Rather than arising from discrete abnormalities within single biochemical pathways, these diseases reflect disturbances across interconnected metabolic networks that evolve over time and vary substantially between individuals (3).

Clinical biochemistry has long provided the foundation for disease diagnosis and monitoring through the measurement of individual biomarkers. While this paradigm remains indispensable in routine practice, it offers only a partial view of systemic metabolism, particularly in conditions driven by complex interactions among multiple pathways (4). In such settings, apparently "normal" laboratory values may coexist with ongoing metabolic dysregulation, underscoring the limitations of interpreting biochemical parameters in isolation.

Metabolic profiling seeks to address these limitations by enabling the simultaneous assessment of multiple metabolites and pathways, thereby offering a more integrated representation of metabolic state (5, 6). This transition toward a systems-level perspective also introduces substantial analytical challenges. Machine learning has therefore gained attention as a complementary framework capable of extracting meaningful structure from complex biochemical datasets (7, 8).

While metabolic profiling provides a systems-level view of metabolic regulation, translating high-dimensional metabolomic data into clinically meaningful insights remains a major challenge. Traditional biomarker paradigms in clinical biochemistry rely largely on the interpretation of isolated biochemical parameters, whereas metabolomic profiling

generates complex datasets composed of numerous interrelated metabolites. Such data structures cannot be adequately interpreted using conventional univariate analytical approaches. Instead, they require analytical frameworks capable of capturing multidimensional patterns and nonlinear metabolic interactions. In this context, machine learning methods have emerged as powerful tools for identifying latent metabolic signatures associated with complex diseases. Nevertheless, the effective integration of metabolomic profiling and machine learning into clinical biochemistry practice remains limited, particularly with respect to interpretability, validation, and clinical applicability. This chapter discusses the conceptual foundations of metabolic profiling and examines how machine learning approaches can enhance the interpretation of complex metabolic data within the framework of clinical biochemistry.

2. Metabolic Profiling: Concept and Scope

Traditional biology often relies on the single mutation-single disease paradigm to explain complex disease mechanisms, while systems biology aims to comprehensively study the complex interaction networks of biological processes at the cellular and tissue levels. Within this multilayered omic (genomic, epigenomic, transcriptomic, proteomic, and metabolomic) architecture, metabolomics occupies the lowest point of cellular organization and biochemical activity and is closest to the phenotype. The conceptual foundations of metabolic profiling can be traced back to the work of Roger Williams in the late 1940s, who introduced the concept of "metabolic individuality." Williams proposed that individuals possess distinct metabolic characteristics shaped by genetic, environmental, and physiological factors, suggesting that metabolic patterns vary substantially between individuals and may influence susceptibility to disease and therapeutic responses. Within the multi-layered omics architecture, the metabolome represents the biochemical endpoint of cellular regulation and is therefore considered the molecular layer closest to phenotype. Unlike genomic information, which remains relatively stable, the metabolome is highly dynamic and reflects the integrated effects of genetic background, environmental exposures, diet, microbiome interactions, and physiological conditions. Consequently, metabolomic profiling has emerged as a promising approach for precision medicine, enabling the identification of disease-associated metabolic signatures and patient-specific metabolic phenotypes (1, 5, 9, 10).

Metabolic profiling refers to the systematic evaluation of multiple metabolites with the aim of characterizing global metabolic states rather than isolated biochemical measurements (11). In contrast to conventional laboratory testing, which emphasizes individual analytes, metabolic profiling focuses on coordinated changes across pathways, reflecting the interconnected nature of metabolism (4).

Current profiling strategies may be broadly divided into targeted and untargeted approaches. Targeted profiling prioritizes predefined metabolites of known biological relevance, offering high quantitative accuracy and interpretability. Untargeted profiling, by

contrast, seeks to capture a broad spectrum of metabolic features without prior assumptions, enabling hypothesis generation and the detection of unexpected alterations (6, 12, 13, 14). In practice, these approaches are often complementary rather than mutually exclusive.

A defining feature of metabolic profiles is their context dependency. Diet, circadian rhythms, medication use, and comorbid conditions all influence metabolic measurements, complicating interpretation. This dynamic nature distinguishes metabolic profiling from static biomarker assessment and reinforces the importance of clinical and biochemical context in evaluating metabolomic data (4).

Advances in metabolomic research have been closely linked to the development of high-throughput analytical technologies. Among these, liquid chromatography–mass spectrometry (LC-MS), gas chromatography–mass spectrometry (GC-MS), and nuclear magnetic resonance (NMR) spectroscopy are the most widely used platforms. LC-MS and GC-MS offer high sensitivity and broad metabolite coverage, enabling the detection of numerous small molecules across diverse biochemical pathways. NMR spectroscopy, while generally less sensitive than mass spectrometry-based techniques, provides highly reproducible and quantitative measurements with minimal sample preparation (15, 16). More recently, high-resolution mass spectrometry (HRMS) has further expanded the capabilities of untargeted metabolomics by improving the accuracy of metabolite detection and identification (17). Together, these analytical platforms form the technological basis of contemporary metabolomic profiling. However, the scale and complexity of the resulting datasets necessitate advanced computational approaches for reliable interpretation.

3. Machine Learning in Metabolic Data Analysis

The analytical complexity of metabolic profiling data arises from high dimensionality, intercorrelated variables, and substantial biological variability. Traditional statistical methods, particularly those relying on linear assumptions and single-variable testing, are often ill-suited to capture the structure of such data (18).

In complex diseases, metabolite metabolite interactions are rarely independent or linear. Instead, they reflect nonlinear feedback mechanisms and context-dependent network behavior. As a result, individual metabolite concentrations may fall within conventional reference ranges while collectively forming disease-associated metabolic patterns that remain invisible to univariate analysis. Machine learning approaches address this limitation by modeling multivariate relationships simultaneously, enabling the detection of emergent metabolic signatures arising from coordinated biochemical dysregulation (18, 19, 20).

It is known that the data produced by clinical metabolomics studies are multidimensional, noisy, and complex. In these studies where thousands of independent metabolites are measured simultaneously, it is often encountered that the number of samples (patients) included in the analysis is much lower than the number of measured variables (metabolites) (21). This situation results in the well-known "p >> n" problem, where the

number of measured variables greatly exceeds the number of available samples, posing substantial challenges for conventional statistical analysis. In the multidimensional data space, traditional univariate statistical tests fall short due to multiple testing errors, type I error rates, and high multicollinearity problems among metabolites (9). Therefore, in the data analysis process, machine learning (supervised-unsupervised) algorithms and advanced biostatistical methods come to the forefront and serve as a critical analytical bridge in metabolic data mining and the development of clinical diagnosis models for complex diseases (10).

Both supervised and unsupervised machine learning strategies have been applied to metabolic data. Supervised methods associate metabolic patterns with predefined clinical outcomes, whereas unsupervised methods aim to uncover latent structures within the data, such as metabolic subtypes. Despite their potential, these approaches are highly sensitive to data quality, sample size, and validation strategies. Issues of overfitting and limited interpretability remain central concerns, particularly in clinical contexts where biological plausibility and transparency are essential. In addition, broader concerns regarding reproducibility and bias in biomedical research further emphasize the importance of robust validation and transparent analytical practices in data-driven studies (22), particularly when developing predictive models based on high-dimensional metabolomic data (23). In metabolomics research, a variety of machine learning algorithms have been applied to identify disease-related metabolic signatures, including Random Forest, Support Vector Machines, gradient boosting approaches such as XGBoost, and deep neural Networks (10).

4. Applications in Complex Disease

While high performances are observed in clinical predictions using ML models (XGBoost, Random Forest, and Deep Neural Networks, etc.), the black box problem arises in medical decision-making processes. Therefore, the requirements for explainability and accountability are gaining importance in the use of Explainable Artificial Intelligence (XAI) techniques in clinical biochemistry diagnostic algorithms (24). Commonly applied XAI approaches include SHapley Additive exPlanations (SHAP) and Local Interpretable Model-agnostic Explanations (LIME), which provide insight into the contribution of individual metabolites to model predictions and enhance the interpretability of machine learning models (25) With XAI models, clinical models for physicians gain transparency, and the effects of confounding factors can also be analyzed (26).

In model evaluations, metrics such as accuracy, sensitivity, specificity, and the area under the receiver operating characteristic curve (ROC-AUC) are commonly used to assess classification performance. Additional evaluation metrics include F1 score, Matthews correlation coefficient (MCC), the precision–recall area under the curve (PR-AUC), the Brier score for calibration assessment, and decision curve analysis (DCA) for evaluating clinical utility (27, 28, 29).

In metabolic disorders such as metabolic syndrome and type 2 diabetes, metabolic profiling has revealed coordinated alterations in amino acid, lipid, and energy metabolism that are not captured by single-biomarker analysis (30, 31). Machine learning-assisted analyses further enable stratification of individuals based on metabolic signatures associated with insulin resistance and disease progression (32, 33, 34). Importantly, individuals with similar clinical indicators such as comparable fasting glucose or HbA1c levels may exhibit markedly different underlying metabolic architectures. These latent metabolic subtypes, which cannot be resolved through conventional clinical markers alone, may have distinct pathophysiological trajectories and therapeutic responses. Machine learning assisted stratification enables the identification of such hidden metabolic phenotypes, highlighting the limitations of uniform clinical thresholds in heterogeneous disease (30, 31, 32).

Prospective studies further suggest that metabolite profiles can predict future risk of diabetes and cardiometabolic disease (35). In cardiovascular research, integrated metabolomic and machine learning approaches have identified metabolic patterns associated with cardiovascular risk beyond traditional clinical factors (36, 37, 38)

Metabolic profiling has also been applied to neurodegenerative diseases, where disruptions in energy metabolism and oxidative stress play central roles (39, 40). Notably, metabolic alterations may precede overt clinical symptoms, positioning metabolic profiling as a potential tool for identifying early biochemical signals of neurodegeneration. Machine learning methods can assist in distinguishing disease-related metabolic changes from age-associated metabolic variability, supporting exploratory efforts toward earlier and more biologically grounded disease characterization (39, 40). Beyond these conditions, metabolomic profiling combined with machine learning approaches is increasingly being applied to a broader spectrum of complex disorders, including obesity, non-alcoholic fatty liver disease (NAFLD), cancer, and sepsis, where metabolic dysregulation plays a central role in disease development and progression (10, 41, 42)

Despite its promise, the integration of metabolic profiling and machine learning faces several challenges. Biological heterogeneity, pre-analytical variability, and platform-specific effects can confound interpretation if not rigorously controlled (43, 44). Furthermore, batch effects resulting from technical variations across analytical runs may introduce systematic bias and complicate the interpretation of metabolomic datasets. Statistical issues, including false discoveries and model overfitting, further complicate biomarker identification and limit reproducibility (45).

Due to deficiencies in the data preprocessing process, incorrect approaches to filling in missing data, and normalization errors, erroneous results and incorrect model performances can be obtained. Therefore, the process of preparing the data for analysis is the most critical stage for model performance (46, 47).

Equally important is the challenge of interpretability. Without careful validation and biochemical contextualization, algorithm-derived patterns risk remaining mathematically robust yet biologically opaque. This gap between computational performance and clinical meaning represents a major barrier to translation (20, 48, 49).

5. Results

Metabolic profiling provides a powerful framework for understanding complex diseases by capturing coordinated alterations across metabolic pathways rather than relying solely on isolated biomarkers. Machine learning approaches complement this framework by enabling the analysis of high-dimensional metabolomic data and revealing latent metabolic signatures associated with disease risk, progression, and therapeutic response.

However, successful integration requires more than computational sophistication. Rigorous study design, standardized analytical workflows, and robust model validation are essential to ensure that data-driven insights translate into biologically meaningful and clinically relevant findings. From a clinical biochemistry perspective, the integration of metabolomic profiling with interpretable machine learning models offers considerable potential for improving biomarker discovery, refining disease stratification, and supporting more precise diagnostic and prognostic decision-making.

Future advances in this area will likely rely on the integration of metabolomics with other omics layers, as well as the development of transparent and clinically applicable analytical frameworks that can be implemented in routine laboratory workflows. Ultimately, the convergence of metabolomic profiling and interpretable machine learning approaches may enable a shift from single biomarker diagnostics toward a systems-level biochemical characterization of complex diseases.

6. References

1. Nicholson, J. K.,& Lindon, J. C. (2008). Systems biology: Metabonomics. Nature, 455(7216), 1054–1056. https://doi.org/10.1038/4551054a
2. Nielsen, J. (2017). Systems biology of metabolism. Annual Review of Biochemistry, 86(1), 245–275. https://doi.org/10.1146/annurev-biochem-061516-044757
3. Barabási, A.-L., Gulbahce, N., & Loscalzo, J. (2010). Network medicine: A network-based approach to human disease. Nature Reviews Genetics, 12(1), 56–68. https://doi.org/10.1038/nrg2918
4. Wishart, D. S. (2019). Metabolomics for investigating physiological and pathophysiological processes. Physiological Reviews, 99(4), 1819–1875. https://doi.org/10.1152/physrev.00035.2018 5.Patti, G. J., Yanes, O., & Siuzdak, G. (2012). Metabolomics: The apogee of the omics trilogy. Nature Reviews Molecular Cell Biology, 13(4), 263–269. https://doi.org/10.1038/nrm3314
6. Johnson, C. H., Ivanisevic, J., & Siuzdak, G. (2016). Metabolomics: Beyond biomarkers and towards mechanisms. Nature Reviews Molecular Cell Biology, 17(7), 451–459. https://doi.org/10.1038/nrm.2016.25
7. Beam, A. L.,& Kohane, I. S. (2018). Big data and machine learning in healthcare. JAMA, 319(13), 1317–1318. https://doi.org/10.1001/jama.2017.18391.
8. Topol, E. J. (2019). High-performance medicine: The convergence of human and artificial intelligence. Nature Medicine, 25(1), 44–56. https://doi.org/10.1038/s41591-018-0300-7
9. Troisi, J., Lombardi, M., Trotta, A., Abenante, V., Ingenito, A., Palmieri, N., Richards, S. M., Symes, S. J. K., & Cavallo, P. (2025). Double-Weighted Bayesian Model Combination for Metabolomics Data Description and Prediction. Metabolites, 15(4), 214. https://doi.org/10.3390/metabo15040214
10. Galal A, Talal M and Moustafa A (2022) Applications of machine learning in metabolomics: Disease modeling and classification. Frontiers in Genetics, 13, 1017340. https://doi.org/10.3389/fgene.2022.1017340
11. Holmes, E., Wilson, I. D., & Nicholson, J. K. (2008). Metabolic phenotyping in health and disease. Cell, 134(5), 714–717. https://doi.org/10.1016/j.cell.2008.08.026
12. Beger, R. D., Dunn, W. B., Schmidt, M. A., Gross, S. S., Kirwan, J., Cascante, M., … & Kaddurah-Daouk, R. (2016). Metabolomics enables precision medicine: A White Paper, Community Perspective. Metabolomics, 12(9),149.https://doi.org/10.1007/s11306-016-1094-613. Dunn, W. B.,& Ellis, D. I. (2005). Metabolomics: Current analytical platforms and methodologies. Trends in Analytical Chemistry, 24(4), 285–294. https://doi.org/10.1016/j.trac.2004.11.021

14. Thistlethwaite, L. R., Li, X., Burrage, L. C., Riehle, K., Hacia, J. G., Braverman, N., … & Milosavljevic, A. (2022). Clinical diagnosis of metabolic disorders using untargeted metabolomic profiling and disease-specific networks learned from profiling data. Scientific Reports, 12(1), 6556.https://doi.org/10.1038/s41598-022-10415-5
15. Tian, H., Lam, S. M., & Shui, G. (2016). Metabolomics, a Powerful Tool for Agricultural Research. International Journal of Molecular Sciences, 17(11), 1871.https://doi.org/10.3390/ijms17111871
16. Emwas, A.-H., Roy, R., Mckay, R. T., Tenori, L., Saccenti, E., Gowda, G. A. N., Raftery, D., Alahmari, F., Jaremko, L., Jaremko, M., & Wishart, D. S. (2019). NMR Spectroscopy for Metabolomics Research. Metabolites, 9(7), 123.https://doi.org/10.3390/metabo9070123
17. Madji Hounoum, B., Blasco, H., Nadal-Desbarats, L., Diémé, B., Montigny, F., Andres, C. R., Emond, P., & Mavel, S.(2015). Analytical methodology for metabolomics study of adherent mammalian cells using NMR, GC-MS and LC-HRMS. Analytical and Bioanalytical Chemistry, 407 (29),8861–8872.https://doi.org/10.1007/s00216-015-9047-x
18. Saccenti, E., Smilde, A. K., Hoefsloot, H. C. J., Westerhuis, J. A., Hendriks, M. M. W. B., & van der Greef, J. (2014). Reflections on univariate and multivariate analysis of metabolomics data. Metabolomics, 10,361–374.https://doi.org/10.1007/s11306-013-0598-6
19. Libbrecht, M. W.,& Noble, W. S. (2015). Machine learning applications in genetics and genomics. Nature Reviews Genetics, 16(6), 321–332. https://doi.org/10.1038/nrg3920
20. Camacho, D. M., Collins, K. M., Powers, R. K., Costello, J. C., & Collins, J. J. (2018). Next-generation machine learning for biological networks.Cell, 173(7), 1581–1592. https://doi.org/10.1016/j.cell.2018.05.015
21. Ghosh, T., Zhang, W., Ghosh, D., & Kechris, K. (2020). Predictive Modeling for Metabolomics Data. Methods in Molecular Biology, 313-336. https://doi.org/10.1007/978-1-0716-0239-3_16
22. Ioannidis, J. P. A. (2005). Why most published research findings are false. PLoS Medicine, 2(8), e124. https://doi.org/10.1371/journal.pmed.0020124
23. Steyerberg, E. W., & Harrell, F. E. (2016). Prediction models need appropriate internal, internal–external, and external validation. Journal of Clinical Epidemiology, 69, 245–247. https://doi.org/10.1016/j.jclinepi.2015.04.005
24. Hettikankanamage, N., Shafiabady, N., Chatteur, F., Wu, R. M. X., Ud Din, F., & Zhou, J. (2025). eXplainable Artificial Intelligence (XAI): A Systematic Review for Unveiling the Black Box Models and Their Relevance to Biomedical Imaging and Sensing. Sensors, 25(21), 6649. https://doi.org/10.3390/s25216649
25. Alkhanbouli, R., Matar Abdulla Almadhaani, H., Alhosani, F., & Simsekler, M. C. E. (2025). The role of explainable artificial intelligence in disease prediction: a systematic literature review and future research directions. BMC Medical Informatics and Decision Making, 25(1). https://doi.org/10.1186/s12911-025-02944-6
26. Bifarin OO, Fernández FM. (2024). Automated Machine Learning and Explainable AI (AutoML-XAI) for Metabolomics: Improving Cancer Diagnostics. Journal of the American Society for Mass Spectrometry, 35(6):1089-1100. https://doi.org/10.1021/jasms.3c00403
27. Chicco, D., Jurman, G. (2020). The advantages of the Matthews correlation coefficient (MCC) over F1 score and accuracy in binary classification evaluation. BMC Genomics, 21, 6. https://doi.org/10.1186/s12864-019-6413-7
28. Vickers, A. J., Van Calster, B., & Steyerberg, E. W. (2016). Net benefit approaches to the evaluation of prediction models, molecular markers, and diagnostic tests. BMJ, 352, i6. https://doi.org/10.1136/bmj.i6
29. Steyerberg, E. W., Vickers, A. J., Cook, N. R., Gerds, T. A., Gonen, M., Obuchowski, N. A., Pencina, M. J., & Kattan, M. W. (2010). Assessing the Performance of Prediction Models: A Framework for Traditional and Novel Measures. Epidemiology, 21, 128-138. https://doi.org/10.1097/EDE.0b013e3181c30fb2
30. Newgard, C. B., An, J., Bain, J. R., et al. (2009). A branched-chain amino acid–related metabolic signature that differentiates obese and lean humans and contributes to insulin resistance. Cell Metabolism, 9(4), 311–326. https://doi.org/10.1016/j.cmet.2009.02.002
31. Arjmand, B., Fana, S. E., Ghasemi, E., Kazemi, A., Ghodssi-Ghassemabadi, R., Dehghanbanadaki, H., … & Razi, F. (2022). Metabolic signatures of insulin resistance in non-diabetic individuals. BMC Endocrine Disorders, 22(1), 212. https://doi.org/10.1186/s12902-022-01130-3
32. Würtz, P., Tiainen, M., Mäkinen, V., Kangas, A. J., Soininen, P., Saltevo, J., … & Ala-Korpela, M. (2012). Circulating Metabolite Predictors of Glycemia in Middle-Aged Men and Women. Diabetes Care, 35(8), 1749-1756. https://doi.org/10.2337/dc11-1838
33. Ferrannini, E., Natali, A., Camastra, S., Nannipieri, M., Mari, A., Adam, K., … & Gall, W. (2013). Early metabolic markers of dysglycemia and type 2 diabetes and their physiological significance. Diabetes, 62(5), 1730–1737. https://doi.org/10.2337/db12-0707
34. Parigi, A. D., Tang, W., Liu, D., Lee, C. S., & Pratley, R. E. (2019). Machine Learning to Identify Predictors of Glycemic Control in Type 2 Diabetes: An Analysis of Target HbA1c Reduction Using Empagliflozin/Linagliptin Data. Pharmaceutical Medicine, 33(3), 209-217. https://doi.org/10.1007/s40290-019-00281-4
35. Wang, T. J., Larson, M. G., Vasan, R. S., et al. (2011). Metabolite profiles and the risk of developing diabetes. Nature Medicine, 17(4), 448–453.https://doi.org/10.1038/nm.2307
36. Rhee, E. P.,& Gerszten, R. E. (2012). Metabolomics and cardiovascular biomarker discovery. Clinical Chemistry, 58(1), 139–147. https://doi.org/10.1373/clinchem.2011.169573
37. Zhou, X., Sun, X., Zhao, H., Xie, F., Li, B., & Zhang, J. (2024). Biomarker identification and risk assessment of cardiovascular disease based on untargeted metabolomics and machine learning. Scientific Reports, 14(1), 25755. https://doi.org/10.1038/s41598-024-77352-3

38. Fereydooni, I., Vosoughi, M., Alighadr, A., Taghipour, N., Javaherinasab, M., Borujeni, M. A., … & Mostafavinia, A. (2025). A Systematic Review of Machine-Learning Models for Cardiovascular Risk Prediction. InfoScience Trends, 2(7), 65-82 https://doi.org/10.61882/ist.202502.07.06
39. Kaddurah-Daouk, R.,& Krishnan, K. R. R. (2009). Metabolomics: A global biochemical approach to the study of central nervous system diseases. Neuropsychopharmacology, 34(1), 173–186. https://doi.org/10.1038/npp.2008.174
40. Trushina, E.,& Mielke, M. M. (2014). Recent advances in the application of metabolomics to Alzheimer's Disease. Biochimica et Biophysica Acta – Molecular Basis of Disease, 1842(8), 1232–1239. https://doi.org/10.1016/j.bbadis.2013.06.014
41. Shao, M., Lü, Y., Xiang, H., Wang, J., Ji, G., & Wu, T. (2022). Application of metabolomics in the diagnosis of non-alcoholic fatty liver disease and the treatment of traditional Chinese medicine. Frontiers in Pharmacology, 13. https://doi.org/10.3389/fphar.2022.971561
42. Beyoğlu, D., Popov, Y., & Idle, J. R. (2024). Metabolomic Hallmarks of Obesity and Metabolic Dysfunction-Associated Steatotic Liver Disease. International Journal of Molecular Sciences, 25(23), 12809. https://doi.org/10.3390/ijms252312809
43. Perez-Sanchez, C, Perez-Campoamor, A, García-Delgado, G.D…& Lopez-Pedrera, C. (2025). Metabolomic and machine learning enhances patient diagnosis and stratification in systemic autoimmune diseases, Computers in Biology and Medicine, 199, 111325. https://doi.org/10.1016/j.compbiomed.2025.111325
44. Shazman, S., Carmel, J., Itkin, M., Malitsky, S., Shalan, M., Soreq, E., … & Kuperman, Y. (2025). Urine Metabolomic Profiling and Machine Learning in Autism Spectrum Disorder Diagnosis: Toward Precision Treatment. Metabolites, 15(5), 332. https://doi.org/10.3390/metabo15050332
45. Broadhurst, D.,& Kell, D. B. (2006). Statistical strategies for avoiding false discoveries in metabolomics and related experiments. Metabolomics, 2(4), 171–196. https://doi.org/10.1007/s11306-006-0037-z
46. Eicher, T., Kinnebrew, G., Patt, A., Spencer, K., Ying, K., Ma, Q., Machiraju, R., & Mathé, E. A. (2020). Metabolomics and Multi-Omics Integration: A Survey of Computational Methods and Resources. Metabolites, 10(5), 202. https://doi.org/10.3390/metabo10050202
47. Sun J, Xia Y. Pretreating and normalizing metabolomics data for statistical analysis. Genes Dis. 2023 Jul 7;11(3):100979. https://doi.org/10.1016/j.gendis.2023.04.018.
48. Scott, I., Carter, S. M., & Coiera, E. (2021). Clinician checklist for assessing suitability of machine learning applications in healthcare. BMJ Health & Care Informatics, 28(1), e100251. https://doi.org/10.1136/bmjhci-2020-100251
49. Zhu, Lin, Jie Feng, Rong Zheng, Jianzhu Wang, Jin Dong, Jing Gao, Qiuliang Yang, et al. 2025. "Development of an Artificial Intelligence Verification System Model for Clinical Biochemistry Laboratories Using Machine Learning." iLABMED: 1–10. https://doi.org/10.1002/ila2.70029

CHAPTER 11

Integrating Artificial Intelligence and Stereology for Quantitative Assessment of Immunohistochemical Staining Patterns in Tissue Sections

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1. Introduction

The basis of histological and pathological research relies on precise visualization and quantitative assessment of tissue structural and functional elements. In this context, immunohistochemistry (IHC) has become an essential method in both research and diagnostic pathology because it uncovers the cellular, subcellular, and regional distribution of specific proteins within tissue sections. Especially in oncology, inflammatory diseases, neuropathology, and translational experimental models, IHC enables the assessment not only of the presence of a marker but also its organization and biological significance within the tissue environment. However, the interpretation of IHC data still largely depends on semi-quantitative and observational systems such as the H-score, Allred score, or Quick score. Although these systems are commonly utilized in clinical practice, they face significant limitations, including inter-observer and intra-observer variability, limited reproducibility, and an inadequate representation of heterogeneous staining patterns. This issue becomes especially prominent when biomarker-based decisions directly impact treatment choices (1, 2).

To overcome these limitations, more objective, unbiased, and reproducible quantification methods are essential. Stereometry is a robust morphometric discipline that enables the objective measurement of three-dimensional biological structures from two-dimensional sections, employing principles of systematic random sampling and mathematical estimation. Stereological tools such as point counting, dissectors, fractal analysis, and volume density facilitate statistically reliable estimation of parameters like volume, count, surface area, and distribution. Consequently, stereology has long been regarded as one of the core methods for unbiased measurement in histomorphometric assessment. However, manual stereological analysis is time-consuming and labor-intensive, requiring consider-

able operator expertise. This limitation creates a significant bottleneck, particularly when analyzing large sample series or extensive tissue regions (1, 3).

The development of digital pathology and the high-resolution digitization of all slide images (whole-slide images, WSI) have greatly expanded the use of computational methods in histopathological assessment. This shift has accelerated the integration of artificial intelligence (AI), particularly deep learning-based image analysis algorithms, into pathology. Today, convolutional neural networks (CNNs), U-Net segmentation architectures, and other deep learning models achieve high performance in tasks such as cell recognition, staining intensity analysis, positive cell ratio calculation, and spatial pattern detection. However, the automation and speed provided by AI are not enough on their own; the effectiveness of algorithms depends heavily on dataset quality, annotation accuracy, staining standardization, and the diversity of training samples. Therefore, there is a need for analysis frameworks that are not only 'automatic' but also 'unbiased and biologically representative' (1, 4-6).

The integration of AI and stereology provides a combined approach that addresses two key needs in the quantitative assessment of immunohistochemical (IHC) staining patterns. AI can swiftly perform segmentation, classification, and measurement across large tissue areas; however, stereology ensures methodological accuracy by defining measurement regions, sampling logic, and statistical confidence. Consequently, it is now possible to evaluate not only basic results such as the positive staining rate but also more detailed biological parameters, including volumetric density, numerical density, and the spatial distribution of staining within tissue. In this section, considering current challenges in IHC quantification, the fundamental principles of stereology and AI, their combined applications, relevant areas, and methodological limitations will be comprehensively discussed.

2. Quantitative Challenges in IHC Staining Evaluation

One of the main challenges in the quantitative evaluation of IHC staining is that the staining often shows biological heterogeneity, multifocality, and spatial irregularity. Within the same tissue section, the intensity, distribution, cellular localization, and variation of the positive signal across tissue compartments can differ considerably. This complexity is increased in areas such as the tumor microenvironment, inflammatory cell infiltration, stromal activation, or neurodegenerative protein build-up (7). Despite this, many studies still assess by selecting only a few 'representative areas' or using subjective intensity scoring. This method introduces measurement bias (sampling bias) and does not accurately reflect true biological variation. The most common methods in traditional IHC assessment include grading staining intensity, calculating the percentage of positive cells, and applying semi-quantitative scoring systems that combine these two parameters. However, these methods often rely too heavily on the observer's experience and can lead to high variability, especially in specimens with borderline positivity, weak staining, or heteroge-

Table 1. Comparative overview of conventional, stereological, and AI-based approaches in IHC analysis

Parameter	Conventional IHC Evaluation	Stereological Approach	AI-Based Analysis
Quantification type	Semi-quantitative	Fully quantitative	Fully quantitative
Observer dependency	High	Moderate	Low
Sampling strategy	Selective (subjective fields)	Systematic random sampling	Whole-slide or patch-based
Reproducibility	Limited	High	High (if validated)
Throughput	Low	Low–moderate	High
Spatial analysis	Limited	Moderate	Advanced
Handling heterogeneity	Poor	Good	Excellent
Complexity	Low	Moderate–high	High
Time requirement	Low	High	Low
Clinical adoption	Established	Limited	Emerging

neous distribution. Additionally, these scores often do not accurately represent the actual three-dimensional distribution within the tissue or the spatial organisation of positive cells (8). These limitations are especially clear in the assessment of markers such as PD-L1, HER2, ER/PR, and Ki-67 in clinical pathology. Standardizing manual scoring is particularly difficult for markers like PD-L1, which require interpretation across different contexts in both tumor and immune cells. Furthermore, IHC results fluctuate not only during the image analysis stage but also throughout the pre-analytical and analytical processes. Several technical factors, such as fixation time, tissue processing protocol, section thickness, antigen retrieval, the antibody clone used, chromogen concentration, and scanner parameters, can directly impact the final staining pattern. Therefore, a truly reliable quantification method requires a multi-layered framework that includes not only 'image measurement' but also principles of sampling, standardization, and validation. This makes the combined use of stereometry and AI more methodologically significant (2, 3).

3. Stereology as an Unbiased Quantitative Approach in Histopathology

Stereology is an objective analytical method grounded in mathematical and statistical principles that enables quantitative three-dimensional analysis of biological structures from two-dimensional histological sections. Its main goal is to produce estimates from tissue samples that are not only measurable but also reproducible and statistically valid. The key difference between stereology and traditional histomorphometric techniques is that stereology explicitly defines both the measurement and the sampling strategy used to obtain it. Central to this approach is the principle of systematic random sampling, which reduces selection bias by preventing the researcher from focusing only on areas that are visually prominent, heavily stained, or morphologically "most appealing," thus ensuring

that analysis areas more accurately reflect the tissue. Especially given that lesions, inflammatory cell infiltration, or immunoreactivity are not evenly distributed in histopathological preparations, this method yields results that are more biologically representative and methodologically more dependable. Therefore, in IHC assessments where heterogeneous staining patterns are common, stereology offers greater accuracy and representativeness than traditional methods that focus on selected "hot spot" areas. As defined by Gundersen and colleagues, modern stereological tools have significantly improved the estimation of three-dimensional parameters such as volume, count, surface area, and length in pathological studies; subsequent applications have shown that stereology provides a standardized and reproducible framework not only in neuroscience but also in wider histopathological and experimental tissue research (9).

The most common stereological tools in histopathological analyses include point counting, the dissector method, the fractal method, volume fraction (Vv), numerical density (Nv), and surface density (Sv). These parameters allow for objective estimation of the proportion of specific structures within the total tissue volume, the number of cells per unit volume, or surface characteristics. For instance, volume fraction is utilized to assess the proportion of the immunopositive area within the entire tissue, while numerical density is valuable for revealing the quantitative distribution of a particular cell population within the tissue. Methods such as the dissector and fractionator, meanwhile, offer notable advantages, especially for cell counting and estimating particle-like structures within the tissue (10).

In the context of IHC, these methods can generate outputs such as the ratio of positive-stained areas to the total tissue area, positive cell density, the volumetric distribution of specific immunoreactivity within the tissue, or the numerical distribution of cellular structures. Using these methods, the numerical density of positively stained cells, the volumetric distribution of a specific immunoreactivity within the tissue, and the distribution of staining across tissue compartments can be assessed more reliably. For example, in an inflammatory experimental model, the numerical density of CD68-positive macrophages per unit tissue area can be estimated more objectively than by conventional visual scoring (11). Similarly, the volumetric density of Ki-67-positive nuclear staining in neoplastic tissues, or the proliferative heterogeneity within a specific tumor region, can also be analyzed more meaningfully using stereological methods. This approach is particularly important when biomarker expression is not uniform throughout the section (12).

The most significant advantage of stereology is not just that it provides quantitative data but also that it improves the statistical representativeness of this data. In other words, stereological estimates can more accurately reflect biological variability within tissue. This feature enhances the comparability of data collected in diagnostic pathology, translational research, and experimental disease models (13, 14). Recent protocol publications show that, when combined with appropriate sampling, stereology offers high reliability for assessing parameters such as tissue damage, neurodegeneration, cell loss, and the distribution of immunoreactivity. However, the routine use of traditional stereological methods has been limited by the need for manual counting, high time requirements, and user de-

pendence. Especially in the digital pathology era, where high-resolution whole-slide images are readily accessible, integrating stereological principles with automated analysis systems has become a necessary field (15, 16). In this context, AI provides a powerful tool to overcome stereology's limitations in speed and scalability. Moreover, stereology offers not only area-based but also three-dimensional insights into tissue analysis. Although histological sections are inherently two-dimensional, biological processes occur within a three-dimensional organization. Since stereological methods aim to generate accurate predictions of three-dimensional structures from two-dimensional views, they have greater biological significance than approaches based solely on visual intensity grading. This advantage is particularly relevant in fields where spatial organization is vital, such as angiogenesis, cellular infiltration, neurodegenerative protein accumulation, and tumor heterogeneity (17). However, substantial challenges hinder the widespread use of stereological methods in routine histopathology. Firstly, traditional stereological analyses often require manual counting or semi-automated measurements, thereby increasing the time required. Secondly, although the method is theoretically unbiased, its practical success depends on factors such as an appropriate sampling plan, enough sections, correct field selection, and operator experience. Therefore, it cannot be claimed that stereology completely removes user dependence; however, this dependence remains within a more controlled framework compared to classical histomorphometry, which relies on non-random area selection. Especially in studies with large sample sizes, manual stereological analysis can impose a considerable workload (2, 18).

In the age of digital pathology, the ability to scan all slide images at high resolution has created both opportunities and new requirements for stereological analysis. Manually evaluating very large image areas is impractical; however, these images serve as an ideal data source for automated or semi-automated processing (19). As a result, in current literature, the integration of stereological principles with computer-aided image analysis is increasingly significant. AI-supported segmentation and object recognition systems have the potential to address issues related to speed, scalability, and reproducibility in stereology (20).

AI, especially through deep learning-based image analysis, can rapidly perform tasks such as cell detection, segmentation, classification, and quantification in histopathological images. However, the reliability of automated analysis systems depends not only on algorithmic accuracy but also on the validity of the sampling strategy. Here, stereology and AI emerge as two complementary approaches: while stereology provides the foundation of unbiased sampling for measurement, AI allows this measurement to be conducted at scale and speed. A deep learning-based automated stereology study published in 2024 reported over 90% accuracy compared to manual stereology, full test-retest agreement, and about 60-fold higher efficiency; these findings show that stereological principles can be successfully integrated into automated analysis systems. Therefore, in current histopathology, stereology should be viewed not merely as a traditional morphometric method but also as a methodological framework that can be combined with digital pathology and AI. Particularly in quantitative analysis of IHC staining patterns, combining the objectiv-

ity of stereology with the speed and pattern recognition of AI can yield more objective, reproducible, and biologically meaningful results (21).

4. AI in Digital IHC Analysis

AI has brought about a remarkable transformation in digital pathology in recent years, especially through deep learning-based approaches. With the high-resolution digitization of all whole-slide images (WSIs), histopathological assessment has shifted from a purely observational process conducted at the microscope to a computational field in which large volumes of image data can be processed algorithmically. This change has enabled not only traditional tasks such as diagnostic classification and lesion detection but also more advanced tasks like quantitative analysis of IHC staining patterns, separation of tissue compartments, and examination of spatial biomarker patterns. Recent reviews show that AI significantly contributes to digital pathology, particularly in diagnostic accuracy, workflow efficiency, and reproducibility (22).

One of the most significant contributions of AI in IHC analysis is its ability to process large image areas quickly and consistently. In traditional assessment, the pathologist or researcher often comments on positivity rate, staining intensity, or cellular distribution based on a limited number of areas (19). In contrast, AI-based analysis systems can process thousands or even millions of cellular elements simultaneously across extensive areas covering the entire slide. This not only reduces the workload but also allows for a more comprehensive assessment of heterogeneous staining patterns. This capability is particularly important in fields such as the tumor microenvironment, inflammatory cell infiltration, stromal remodeling, and vascular marker distribution (23).

Cell and tissue segmentation is among the most common applications of AI in digital IHC analysis. Segmentation is the process of automatically identifying and separating meaningful structures within an image, such as nuclei, membranes, cytoplasmic signal areas, stromal regions, or necrotic areas. This task is crucial, especially in IHC assessment, because the accurate identification of cell type, tissue region, and cellular compartment for a positive stain is vital for understanding the biological significance of the quantitative data (24). One of the most widely used architectures in this field is the U-Net, along with its variants. Thanks to its encoder–decoder structure, developed for biomedical image segmentation, U-Net can process both local morphological details and broader contextual information simultaneously. This architecture has been successfully applied in a variety of tasks, including cell nucleus segmentation, membrane labeling, cytoplasmic staining analysis, and stromal compartment differentiation. The advanced versions of U-Net, such as 3D U-Net, offer advantages for analyzing volumetric data or multilayer images, while nnU-Net has become a notable standard in biomedical segmentation due to its architecture, which can optimize itself according to the dataset. Such architectures have the potential to provide more adaptable analysis across different laboratory conditions and tissue types. For more complex segmentation tasks, Mask R-CNN, HoVer-Net,

CellViT and transformer-based hybrid models stand out. Particularly in areas containing overlapping or morphologically irregular cell nuclei, instance segmentation-based approaches enable the individual separation of cells. The increasing use of vision transformer-based models for pathology images in recent years has enabled modeling not only local pixel relationships but also contextual relationships between distant areas. This is particularly important in the analysis of heterogeneous tumor areas, irregular inflammatory infiltration, or irregular staining patterns. It has been demonstrated that state-of-the-art transformer-based models, such as CellViT, exhibit high performance in core segmentation and classification (4, 5, 25-27). However, the use of AI applications in IHC should not be assessed solely on technical success. The fact that a model demonstrates high accuracy does not automatically mean that it is clinically or biologically reliable. As AI models are sensitive to patterns in the training data, they may show excessive adaptation to staining protocols from limited centers or to specific scanner characteristics. This situation may reduce generalizability across different laboratories or patient cohorts. Systematic reviews published in recent years highlight that AI holds strong potential in digital pathology; however, they emphasize that requirements for multi-center validation, standardization and explainability are critical for clinical integration. Consequently, the most valuable application of AI in IHC is not merely the automated generation of scores that 'mimic' manual assessment, but also its ability to quantitatively visualize tissue patterns that were previously impossible to measure routinely. However, for this potential to translate into biologically and methodologically reliable results, it must be supported by a stereological framework (1, 6).

5. Integrating AI and Stereology: A Hybrid Quantification Framework

Both conventional observational scoring and algorithmic analysis alone have clear limitations when evaluating IHC staining patterns. Traditional manual assessment, even when performed by experienced observers, inevitably involves subjectivity in stages such as field selection, interpretation of staining intensity, and identification of positive cells. Conversely, while AI-based analysis systems offer high speed, automation, and large-scale data processing capabilities, their outputs are reliable only when grounded in a sampling strategy that is both biologically representative and methodologically unbiased. In other words, even a highly advanced segmentation model can produce biologically limited or biased results if the analyzed areas do not reflect the tissue's true heterogeneity. Therefore, the combined use of AI and stereology should be viewed not merely as a technical combination but as a methodological integration that enhances measurement validity. While stereology determines the sampling logic, the predictive framework, and the statistical representativeness of the quantitative output, AI automates processes such as recognition, classification, segmentation, and density analysis within this sampling framework. As a result, high efficiency and biological validity are integrated within a single analytical approach. Recent systematic reviews in digital pathology highlight that AI applications

have great potential, but they require sampling, validation, and explainability methods to ensure reliable outcomes in clinical and research settings (6, 28, 29).

To comprehend the integration of AI with stereology, it is essential to clearly demonstrate the complementary nature of these two methods. Stereology addresses the question of "where and how measurements should be taken," identifying representative tissue areas using tools such as systematic random sampling, test grids, point counting, dissectors, or fractionators, and providing unbiased quantitative estimates of three-dimensional biological structures from these areas. AI, on the other hand, focuses on the question of "what should be measured in these areas and how it should be identified." Deep learning-based segmentation and classification models can quickly identify cell nuclei, membrane or cytoplasmic staining patterns, stromal components, and immunopositive structures. Consequently, the core of the hybrid framework involves the following division of labor: i. Stereology establishes the methodological backbone of sampling and estimation. ii. AI ensures the high-accuracy processing of image content. Thanks to this integration, IHC analysis can provide not only the positivity rate but also more meaningful parameters such as volumetric density, numerical density, area fraction, spatial distribution patterns, and compartment-specific expression. Particularly in complex tissue patterns such as heterogeneous tumor tissues, areas of inflammatory infiltration, fibrotic regions, or vascular remodeling, these outputs provide greater informational value than traditional manual scoring systems (30-32).

In practice, a hybrid IHC quantification framework involves several key stages. The first stage covers image acquisition and preprocessing. All slide images are scanned at high resolution, with processes such as color standardization, artifact reduction, and contrast balancing applied. This stage is crucial because technical variations in staining intensity can directly affect the generalizability of AI models. Specifically, differences in color and intensity in specimens from different laboratories or scanner systems can introduce bias into algorithmic analyses. Therefore, digital pre-processing and stain normalization are regarded as essential components of hybrid systems. The second stage is tissue and cell segmentation (32, 33). In this step, positive and negative cells, stromal areas, necrotic regions, or specific immunoreactive areas are automatically identified using U-Net, nnU-Net, Mask R-CNN, HoVer-Net, or transformer-based models. This process decomposes the image into its biologically meaningful subcomponents. It is especially important in the context of IHC, as it determines not only the 'presence' of staining but also in which cell, compartment, and tissue context it is observed. The third stage involves integrating stereological sampling, a distinctive feature of the hybrid framework. Here, virtual stereological grids are applied either across the entire slide image or to image areas selected by systematic random sampling. Thus, whilst the AI's capacity to scan the entire slide is preserved, the measurement outputs are based not only on non-random "notable" areas but also on statistically representative ones. This method can both reduce computational costs and improve biological accuracy, particularly in large WSI datasets. In the final stage, quantitative stereological outputs are calculated. These may include the following parameters (34-36):

Volume density (Vv): The ratio of the positive-stained area to the total tissue volume

Table 2. Major stereological parameters and their applications in IHC analysis

Parameter	Definition	Application in IHC	Biological Interpretation
Volume density (Vv)	Fraction of structure volume relative to total tissue	Estimation of positive staining area	Extent of biomarker expression
Numerical density (Nv)	Number of particles per unit volume	Counting positive cells	Cellular infiltration or proliferation
Surface density (Sv)	Surface area per unit volume	Membrane staining analysis	Cell–cell or cell–matrix interaction
Area fraction	Ratio of stained area to total area	Quantification of immunoreactivity	Marker distribution
Disector method	3D counting method avoiding bias	Cell number estimation	True cell counts
Fractionator	Sampling-based counting approach	Estimation of total cell number	Population size

Numerical density (Nv): The estimated number of a specific immunopositive cell population per unit volume

Surface density (Sv): Surface-related estimates for membrane-bound or boundary-associated markings

Area fraction: The percentage of tissue area occupied by positive immunoreactivity

Spatial pattern analysis: Cell clustering, tumor-stroma interaction, perivascular localization, or inflammatory niche organization

This approach can generate multi-layered biological information that is difficult, or often impossible, to obtain through manual scoring.

The integration of AI with stereology is crucial not only during the analysis phase but also in model training and validation. Many deep learning models are only as effective as the quality of the annotations used during training. However, if training data is chosen solely from 'well-defined' or prominent positive areas, the model may fail to learn the true tissue heterogeneity. This is especially important in applications such as IHC, where staining intensity varies across regions within the tissue. Stereological sampling principles provide a robust solution here. Selecting image patches for training through systematic random sampling ensures the model learns not only highly distinctive patterns but also a wider range of biological variation (37). Likewise, during the validation phase, model performance must be assessed not just against "easy regions" but against representative sampling areas. This approach helps the model demonstrate more reliable performance under real-world conditions. Recent meta-analyses in the field of digital pathology have shown significant heterogeneity in study design, data structure, and validation quality, despite AI models reporting high accuracies; this highlights the importance of data design supported

Table 3. Common artificial intelligence methods used in digital IHC analysis

Method	Description	Application in IHC	Strengths	Limitations
U-Net	Encoder–decoder CNN for segmentation	Cell/nucleus segmentation	High accuracy	Requires annotated data
nnU-Net	Self-configuring segmentation framework	Multi-dataset adaptability	Robust performance	Computational cost
Mask R-CNN	Instance segmentation model	Individual cell detection	Precise object separation	Complex training
HoVer-Net	Multi-task network	Nuclear segmentation + classification	Multi-output	Training complexity
Vision Transformers (ViT)	Attention-based models	Tissue pattern recognition	Global context modeling	High data demand
Deep CNNs	Feature extraction networks	Intensity and pattern analysis	High scalability	Limited explainability

by stereological logic. A key benefit of AI-supported stereological analyses is their capacity to generate more insightful biological results that surpass traditional IHC scoring. Usually, many IHC assessments depend solely on subjective grading of the percentage of positive cells or staining intensity. In contrast, the hybrid framework enables a far more refined, multidimensional evaluation of these parameters. For example, a Ki-67 assessment in a tumor can be analyzed not only as the 'percentage of positive nuclei' but also in terms of whether proliferative cells are concentrated at the tumor periphery or center, whether they are associated with the stroma or invasive margins, and how this distribution relates to intratumoral heterogeneity. Similarly, in PD-L1 analysis, it is not just tumor cell positivity that is assessed; the distribution within the immune cell compartment, tumor-immune contact zones, and infiltration density can also be evaluated together. Such spatial and density-based outputs may have translational value, especially regarding immunotherapy response or biomarker-based patient stratification. AI compilations focused on IHC also show that the field now aims for more than just 'automatic score generation'; it is progressing towards approaches that evaluate the spatial and quantitative aspects of tissue biology in tandem (38-40).

6. Applications in Research and Diagnostic Pathology

The combined use of AI and stereology not only offers technical convenience for assessing IHC staining patterns but also introduces a new analytical framework that boosts the clinical relevance of biomarker quantification. This hybrid approach allows high-volume automated analysis over large tissue areas while improving the biological representative-

ness and methodological objectivity of measurements through stereological sampling principles. Especially for biomarkers with heterogeneous expression, it becomes feasible to evaluate more detailed parameters such as distribution patterns, cellular density, and compartment-specific localization, rather than relying solely on average density or limited-area scoring. As a result, the integration of AI and stereology is becoming increasingly important in both research pathology and clinical decision-making (22, 41).

6.1. Oncopathology

Oncopathology is one of the most significant applications for AI-supported stereological IHC analysis. In current oncology practice, biomarkers are used not only for diagnostic classification but also for determining prognostic risk, selecting targeted therapies and assessing suitability for immunotherapy. Consequently, even minor differences in biomarker scoring can directly influence treatment decisions. In breast cancer, markers such as ER, PR, HER2 and Ki-67, and in other tumor types, markers such as PD-L1, play a central role in clinical management. Current consensus documents also clearly emphasize that the assessment of ER, PR, Ki-67 and HER2 is fundamental to treatment planning, particularly in early-stage breast cancer (2, 42, 43).

In breast cancer, the status of the estrogen receptor (ER), progesterone receptor (PR), and HER2 is a vital biomarker for understanding tumor biology and guiding systemic treatment choices. However, the expression of these markers can vary across regions within the same tumor; notably, borderline positivity, low-level expression, and intratumoral heterogeneity can lead to substantial variability in manual scoring. AI-based digital pathology tools are better suited to capture this heterogeneity because they can assess much larger areas across entire slide images. When combined with stereological sampling strategies, they facilitate a more representative analysis of quantitative data from various tumor regions. This method goes beyond assessments limited to a single H-score by providing additional insights into the regional distribution of differences in expression and intensity. Recent studies reviewing the application of AI in breast pathology also highlight its potential to enhance inter-observer agreement in hormone receptor evaluation, tumor grading, and mitotic activity analysis (41, 44, 45).

PD-L1 assessment is one of the most challenging yet crucial IHC analyses in modern oncological practice. The main reasons include the following: the staining pattern can differ between tumor and immune cells; the membrane signal exhibits variability in both intensity and continuity; and there is notable spatial heterogeneity within the tumor microenvironment. Consequently, PD-L1 scoring is marked by a high degree of variability from both technical and observational standpoints. AI-based analyses can automatically differentiate tumor cells from immune cells across the entire slide, providing a more objective calculation of the proportion of positive cells. Additionally, density and distribution analyses conducted on regions sampled using stereological principles have the potential to more reliably assess immune cell infiltration within the tissue. A study published in 2024 reported that an AI-based PD-L1 assessment method for diffuse large B-cell lymphoma

enhances objectivity and interpretability through large-scale cell annotations and showed high agreement between AI and pathologist assessments. These findings strengthen the clinical-translational potential of AI-supported quantitative methods for complex biomarkers such as PD-L1 (46, 47).

In the context of colorectal cancer, digital immune profiling approaches based on immune cell density and the relationship with the tumor-invasive margin provide valuable insights into prognosis. The ability to measure the density and spatial relationships of immune cell populations, such as CD3/CD8, using digital image analysis and machine learning has made classical immune scoring approaches more detailed and scalable. In this context, the combined use of AI and stereological sampling can yield more biologically meaningful results by incorporating not only the total number of immune cells but also their spatial relationships with tumor nests, stromal areas and the invasive margin into the analysis (48).

The Ki-67 proliferation index, while important in treatment planning, especially for breast cancer, is one of the biomarkers that shows poor reproducibility in manual assessment. Key challenges include distinguishing between positive and negative nuclei, selecting hotspots, subjectively determining staining thresholds, and accounting for tumor heterogeneity. AI-based systems can automatically differentiate between positive and negative nuclei through nuclear segmentation and classification; when combined with stereological sampling, they can offer a more representative proliferation analysis by reducing hot-spot bias. A 2024 multi-observer study demonstrated that AI use reduced the error rate in Ki-67 assessment in breast cancer, significantly enhanced inter-observer agreement, and shortened assessment times. These findings suggest that AI-supported stereological analyses could provide a notable clinical advantage for numerical markers such as Ki-67, which demonstrate high variability (49-52).

6.2. Neuroscience and Neuropathology

Stereology has historically been one of the most effective quantitative methods in neuroscience and neuropathology. This is mainly due to the dense cellular organization, regional heterogeneity, and three-dimensional structural complexity of neural tissue. Many parameters, such as neuron counting, glial cell density, plaque burden, the distribution of protein aggregates, and the assessment of synaptic changes, have been examined using stereological methods for years. However, traditional stereological techniques are very time-consuming, especially when assessing large brain regions or numerous sections (13, 14, 17, 53).

Digital neuropathology and AI-driven image analysis offer the potential to significantly ease this bottleneck. Recent reviews emphasize that AI in digital neuropathology is becoming increasingly important, not only for classification but also for quantitative tissue analysis and transparent pattern recognition in experimental neurodegeneration models. Parameters such as the numerical density of specific neuronal populations, the regional distribution of astrocytic and microglial responses, and the surface or volumetric density

of synaptic structures are fundamental to neuroanatomical and experimental studies of neuroinflammation (37). AI-supported image analysis provides scalable measurement capabilities across large datasets by automating the segmentation and classification of these structures. When combined with stereological principles, the results obtained are not only rapid but also more biologically representative. This approach offers a robust methodological framework, especially for comparing treatment effects, regional cellular responses, and patterns of protein accumulation in experimental models. The current literature suggests that developing interpretable and generalizable AI models is a key objective for the future of experimental neuropathology (54-59).

In Alzheimer's disease and related neurodegenerative disorders, the quantitative distribution of pathological components within tissue, such as beta-amyloid plaques, hyperphosphorylated tau accumulation, glial activation and synaptic loss, is of great importance. The traditional manual assessment of these structures often relies on area selection and is particularly prone to measurement bias in regions with focal accumulation. AI-based analyses can automatically identify immunopositive plaques or aggregates, enabling counting and density measurements across larger areas; stereological sampling ensures that these measurements are based on unbiased, statistically valid sampling logic. In 2024, it was reported that cases of multiple system atrophy could be stratified into subgroups based on region-specific variability through computer-assisted morphological analysis of α-synuclein pathology; such studies demonstrate that computer-assisted quantitative analyses in neurodegenerative proteinopathies can contribute not only to descriptive characterization but also to the identification of new biological subtypes (53, 58, 60-65).

6.3. Inflammation, Fibrosis and Experimental Models

The potential of AI-assisted stereological analyses goes beyond oncology and neuropathology; it is becoming increasingly important in many other areas, including cardiovascular pathology, hepatic fibrosis, renal interstitial changes, and chronic inflammatory tissue responses. Key parameters to assess in these systems include the extent of fibrosis, immune cell infiltration density, vascularization patterns, and stromal remodeling. Since most of these parameters are derived from only a few selected regions in traditional observational assessments, they are vulnerable to measurement bias; thus, AI analyses supported by stereological sampling can offer a significant advantage. Parameters such as macrophage infiltration, lymphocyte density, fibroblast activation, angiogenesis, or apoptotic signaling are often measured using IHC in experimental tissue models. In this context, analyzing markers such as CD68, CD3, α-SMA, VEGF, Caspase-3, or IL-6 using AI-based analyses with stereological sampling rather than traditional 'visual scoring' may yield more reliable and reproducible outcomes. This hybrid approach is especially beneficial for the objective comparison of tissue responses in experimental animal models. In cardiovascular diseases, myocardial fibrosis is a key marker of tissue remodeling and clinical prognosis. However, manual assessment of fibrosis in histological sections can cause inter-observer variability, particularly in areas with mild to moderate fibrosis. A 2023 study demonstrated that

AI-assisted automated quantification of myocardial fibrosis in endomyocardial biopsies significantly improved measurement consistency among experienced pathologists. These findings suggest that digital analysis tools may provide more reliable measurements of parameters such as collagen accumulation or inflammatory infiltration in cardiac tissue. When combined with stereological sampling principles, this approach could provide a more precise estimate of fibrosis across extensive and diverse tissue regions. The quantitative assessment of fibrosis and inflammation in the liver, kidneys, and other organ systems is highly significant in preclinical model studies and translational research. A study conducted in 2024 using a human 3D MASH model reported that AI-based digital pathology analysis can be utilized to evaluate the efficacy of antifibrotic compounds and enables the automatic quantitative analysis of fibrotic patterns. Similarly, a 2023 study demonstrated that hepatic fibrosis in a CCl4-induced mouse model could be automatically assessed using multi-scale CNN-based algorithms. These studies emphasize that common yet heterogeneous patterns, such as fibrosis, can be evaluated not only by area percentage but also in the context of distribution and tissue organization. AI-based analyses, supported by stereological principles, can provide more reliable volumetric density estimates and comparative tissue analyses in such systemic pathologies (27, 66-71).

When the various application areas are considered together, the key benefit of AI-stereology integration is its ability to assess heterogeneous tissue patterns on a larger scale in a more objective and reproducible manner. In oncopathology, biomarker quantification and analysis of the immune microenvironment; in neuropathology, protein aggregates and cellular density measurements; and in cardiovascular and other systemic pathologies, the quantitative analysis of fibrosis and inflammation are the primary areas where this approach excels. However, the true clinical benefit of these systems will only become clear once requirements for multi-center validation, standardization and explainability are met, rather than merely through reports of high accuracy. Current literature demonstrates that this approach is a powerful research and decision-support tool; however, it highlights the need for the methodological framework to mature further for full integration into routine practice. The most notable advantage of the hybrid AI-stereology framework is its ability to provide unbiased and reproducible measurements from high-volume data. This approach is particularly valuable in the following respects (1, 13, 17, 27, 72, 73).

Unbiased sampling: Stereology more accurately represents tissue heterogeneity by reducing area-selection bias.

Automation and speed: AI overcomes the time-consuming nature of manual analyses, enabling the processing of large cohorts.

Production of in-depth biological outputs: Analyses of density, distribution, clustering and compartment-specific expression can be performed beyond classical semi-quantitative scores.

Reproducibility: The ability to reanalyze the same image using the same parameters enhances research quality and comparability.

Table 4. Proposed hybrid workflow integrating AI and stereology for quantitative IHC analysis

Step	Process	Description	Output
1	**Slide digitization**	Whole-slide image acquisition	High-resolution WSI
2	**Preprocessing**	Color normalization, artifact removal	Standardized images
3	**AI-based segmentation**	Detection of cells and tissue compartments	Segmented structures
4	**Classification**	Identification of positive/negative cells	Labeled data
5	**Stereological sampling**	Systematic random sampling	Representative regions
6	**Quantification**	Calculation of Vv, Nv, Sv	Quantitative metrics
7	**Spatial analysis**	Distribution and clustering assessment	Spatial biomarkers
8	**Validation**	Comparison with manual/stereological gold standard	Reliability metrics

Clinical and translational applicability: This hybrid structure is significant not only for research purposes but also for biomarker standardization and digital pathology-based decision support systems. These advantages are particularly evident in oncopathology, inflammatory tissue biology, neuropathology and experimental animal models.

7. Methodological Challenges and Limitations

Despite the strengths of this approach, there are significant methodological limitations to consider when combining AI and stereology. Firstly, the pre-analytical and analytical variability of IHC remains a fundamental issue. Tissue fixation, section thickness, antigen retrieval, antibody clone, chromogen concentration and scanner variations can directly affect the performance of the algorithms. Therefore, the models developed must be tested not only on single-center data but also under different laboratory and field conditions (6, 69). The second major issue is that most deep learning models are black box in nature. From a pathologist's perspective, it is crucial for clinical confidence that not only the result but also the process by which it was reached is understandable. As a result, explainable AI (XAI) approaches have become more prominent in recent years. Heatmaps, attention maps, pixel-based regions of interest, and decision visualization techniques can help reveal the morphological cues the model relies on. This both improves algorithmic reliability and fosters better human-machine collaboration (20, 74). Thirdly, the integration of stereological sampling principles into AI systems has not yet been fully standardized. Although digital grid-based sampling and virtual stereological region selection are possible, research is still ongoing to determine which sampling density is optimal for each tissue type, which parameters produce the most meaningful output, and which clinical outcomes these approaches are most closely associated with. Consequently, this field should be regarded as a research area that is methodologically evolving but holds high translational potential (6, 69).

Table 5. Advantages and limitations of AI-stereology integration in the IHC analysis

Aspect	Advantages	Limitations
Accuracy	Reduces observer bias	Dependent on data quality
Reproducibility	Standardized analysis	Requires validation
Throughput	High-speed processing	Computational demands
Biological insight	Enables spatial and density analysis	Interpretation complexity
Scalability	Suitable for large datasets	Infrastructure requirement
Clinical use	Supports decision-making	Regulatory barriers

8. Future Perspectives

One of the most significant trends shaping the future development of this field is the integration of multiplex IHC, spatial biology, and multimodal digital pathology. The simultaneous assessment of multiple markers within a single tissue section will enable a more detailed analysis of cellular phenotypes and cell-cell interactions. While AI can process this multi-layered image data, stereometry will enhance its quantitative representational power. Another key trend is the development of not only descriptive but also prognostic and predictive modelling capabilities. In the future, the heterogeneity index, spatial clustering coefficient, cellular neighborhood patterns, and stereological density parameters, when combined with classical pathology scores, may provide stronger predictions of patient prognosis, treatment response, or biological aggressiveness. However, for this potential to translate into reliable clinical use, transparent algorithms, multi-center validation and standardized workflows will remain fundamental requirements.

9. Conclusion

The evaluation of IHC staining patterns is indispensable for modern pathology and translational biomedical research; however, traditional semi-quantitative approaches have significant limitations due to subjectivity and limited reproducibility. Stereology provides an unbiased, mathematically robust quantitative framework in this field, while AI enhances speed, scalability, and pattern recognition by automating high-volume image analysis. The integration of these two approaches has the potential to make IHC assessment not only faster but also more reliable, more representative, and more biologically meaningful. As standardisation, explainability, and clinical validation processes advance, AI-assisted stereological analyses are expected to become a key component of the digital pathology workflow. Therefore, the combined consideration of AI and stereology represents not merely a technical innovation but a powerful paradigm shift, signifying a methodological transformation in histopathological quantification.

10. References

1. McGenity C, Clarke EL, Jennings C, Matthews G, Cartlidge C, Freduah-Agyemang H, et al. Artificial intelligence in digital pathology: a systematic review and meta-analysis of diagnostic test accuracy. NPJ digital medicine. 2024;7(1):114.
2. Knudsen BS, Jadhav A, Perry LJ, Thagaard J, Deftereos G, Ying J, et al. A pipeline for evaluation of machine learning/artificial intelligence models to quantify programmed death ligand 1 immunohistochemistry. Lab Invest. 2024;104(6):102070.
3. Aggarwal A, Bharadwaj S, Corredor G, Pathak T, Badve S, Madabhushi A. Artificial intelligence in digital pathology—time for a reality check. Nature Reviews Clinical Oncology. 2025;22(4):283–91.
4. Ronneberger O, Fischer P, Brox T, editors. U-net: Convolutional networks for biomedical image segmentation. International Conference on Medical image computing and computer-assisted intervention; 2015: Springer.
5. Çiçek Ö, Abdulkadir A, Lienkamp SS, Brox T, Ronneberger O, editors. 3D U-Net: learning dense volumetric segmentation from sparse annotation. International conference on medical image computing and computer-assisted intervention; 2016: Springer.
6. Matthews GA, McGenity C, Bansal D, Treanor D. Public evidence on AI products for digital pathology. NPJ Digital Medicine. 2024;7(1):300.
7. Kohale MG, Dhobale AV, Bankar NJ, Noman O, Hatgaonkar K, Mishra V. Immunohistochemistry in pathology: A review. Journal of Cellular Biotechnology. 2023;9(2):131–8.
8. Mebratie DY, Dagnaw GG, editors. Review of immunohistochemistry techniques: Applications, current status, and future perspectives. Semin Diagn Pathol; 2024: Elsevier.
9. West MJ. Introduction to stereology. Cold Spring Harbor Protocols. 2012;2012(8):pdb. top070623.
10. Mandarim-de-Lacerda CA. Stereological tools in biomedical research. An Acad Bras Cienc. 2003;75(4):469–86.
11. Mucke J, Hoyer A, Brinks R, Bleck E, Pauly T, Schneider M, et al. Inhomogeneity of immune cell composition in the synovial sublining: linear mixed modelling indicates differences in distribution and spatial decline of CD68+ macrophages in osteoarthritis and rheumatoid arthritis. Arthritis Res Ther. 2016;18(1):170.
12. Dias EP, Oliveira NSC, Serra-Campos AO, da Silva AKF, da Silva LE, Cunha KS. A novel evaluation method for Ki-67 immunostaining in paraffin-embedded tissues. Virchows Arch. 2021;479(1):121–31.
13. Gundersen H, Bagger P, Bendtsen T, Evans S, Korbo L, Marcussen N, et al. The new stereological tools: disector, fractionator, nucleator and point sampled intercepts and their use in pathological research and diagnosis. APMIS. 1988;96(7-12):857–81.
14. Gundersen HJG, Jensen E. The efficiency of systematic sampling in stereology and its prediction. J Microsc. 1987;147(3):229–63.
15. Brown DL. Practical stereology applications for the pathologist. Vet Pathol. 2017;54(3):358–68.
16. Brown DL. Bias in image analysis and its solution: unbiased stereology. J Toxicol Pathol. 2017;30(3):183–91.
17. Mouton PR. Unbiased stereology: a concise guide: JHU Press; 2011.
18. Warille AA, Kocaman A, Elamin AA, Mohamed H, Elhaj AE, Altunkaynak BZ. Applications of various stereological tools for estimation of biological tissues. Anat Histol Embryol. 2023;52(2):127–34.
19. Seven M, Rağbetli MÇ, Erten R. Investigation of renal COX-2 distribution of prenatally administered diclofenac sodium in postnatal rats using stereological and immunohistochemical methods. J Mol Histol. 2025;56(4):202.
20. Biswas AA. A comprehensive review of explainable AI for disease diagnosis. Array. 2024;22:100345.
21. Morera H, Dave P, Kolinko Y, Alahmari S, Anderson A, Denham G, et al. A novel deep learning-based method for automatic stereology of microglia cells from low magnification images. Neurotoxicol Teratol. 2024;102:107336.
22. Omoush SA, Alzyoud JA, El-Omari NKT, Alzyoud AJ. The role of whole slide imaging in AI-based digital pathology: current challenges and future directions—an updated literature review. Journal of Molecular Pathology. 2026;7(1):2.
23. Kayser K, GÄśrtler J, Bogovac M, Bogovac A, Goldmann T, Vollmer E, et al. AI (artificial intelligence) in histopathology--from image analysis to automated diagnosis. Folia Histochem Cytobiol. 2009;47(3):355–61.
24. Koelzer VH, Sirinukunwattana K, Rittscher J, Mertz KD. Precision immunoprofiling by image analysis and artificial intelligence. Virchows Arch. 2019;474(4):511–22.
25. Dolezal JM, Wolk R, Hieromnimon HM, Howard FM, Srisuwananukorn A, Karpeyev D, et al. Deep learning generates synthetic cancer histology for explainability and education. NPJ precision oncology. 2023;7(1):49.
26. Dolezal JM, Kochanny S, Dyer E, Ramesh S, Srisuwananukorn A, Sacco M, et al. Slideflow: deep learning for digital histopathology with real-time whole-slide visualization. BMC Bioinformatics. 2024;25(1):134.
27. Zhang X-M, Gao T-H, Cai Q-Y, Xia J-B, Sun Y-N, Yang J, et al. Artificial intelligence in digital pathology diagnosis and analysis: technologies, challenges, and future prospects. Military Medical Research. 2025;12(1):93.
28. D'Adderio L, Bates DW. Transforming diagnosis through artificial intelligence. Npj Digital Medicine. 2025;8(1):54.
29. Ma Y, Jamdade S, Konduri L, Sailem H. AI in Histopathology Explorer for comprehensive analysis of the evolving AI landscape in histopathology. Npj Digital Medicine. 2025;8(1):156.
30. Bao S, Li J, Cui C, Tang Y, Deng R, Remedios LW, et al., editors. MxIF Q-score: Biology-informed quality assurance for multiplexed immunofluorescence imaging. International Workshop on Medical Optical Imaging and Virtual Microscopy Image Analysis; 2022: Springer.
31. Harris CR, McKinley ET, Roland JT, Liu Q, Shrubsole MJ, Lau KS, et al. Quantifying and correcting slide-to-slide variation in multiplexed immunofluorescence images. Bioinformatics. 2022;38(6):1700–7.

32. Omar M, Nicolo'Fanelli G, Socciarelli F, Ullanat V, Puchala SR, Wen J, et al. Antibody-based multiplex image analysis: standard analytical workflows and tools for pathologists. Lab Invest. 2025:104220.
33. Zheng Y, Abila E, Chrenková E, Buljan I, Winkler J, Rendeiro AF. LazySlide: accessible and interoperable whole-slide image analysis. Nature Methods. 2026:1–4.
34. Winfree S. User-accessible machine learning approaches for cell segmentation and analysis in tissue. Front Physiol. 2022;13:833333.
35. Liu P, Li J, Chang J, Hu P, Sun Y, Jiang Y, et al. Software tools for 2D cell segmentation. Cells. 2024;13(4):352.
36. Riendeau JM, Gillette AA, Guzman EC, Cruz MC, Kralovec A, Udgata S, et al. Cellpose as a reliable method for single-cell segmentation of autofluorescence microscopy images. Sci Rep. 2025;15(1):5548.
37. Kaplan S, Onger ME, Altunkaynak BZ, Elibol E, Deniz OG, Karayiğit MÖ, et al. Effects of spermine and the passive avoidance learning (PAL) following cerebral ischemia in chicks: Association with neuroprotection of pyramidal cells. J Chem Neuroanat. 2018;88:41–5.
38. Checcucci C, Wicinski B, Mazzamuto G, Scardigli M, Ramazzotti J, Brady N, et al. Deep learning-based localization algorithms on fluorescence human brain 3D reconstruction: a comparative study using stereology as a reference. Sci Rep. 2024;14(1):14629.
39. Nelli F, Ge Z, Blackall L, Taheriashtiani N, Henry R, Brumley DR, et al. Machine learning driven image segmentation and shape clustering of algal microscopic images obtained from various water types. Computational and Structural Biotechnology Reports. 2024;1:100014.
40. Chen S, Song H, Feng H, Hu J, Bai Q, He F. SPSC-Net: Shared parallel space-channel attention mechanism transformer network for cell sequence image segmentation. Computer Vision and Image Understanding. 2025:104562.
41. Paassen I, Rubin MA. Going beyond genomics in precision oncology: Cancer therapy. Nat Med. 2026:1–3.
42. Cheng Y, Lama N, Chen M, Amidi E, Ramzanpour M, Rahman MA, et al. Synergistic H&E and IHC image analysis by AI predicts cancer biomarkers and survival outcomes in colorectal and breast cancer. Communications Medicine. 2025;5(1):328.
43. Bani M-A. Smart Lies and Sharp Eyes: Pragmatic Artificial Intelligence for Cancer Pathology: Promise, Pitfalls, and Access Pathways. Cancers (Basel). 2026;18(3):421.
44. Abdullakutty F, Akbari Y, Al-Maadeed S, Bouridane A, Talaat IM, Hamoudi R. Histopathology in focus: a review on explainable multi-modal approaches for breast cancer diagnosis. Frontiers in Medicine. 2024;11:1450103.
45. Egbuna I, Olatokun T, Ozo-Ogueji P, Ekechi C, Akinbo O, Olowe E, et al. Revolutionizing cancer surgery: Harnessing artificial intelligence and augmented reality for next-generation precision oncology. International Journal of Life Science Research Archive. 2025;9(1):147–76.
46. Bossard C, Magois C, Roussel H, Thomas F, Cormier B, Collin A, et al. Clinical evaluation of an automated pan-organ combined PD-L1 scoring using artificial intelligence on immunostained whole-slide images. ESMO Real World Data and Digital Oncology. 2025;10:100181.
47. Wang M, Chang W, Zhang Y. Artificial Intelligence for the Diagnosis and Management of Cancers: Potentials and Challenges. MedComm. 2025;6(11):e70460.
48. Perez-Meana H, Nakano-Miyatake M. Digital Image Processing: Technologies and Applications. MDPI; 2025. p. 12709.
49. Acs B, Pelekanou V, Bai Y, Martinez-Morilla S, Toki M, Leung SC, et al. Ki67 reproducibility using digital image analysis: an inter-platform and inter-operator study. Lab Invest. 2019;99(1):107–17.
50. Ai D, Turashvili G, Gjeorgjievski SG, Wang Q, Ewaz AM, Gao Y, et al. Subspecialized breast pathologists have suboptimal interobserver agreement in Ki-67 evaluation using 20% as the cutoff. Breast Cancer Res Treat. 2024;204(2):415–22.
51. Bocklage T, Cornea V, Hickey C, Miller J, Moss J, Chambers M, et al. Ki-67 Testing in Breast Cancer: Assessing Variability With Scoring Methods and Specimen Types and the Potential Subsequent Impact on Therapy Eligibility. Appl Immunohistochem Mol Morphol. 2024;32(3):119–24.
52. Dawe M, Shi W, Liu TY, Lajkosz K, Shibahara Y, Gopal NE, et al. Reliability and variability of Ki-67 digital image analysis methods for clinical diagnostics in breast cancer. Lab Invest. 2024;104(5):100341.
53. West M, Slomianka L, Gundersen HJG. Unbiased stereological estimation of the total number of neurons in the subdivisions of the rat hippocampus using the optical fractionator. The Anatomical Record. 1991;231(4):482–97.
54. Schmitz C, Hof PR. Design-based stereology in brain aging research. Brain Aging. 2007:63–96.
55. Armstrong RA. Quantitative methods in neuropathology. Folia Neuropathol. 2010;48(4).
56. Lemmens MA, Steinbusch HW, Rutten BP, Schmitz C. Advanced microscopy techniques for quantitative analysis in neuromorphology and neuropathology research: current status and requirements for the future. J Chem Neuroanat. 2010;40(3):199–209.
57. Schmitz C, Eastwood BS, Tappan SJ, Glaser JR, Peterson DA, Hof PR. Current automated 3D cell detection methods are not a suitable replacement for manual stereologic cell counting. Front Neuroanat. 2014;8:27.
58. Walker L, McAleese KE, Johnson M, Khundakar AA, Erskine D, Thomas AJ, et al. Quantitative neuropathology: an update on automated methodologies and implications for large scale cohorts. J Neural Transm. 2017;124(6):671–83.
59. Alzoubi I, Bao G, Zheng Y, Wang X, Graeber MB. Artificial intelligence techniques for neuropathological diagnostics and research. Neuropathology. 2023;43(4):277–96.
60. Neltner JH, Abner EL, Schmitt FA, Denison SK, Anderson S, Patel E, et al. Digital pathology and image analysis for robust high-throughput quantitative assessment of Alzheimer disease neuropathologic changes. J Neuropathol Exp Neurol. 2012;71(12):1075–85.

61. Jack Jr CR, Bennett DA, Blennow K, Carrillo MC, Dunn B, Haeberlein SB, et al. NIA-AA research framework: toward a biological definition of Alzheimer's disease. Alzheimer's & dementia. 2018;14(4):535–62.
62. Alahmari SS, Goldgof D, Hall L, Phoulady HA, Patel RH, Mouton PR. Automated cell counts on tissue sections by deep learning and unbiased stereology. J Chem Neuroanat. 2019;96:94–101.
63. Long B, Li X, Zhang J, Chen S, Li W, Zhong Q, et al. Three-dimensional quantitative analysis of amyloid plaques in the whole brain with high voxel resolution. Sci Sin Vitae. 2019;49:140–50.
64. Signaevsky M, Prastawa M, Farrell K, Tabish N, Baldwin E, Han N, et al. Artificial intelligence in neuropathology: deep learning-based assessment of tauopathy. Lab Invest. 2019;99(7):1019–29.
65. Abdalrada AS. Comprehensive Review of Machine Learning Approaches for Alzheimer's Disease Diagnosis and Prognosis. International Journal of Ethical AI Application. 2025;1(2):47–56.
66. Mühlfeld C. Stereology and three-dimensional reconstructions to analyze the pulmonary vasculature. Histochem Cell Biol. 2021;156(2):83–93.
67. Naoumov NV, Brees D, Loeffler J, Chng E, Ren Y, Lopez P, et al. Digital pathology with artificial intelligence analyses provides greater insights into treatment-induced fibrosis regression in NASH. J Hepatol. 2022;77(5):1399–409.
68. Kim H-J, Baek EB, Hwang J-H, Lim M, Jung WH, Bae MA, et al. Application of convolutional neural network for analyzing hepatic fibrosis in mice. J Toxicol Pathol. 2023;36(1):21–30.
69. Kostadinova R, Ströbel S, Chen L, Fiaschetti-Egli K, Gadient J, Pawlowska A, et al. Digital pathology with artificial intelligence analysis provides insight to the efficacy of anti-fibrotic compounds in human 3D MASH model. Sci Rep. 2024;14(1):5885.
70. Miyaaki H, Miuma S, Fukusima M, Sasaki R, Haraguchi M, Nakao Y, et al. Liver fibrosis analysis using digital pathology. Med Mol Morphol. 2024;57(3):161–6.
71. Poalelungi DG, Neagu AI, Fulga A, Neagu M, Tutunaru D, Nechita A, et al. Revolutionizing pathology with artificial intelligence: innovations in immunohistochemistry. Journal of Personalized Medicine. 2024;14(7):693.
72. Plass M, Kargl M, Kiehl TR, Regitnig P, Geißler C, Evans T, et al. Explainability and causability in digital pathology. The Journal of Pathology: Clinical Research. 2023;9(4):251–60.
73. Faa G, Fraschini M, Barberini L. Reproducibility and explainability in digital pathology: The need to make black-box artificial intelligence systems more transparent. SAGE Publications Sage UK: London, England; 2024. p. 22799036241284898.
74. Abbas Q, Jeong W, Lee SW, editors. Explainable AI in clinical decision support systems: a meta-analysis of methods, applications, and usability challenges. Healthcare; 2025: MDPI.

CLINICAL SCIENCES

CHAPTER 12

From Digital Transformation to a Healthier Future: The Role of Artificial Intelligence in Public Health

Prof. Dr. Kemal Macit Hisar

1. Introduction

Public health encompasses the organized scientific and practical efforts to protect and improve the health of the entire community, not just individuals (12). Throughout history, milestones such as the sanitation revolution, the widespread use of vaccines, and the discovery of antibiotics have led to dramatic improvements in public health indicators. As the 21st century began, medicine and the health sciences were at the center of a new revolution termed "digital transformation." Petabytes of health data are generated daily through electronic health records (EHRs), wearable technologies, genomic sequencing, and Internet of Things (IoT) devices (10). However, this mass of "big data" alone is meaningless; the data must be processed, interpreted, and transformed into actionable public health policies. At this juncture, artificial intelligence (AI) and machine learning (ML) algorithms come into play.

At its most basic, artificial intelligence is the development of computer systems capable of performing tasks that normally require human intelligence (such as learning, reasoning, problem-solving, perception, and language understanding) (4). From a public health perspective, AI is an unparalleled tool for predicting disease patterns, distributing health resources fairly and rationally, and developing more accurate preventive medicine strategies by analyzing environmental and social determinants. This chapter will examine current applications of AI in public health, its impact on epidemiology and health management, and the ethical, legal, and social challenges encountered during the adoption of this technology.

2. Application Areas of Artificial Intelligence in Public Health

The applications of artificial intelligence in the public health discipline span a highly broad spectrum. These applications are primarily concentrated in the processes of data collection, analysis, and integration into preventive health services.

2.1. Epidemiological Surveillance and Outbreak Management

Epidemiology is the fundamental public health science that studies the distribution of diseases in the community and the factors affecting this distribution. Traditional epidemiological surveillance systems often suffer from time lags because they rely on clinical reporting and laboratory results (1). AI, on the other hand, can simultaneously (real-time) analyze non-traditional data sources such as social media posts, search engine queries, news feeds, and travel data through an approach called "syndromic surveillance." By using Natural Language Processing (NLP) algorithms, abnormal increases in the search frequency of symptoms like "fever," "cough," or "shortness of breath" in a specific geographic area can be detected, catching the signals of a potential outbreak weeks before official case reports (6).

Particularly during the COVID-19 pandemic, AI models played a critical role in predicting the virus's spread rate (R0 value) and modeling intensive care unit bed and ventilator requirements. By simulating the effects of different intervention scenarios (e.g., school closures, mask mandates) on transmission dynamics, AI supported evidence-based decision-making processes (5).

2.2. Environmental Health and Risk Analysis

Public health is closely concerned not only with biological agents but also with environmental risk factors. Air pollution, water quality, climate change, and the spread of vector-borne diseases can be modeled much more precisely via AI. For instance, deep learning algorithms using satellite imagery and meteorological data can predict particulate matter (PM2.5 and PM10) concentrations on a street-by-street basis and send notifications via early warning systems to individuals in the risk group for asthma or COPD (Chronic Obstructive Pulmonary Disease) (2). Similarly, by utilizing climate data and geographic information systems (GIS), the future potential spread areas of mosquito-borne diseases like malaria or dengue fever can be predicted with high accuracy.

2.3. Health Management, Resource Optimization, and Policies

The equivalent of "Scientific Management" principles in the governance of healthcare systems in the digital age is AI-supported decision support systems. Predicting emergency room congestion in hospitals, optimizing shift and work schedules for healthcare personnel, and managing the supply chain (medicines, vaccines, consumables) become much more efficient with ML algorithms. By analyzing demographic aging data, morbidity rates, and migration patterns, algorithms can plan at the regional level where new family health

centers or geriatric specialists will be needed over the next 10 years (9). This approach not only increases cost-effectiveness but also ensures that limited healthcare resources are distributed fairly and rationally according to societal needs.

2.4. Early Diagnosis and Preventive Medicine

Artificial intelligence has created a massive momentum in detecting diseases before symptoms even appear. By analyzing individuals' genetic data, lifestyle habits, and family histories, personalized risk scores for diabetes, cardiovascular diseases, and various cancer types can be calculated. Advancements in image processing technologies (especially Convolutional Neural Networks - CNNs) can detect micro-calcifications in mammograms, nodules in lung CTs, or dermatological lesions much earlier and with higher precision than the human eye (3). This situation dramatically increases the effectiveness of public health screening programs.

3. Discussion

Although the integration of artificial intelligence into public health offers enormous opportunities, this transformation process brings significant ethical, legal, and socio-economic debates.

First, the problem of algorithmic bias poses a major risk. Machine learning models are dependent on the quality and diversity of the data on which they are trained. If an AI model is trained with historical health data where a certain ethnic group, gender, or socioeconomic class is underrepresented, the results and predictions generated by this model will be inaccurate to the detriment of minority or disadvantaged groups (7). This could lead to a deepening of existing health inequalities under an algorithmic guise, rather than resolving them.

The second major topic of debate is data privacy and security. For AI models to be successful in public health, personal health data belonging to broad populations must be collected and processed in centralized databases. However, who owns this data? Even if data is anonymized, there is a risk of re-identification of individuals by merging different datasets (location, spending habits, etc.) (8). Transparent legal frameworks are required to strike a balance between individual rights and the benefit of public health (utilitarian approach).

Third is the "black box" problem of AI systems. Often, exactly how complex deep learning algorithms arrive at a conclusion or diagnosis cannot be fully explained even by their designers. It is problematic in terms of legal liability and transparency for public health authorities or physicians to make decisions at the societal level (such as a quarantine order) based on an algorithmic recommendation whose rationale they cannot understand (11). Therefore, prioritizing "Explainable AI" (XAI) studies in the field of public health is essential.

Finally, in the context of the digital divide, while developed countries or high-income groups rapidly benefit from these technologies, regions with weak technological infra-

structure and data collection capacity seem inevitably left behind. Global public health can only be secured by minimizing inequalities at the global level as well.

4. Conclusion

Digital transformation and artificial intelligence mark a turning point for the public health discipline. AI is the most powerful tool in the transition from a traditional approach where diseases are treated reactively, to a modern public health paradigm where diseases are prevented with proactive, predictable, and personalized strategies. Strengthening surveillance systems, making science-based rational planning in health management, and expanding preventive medicine applications to large masses will directly improve the quality of life of society.

However, achieving healthy tomorrows is not solely about the technical success of algorithms but about how these technologies are shaped by ethical values. When developing AI applications, data privacy must be safeguarded, algorithmic biases must be prevented, and the principle of justice must serve as a foundation. Training curricula must be updated so healthcare professionals can use AI tools, and a multidisciplinary approach (engineering, medicine, sociology, and law) must be adopted. Consequently, artificial intelligence should be positioned not as a competitor to replace physicians or public health experts, but as their greatest supporter and "scientific manager" in building the common welfare of humanity and a more egalitarian healthcare system.

5. References

1. Bates, D. W., Saria, S., Ohno-Machado, L., Shah, A., & Escobar, G. (2014). Big data in health care: using analytics to identify and manage high-risk and high-cost patients. Health Affairs, 33(7), 1123-1131. https://doi.org/10.1377/hlthaff.2014.0041
2. Bellingko, J. D., Bellinger, D. C., & Schwartz, J. (2020). Machine learning and the future of environmental epidemiology. Environmental Epidemiology, 4(2), e086.
3. Esteva, A., Kuprel, B., Novoa, R. A., Ko, J., Swetter, S. M., Blau, H. M., & Thrun, S. (2017). Dermatologist-level classification of skin cancer with deep neural networks. Nature, 542(7639), 115-118. https://doi.org/10.1038/nature21056
4. Jiang, F., Jiang, Y., Zhi, H., Dong, Y., Li, H., Ma, S., ... & Wang, Y. (2017). Artificial intelligence in healthcare: past, present and future. Stroke and Vascular Neurology, 2(4), 230-243. https://doi.org/10.1136/svn-2017-000101
5. McCall, B. (2020). COVID-19 and artificial intelligence: protecting health-care workers and curbing the spread. The Lancet Digital Health, 2(4), e166-e167.
6. Mooney, S. J., & Pejaver, V. (2018). Big data in public health: terminology, machine learning, and privacy. Annual Review of Public Health, 39, 95-112.
7. Obermeyer, Z., Powers, B., Vogeli, C., & Mullainathan, S. (2019). Dissecting racial bias in an algorithm used to manage the health of populations. Science, 366(6464), 447-453. https://doi.org/10.1126/science.aax2342
8. Price, W. N., & Cohen, I. G. (2019). Privacy in the age of medical big data. Nature Medicine, 25(1), 37-43.
9. Rajkomar, A., Dean, J., & Kohane, I. (2019). Machine learning in medicine. New England Journal of Medicine, 380(14), 1347-1358.
10. Topol, E. J. (2019). High-performance medicine: the convergence of human and artificial intelligence. Nature Medicine, 25(1), 44-56.
11. Vayena, E., Blasimme, A., & Cohen, I. G. (2018). Machine learning in medicine: addressing ethical challenges. PLoS Medicine, 15(11), e1002689.
12. Winslow, C. E. A. (1920). The untilled fields of public health. Science, 51(1306), 23-33.

CHAPTER 13

Algorithmic Epidemiology: Artificial Intelligence in Medical Research from Data to Decision-Opportunities and Scientific Limits

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1. Introduction

Epidemiology analyzes clinical observations across populations to establish causal relationships. As digital data sources like electronic health records (EHR), administrative records, and digital traces grow, along with advances in computational techniques, the framing and answering of epidemiological questions are changing. Artificial intelligence (AI) should be seen not as a marketing hype, but as an extension of data-driven medicine that emphasizes scientific rigor, bias mitigation, and causal clarity governance (1).

Classical epidemiology formulates research questions through study design by identifying the target population, setting suitable comparisons, ensuring accurate measurement, and managing systematic error. Its methodological foundation goes beyond statistical modeling to encompass validity evaluation, bias analysis, sensitivity assessments, and explicit causal inference reasoning (2). This tradition emphasizes that before exploring what can be done with data, researchers need to clarify the specific claim, the assumptions involved, and possible errors. Foundational texts similarly focus on disease frequency, measures of association, screening, study designs, bias, and confounding within clinical frameworks, underscoring that epidemiology is ultimately a disciplined science centered on asking the right questions question (3).

The growth of the data ecosystem largely fuels this change. As healthcare becomes more digital, data sources like EHRs, claims data, registries, and digital health tools are grouped under real-world data (RWD). The U.S. Food and Drug Administration (FDA) describes RWD as data routinely gathered on patient health or healthcare services, while real-world evidence (RWE) is defined as clinical evidence obtained through analysis of this data data (1). However, these data are produced for clinical care rather than research.

Table 1. below summarizes the core tension between classical (design-centered) epidemiology and the increasingly prominent algorithmic (prediction or pattern centered) approach (4).

Dimension	Classical Epidemiology	Algorithmic Epidemiology
Starting Logic	Hypothesis and design (comparison/sampling)	Data and pattern (feature and modeling)
Main Goal	Explanation and causal interpretation	Prediction, risk classification, early signaling
Primary Strength	Bias control, inference logic	Scale, speed, capturing high-dimensional patterns
Vulnerable Point	Measurement error / residual confounding	Representativeness, data drift, lack of transparency
Success Metric	Internal validity and interpretable effect	Discrimination + calibration + utility in decision context

Issues such as missing data, miscodes, timing mismatches, and institutional differences can cause systematic errors. EHR data quality frameworks outline five key dimensions—completeness, correctness, concordance, plausibility, and currency—and highlight that data quality depends on the specific task, or its suitability for purpose (5).

Regulatory guidance embodies this principle. The FDA's final guidance on utilizing EHR and claims data for regulatory decisions mandates a systematic assessment of data source appropriateness, measurement methods, and reliability (6). Thus, the value of big data lies not in volume alone, but in traceable data generation processes and transparent methodological chains.

The increasing prominence of AI in medical research has been driven by large labeled datasets, scalable computing resources, and developing algorithms. Reviews highlight that deep learning became possible thanks to this convergence, while also pointing out issues related to bias, privacy, and transparency as key concerns limitations (7). Beam and Kohane warn against revolution stories, stressing the importance of staying aligned with traditional statistical models and advocating for properly calibrated approaches expectations (4).

Clinical examples highlight both potential and vulnerabilities. Early warning systems (EWS) integrated into EHRs can speed up care for time-sensitive conditions like sepsis. However, external validation of a popular commercial sepsis model showed lower performance than initially reported, especially in discrimination and calibration, raising concerns about its clinical utility impact (8). Credibility, therefore, depends on independent validation, transparency, and ongoing monitoring.

The Apple Heart Study showed that it's possible to conduct a large-scale, siteless study evaluating a smartwatch's irregular pulse algorithm for atrial fibrillation detection (9). This work demonstrates how AI extends research beyond hospital environments by leveraging real-world digital data. Typically, these applications focus on three key functions: risk prediction, early signal detection, and scalable monitoring of routine care and digital practices traces (10).

The importance of AI-supported epidemiological research cannot be solely determined by performance metrics. Transparent reporting and bias assessment are crucial. TRIPOD offers structured guidance for reporting the development of prediction models validation (11), PROBAST supports structured risk-of-bias appraisal (12), and CONSORT-AI extends transparency requirements to AI components in clinical trials (13).

Ethical and regulatory issues continue to be key. The World Health Organization (WHO) highlights the importance of integrating human rights, accountability, and social benefits into AI design use (14). The European Union's (EU) AI Act employs a risk-based framework, categorizing specific medical AI systems as high risk and mandating safeguards like data quality, transparency, and human oversight oversight (15). Health data are recognized as sensitive under European data protection law (16). In Türkiye, Law No. 6698 (KVKK) classifies health data as sensitive personal information that requires explicit consent, except in limited cases specified by law conditions (17). Data governance, therefore, is not peripheral but integral to methodological rigor.

This chapter examines how algorithmic approaches expand epidemiological practice from data to decision, while remaining bounded by enduring concerns regarding bias, causality, transparency, and accountability.

2. From Classical to Algorithmic Epidemiology

2.1. Conceptual Foundations

Classical epidemiology produces causal, action-oriented insights by studying disease patterns and factors through careful study design, accurate measurement, bias mitigation, and clear assumptions. Its strength comes not from complex models but from well-defined populations, suitable comparisons, and strict control of systematic errors error (2). Validity depends less on statistical fit than on minimizing bias; even large datasets mislead if measurement error or confounding remain uncontrolled. As data volume grows, the need for design discipline increases rather than diminishes (18). A key aspect of this tradition is treating the ideal randomized trial as a conceptual standard. Hernán and Robins formalized this approach through target trial emulation, which involves clearly defining eligibility, time zero, exposure assignment, and follow-up to avoid biases like immortal time bias during the design phase, rather than having to correct them afterward analytically (18).

Although there is no single formal definition, algorithmic epidemiology typically involves analyzing large-scale digital data—such as EHRs, claims, registries, and digital traces—using computational techniques like machine learning and deep learning. This approach aims to generate predictions, early warnings, classifications, and decision support, extending digital epidemiology with a stronger focus on algorithm-driven modeling and operational applications outputs (19). A Turkish review similarly emphasizes online platforms and digital traces as separate sources of epidemiological data, clarifying the source aspect of this information shift (20).

In practice, the key difference between classical and algorithmic epidemiology is more about their goals than their methods. Classical methods focus on causal explanations, while algorithmic methods tend to emphasize prediction. Beam and Kohane warn against viewing machine learning as a revolutionary change, pointing out that it largely continues traditional statistical models and that the main differences are due to differing research objectives and data use contexts (4).

The digitalization of healthcare has accelerated this shift. The FDA defines RWD as routinely collected information on health status and healthcare delivery, and RWE as clinical evidence derived from such data (1). However, these data are produced for care purposes, not research. Variability in coding, missing data, and workflow differences highlight the importance of data quality. Weiskopf and Weng outline five dimensions of EHR data quality—completeness, correctness, concordance, plausibility, and currency—emphasizing that data should be carefully evaluated before use modeling (5).

Large datasets do not resolve causal challenges. Target trial emulation serves as a reminder that observational data cannot replace randomized designs unless there is clear alignment in the study design validation (18). Algorithmic epidemiology is increasingly focused on prediction and pattern detection. However, explanatory and predictive modeling fulfill different roles. Shmueli illustrates that these differing objectives influence how variables are chosen, validated, and interpreted. A high area under the curve (AUC), for example, does not necessarily indicate causality insight (21).

Pattern discovery aids in hypothesis generation and early detection of signals but can be susceptible to false correlations and proxy issues. The case of Google Flu Trends demonstrates how changes in data-collection processes can diminish performance, highlighting that big data mirrors underlying systems rather than providing objective insights truth (22). Similarly, machine learning offers improved classification and flexibility but carries risks of overfitting, mis-specified targets, and limited interpretability; methodological discipline remains essential (10).

2.2. Comparison with Traditional Epidemiological Approaches

Table 2 highlights common practical differences between classical and algorithmic epidemiology, especially regarding study design and scientific boundaries. This overview is based on recurring themes in the literature, including explanation versus prediction, target trial emulation, real-world data/EHR use, and machine learning in medicine research (21).

From a design standpoint, classical epidemiology inquires, "Does treatment A decrease outcome B?" by mimicking trial procedures; in contrast, algorithmic methods might focus on, "Who is likely to experience the event?" This shift to prediction can be practical but should be approached carefully when forming policies or guidelines. Emulating target trials continues to be crucial for establishing causality claims (18). Because prediction and explanation differ fundamentally, evaluation criteria must differ accordingly (21). Algorithmic epidemiology is therefore most robust when positioned as complementary to, rather than a replacement for, classical causal frameworks (4).

Table 2. Practical Differences Between Classical and Algorithmic Epidemiology

Dimension	Classical Epidemiology (Design-centric)	Algorithmic Epidemiology (Algorithm/ Prediction-centric)
Starting Point	Predefined hypothesis and logic of comparison	Data and problem formulation (prediction/ classification)
Main Output	Effect measures and causal interpretation (with assumptions)	Risk score, early warning, classification; sometimes hypothesis generation
Validation Reflex	Internal validity, bias analysis, sensitivity analyses	Train-test split, cross-validation; pronounced need for external validation
Primary Vulnerability	Confounding, selection/ information bias	Data leakage, data drift, representation and target/proxy error
Clinical Applicability	Strong interpretability; speed may be limited	Strong speed/scale; explainability and trust management are critical
Scientific Boundary	Causal assumptions are explicitly discussed	Risk increases if predictive success is mistakenly treated as causality

Generalizability remains a significant challenge, as models can lose accuracy across different institutions, populations, or time periods. Frameworks differentiate between temporal, geographic, and domain generalizability to help tackle these issues issues (23). Technically, calibration and dataset shift are key issues. Calibration—often called the Achilles' heel of prediction models—requires careful evaluation in external settings validation (24). Temporal data shifts necessitate monitoring and model updating to sustain performance (25).

Interpretability enhances clinical trust. Rudin contends that in high-stakes environments, models that are inherently interpretable should be favored over post-hoc explanations of black-box systems, as the latter may generate false reassurance (26). This underscores the need to align algorithmic practice with epidemiology's tradition of transparent assumptions.

Clinical examples clarify both promise and risk. For instance, early warning models for sepsis demonstrate potential benefits, but external validation has exposed issues with their performance and calibration. This underscores the importance of thorough validation and governance (8). Likewise, flawed proxy selection can generate inequity: using healthcare cost as a proxy for need produced significant racial bias despite strong predictive performance (27).

Due to these tensions, the importance of reporting and appraisal standards continues to grow. TRIPOD+AI enhances the reporting guidelines for regression and machine learning-based predictions models (11,28); PROBAST+AI extends structured bias assessment; and CONSORT-AI improves transparency in AI-enabled trials (12,13).

The transition from classical to algorithmic epidemiology should be seen as an evolution, not a rupture. Its importance in prediction and early warning is significant, but its stability relies on integrating classical principles—such as validity, bias control, causal caution, transparency, and equity—within the algorithm workflows (21).

3. Data Sources Enabling Algorithmic Epidemiology

3.1. Electronic Health Records and Administrative Databases

RWD refers to routinely collected electronic data on patients' health status and healthcare utilization throughout their care. According to FDA guidance, RWD includes data related to patient health and healthcare delivery, gathered from various sources. The main sources are EHR and insurance claims data. EHRs contain clinical documentation created during care, such as medical notes, lab results, prescriptions, and diagnostic codes. In contrast, administrative claims data record coded procedures, services, and prescriptions from billing and reimbursement systems. These data types are increasingly vital for post-marketing safety monitoring and evaluating population health outcomes analyses (29).

The main benefits of EHR and claims data include their large scale, wide population coverage, and representation of real-world clinical practice. These sources allow for analysis of large patient groups, including rare events, and facilitate hypothesis development. Since the data are already compiled, they also save time and costs compared to traditional prospective cohort studies (5). However, since this data is mainly gathered for care rather than research purposes, quality issues are often present. Common problems include missing data, measurement errors, inconsistent coding practices—such as variable use of ICD or SNOMED codes—and structural heterogeneity. Weiskopf and Weng identify five key dimensions of EHR data quality: completeness, correctness, concordance, plausibility, and currency. For example, incomplete recording of laboratory results or diagnoses (a completeness issue) and data entry errors (a correctness issue) may distort epidemiological findings. In clinical settings, documentation serves patient care rather than research purposes; consequently, data may not be uniformly research-ready and quality can vary substantially (5,30). Coding limitations are significant. Diagnostic and procedural codes (like ICD and CPT), which are often used for billing, may not fully or accurately represent the actual clinical condition. Hripcsak and colleagues point out that EHR data often contain gaps or errors, with biases resulting from how care is provided and how data is collected. For instance, patients with more severe illnesses usually have more frequent clinical visits, leading to denser documentation. If not carefully managed, this can skew analysis results addressed (30). In sum, researchers using EHR or claims data are advised to develop rigorous phenotyping algorithms and, where feasible, conduct gold-standard validation procedures such as chart review (29).

3.2. Omics, Imaging, and High-Dimensional Biomedical Data

Molecular omics data, including genomics, proteomics, and metabolomics, are increasingly utilized in epidemiology for risk stratification and subgroup identification. Large-scale genetic studies like GWAS have uncovered many variants that can be integrated into polygenic risk scores (PRS), which estimate an individual's susceptibility to diseases such as cardiovascular disease or cancer. Torkamani and colleagues observe that polygenic risk profiling holds promise for pinpointing high-risk subgroups, although its ability to

discriminate remains limited for widespread clinical application populations (31). Lewis and Vassos also highlight that the effectiveness of polygenic risk scores in the general population is still limited, especially outside European groups populations (32). Thus, while genomic data hold considerable promise for epidemiology, differences in genetic architecture and population-specific variation limit transferability across diverse groups.

Proteomic and other omics data are essential for biomarker discovery. High-throughput proteomics helps identify disease subtypes and forecast treatment responses, while integrating multiple omics types (such as genomics, proteomics, metabolomics) offers a more holistic understanding of complex disease biology. The field encounters methodological issues like correcting for multiple testing, strategies for data integration, and batch effects across different labs. Variability in measurement platforms highlights the importance of standardization and harmonization in multi-cohort research. Additionally, imaging data have broadened epidemiological studies. AI techniques facilitate feature extraction from radiological images (CT, MRI, ultrasound) and pathology slides. Litjens and colleagues point out that deep learning, especially convolutional neural networks, has become a dominant method in medical image analysis, commonly used for classification, detection, and segmentation tasks (33). Imaging data supports epidemiological studies by revealing hidden findings within populations and identifying early diagnostic or prognostic markers. For instance, AI-driven analysis of chest CT scans is being investigated to assess the risk of chronic lung disease. To maximize epidemiological benefits, standardized annotation and harmonization are crucial—such as aligning radiological images in DICOM format and preparing coded pathology data for digital analysis. Additionally, deep learning models require large, precisely labeled training datasets; small or poorly annotated samples increase the risk of overfitting.

3.3. Digital Traces and Population-Level Data

Digital traces are epidemiological data collected from individuals' daily digital interactions, such as wearable devices, smartphones, social media, and search queries. Salathé and colleagues suggest that advances in communication technologies have allowed billions of people to produce health-related data via digital tools. When properly analyzed, these data can offer valuable, near–real-time insights into disease patterns dynamics (19).

Wearable devices such as smartwatches and fitness trackers continuously record biometric signals, including heart rate, physical activity, and sleep patterns. In the Apple Heart Study conducted by Stanford and Apple, 419,000 participants were followed for eight months; among those who received an irregular pulse notification, atrial fibrillation (AF) was confirmed by electrocardiogram (ECG) in 34%, and 84% of notifications were concordant with AF (9). These findings show that large-scale population monitoring is feasible. For example, step counts and heart rate data from devices like Fitbit have tracked reductions in physical activity during the pandemic. However, wearable data can be biased because users often tend to be healthier and have more access to technology. Therefore, it's important to carefully consider how generalizable these findings are.

Mobile health apps enable users to report symptoms, monitor medication adherence, and track lifestyle data via smartphones. For instance, influenza-like illness tracking platforms like Flu Near You collect weekly self-reported symptoms to help identify outbreaks early. Similarly, chronic disease management apps record continuous data for conditions such as diabetes and hypertension. These tools can supplement or replace quick community surveys, offering near real-time epidemiological insights. Nonetheless, since participation is voluntary, biases related to age, socioeconomic status, and digital access should be considered when analyzing the results.

Social media platforms like Twitter, Facebook, and Instagram, along with search engine queries, generate vast amounts of data about symptoms, health behaviors, and public concerns. This data can provide near real-time insights into seasonal influenza, allergies, or mental health trends. However, it is often demographically biased, mainly reflecting younger and more digitally active groups. The Google Flu Trends project, which attempted to estimate influenza activity using search terms, eventually produced misleading results as algorithms and user behaviors changed. This underscores the need for cautious interpretation when analyzing large-scale data data (22). Additional challenges include signal noise and shifting public attention influenced by seasonal patterns or media coverage.

The idea of fit-for-use is crucial when assessing digital data sources. Researchers should evaluate who created the data, when and how it was gathered, its size, and potential biases. For example, wearable device studies need analysis of participants' demographic makeup, while social media research should consider user profiles and posting patterns. Protecting data privacy is also vital; personal health and location information must be securely anonymized and protected to comply with regulations like GDPR or KVKK.

4. AI Methods in Medical Research

Recent progress in data-driven approaches is transforming medical research by allowing new analyses of extensive health datasets, while supporting (not substituting) conventional clinical methods reasoning (8). Machine learning (ML) techniques are now widely used for risk stratification and classification, but they must be employed with careful validation, transparency, and awareness of their limitations, such as bias and the inability to establish causality. Deep learning (DL), a specialized form of ML that involves neural networks, expands these capabilities to handle complex, high-dimensional data like images and time series. Natural language processing (NLP) enables analysis of unstructured clinical text. Collectively, these AI methods provide powerful tools for epidemiological and clinical research, though their implementation requires diligent focus on model calibration, interpretability, and data quality quality (6,8).

4.1. Machine Learning Approaches

Supervised vs unsupervised learning: In supervised learning, models are trained on labeled data (with known outcomes) to predict risks or classify cases, utilizing techniques

from logistic regression to tree ensembles and support vector machines. Conversely, unsupervised learning identifies hidden patterns in unlabeled data, such as through clustering or dimensionality reduction reduction (6). Both paradigms have epidemiological uses: supervised models can predict disease risk or treatment response, while unsupervised models may identify novel patient subgroups (phenotypes) or data-driven endotypes. For example, unsupervised clustering of sepsis patients has revealed distinct subphenotypes with different prognoses (6,8).

Risk prediction and classification: Supervised machine learning is commonly used to develop risk scores and diagnostic classifications. For example, models that predict hospital readmission, long-term cardiovascular risk, or sepsis onset can leverage extensive EHR and claims data. Usually, their performance is evaluated through discrimination metrics like AUC and calibration. However, even well-established models can underperform if not properly validated. Wong et al. (2021) demonstrated this by showing that a commercial sepsis prediction tool had only moderate discrimination (AUROC about 0.63) and poor calibration when tested on external hospital data data (8), raising concerns about using such tools without independent evaluation. This example underscores the need for rigorous evaluation – including calibration analysis and decision-curve (net benefit) analysis – rather than relying on black-box scores alone (8).

Practically, researchers often use ensemble methods like random forests or gradient-boosted trees for tabular data, which can capture nonlinear associations without pre-specifying interaction terms. Neural networks (shallow or deep) and support vector machines are also applied when many predictors are available. Crucially, model building must avoid common pitfalls (data leakage, overfitting) by proper cross-validation, and models should be tested on independent cohorts. Reporting guidelines (e.g., TRIPOD+AI for predictive models (8,28) and PROBAST+AI for bias assessment (6,12)) now exist to ensure transparency. Interpretability is another consideration: for high-stakes clinical decisions, inherently interpretable models are often preferred, as explaining a black-box does not guarantee reliability.

4.2. Deep Learning Models

Time series and sequence modeling: Deep learning uses multi-layer neural nets to learn intricate data representations. In medical research, recurrent neural networks (RNNs) and temporal convolutional networks have been used to model longitudinal health records (e.g. vital signs or lab trajectories), capturing patterns over time that inform prognosis. More recently, Transformer-based architectures – originally developed for language – have been adapted to EHR to embed patients' sequential data. For example, Xian et al. (2025) demonstrated a transformer model that learned patient embeddings from hundreds of thousands of EHR records, improving tasks like future disease prediction and comorbidity analysis (6). Such models can predict risks (e.g. 30-day readmission or complication) by effectively handling irregular time-series and large code vocabularies, often outperforming simpler methods when large datasets are available.

Multimodal data integration: Deep learning is highly effective at integrating diverse data types—such as images, genomics, signals, and text—into unified models. Researchers are actively developing networks that analyze multiple data sources simultaneously, like combining radiologic images with EHR data or genomic profiles with clinical variables, to enhance diagnosis or risk assessment. Multimodal AI can, for example, use both a patient's MRI and lab tests to predict disease progression. Recent reviews show an increasing number of such architectures; one survey notes deep fusion models that combine imaging, genomics, and text for improved diagnostic accuracy. These methods often need extensive data harmonization—like aligning imaging and tabular data—and large sample sizes. Specifically in medical imaging, convolutional neural networks have achieved human-level performance in tasks such as retinal pathology and radiograph analysis. (8,33). Deep learning thus broadens AI methods from simple prediction to rich, integrated models of patient data. However, it also increases the need for large annotated datasets and raises questions of explainability in how different data modalities contribute to the result.

4.3. Natural Language Processing in Epidemiology

Clinical text analysis: NLP employs machine learning techniques to analyze free-text clinical notes, reports, and publications. In epidemiology, it can extract phenotypic details or social determinants from electronic health records, facilitating large-scale patient cohort studies. For example, NLP algorithms can detect mentions of symptoms, diagnoses, or smoking status in chart notes, significantly expanding the data available beyond structured fields. Recent advancements use deep learning, such as Transformer language models, to attain high accuracy in tasks like identifying comorbidities or adverse events from text. These approaches have supported research areas ranging from disease phenotyping to drug safety monitoring. Like other AI techniques, NLP models require training on domain-specific datasets (often limited by privacy concerns) and need thorough error assessment, as misclassification can bias subsequent analyses.

Early outbreak detection: Beyond clinical records, digital epidemiology utilizes public texts and trace data to monitor population health. NLP techniques analyze news, social media, and web searches to detect signals of emerging epidemics. A well-known example is Google Flu Trends (22) and HealthMap, which scraped search queries and online reports to track influenza or infectious disease spread in real time. While promising, these approaches have notable pitfalls: over-reliance on search trends can produce misleading spikes (as seen with Google Flu, which overestimated flu incidence and became a cautionary tale (8). Modern outbreak detection typically integrates various sources such as web news, tweets, and official reports, using NLP to filter relevant information. Salathé et al. introduced the term 'digital epidemiology' to describe this approach, highlighting both its potential and the importance of validation against ground truth. (19). In practice, NLP models may detect unusual disease-related keywords in Twitter data or analyze electronic lab reports for cluster patterns, offering early warnings that are later validated through clinical surveillance. These approaches demonstrate how AI-driven text analysis can sup-

plement traditional epidemiology, although experts warn that such signals need careful interpretation to prevent false alarms or privacy issues.

Throughout, integrating AI into medical research demands vigilance. Human oversight should be incorporated in models to interpret predictions properly and prevent automation bias. Regulatory and reporting standards now highlight the importance of transparency: for instance, AI-based protocols should clearly define algorithms and validation procedures, in accordance with FDA guidelines on real-world data (6). Ethical and governance frameworks from organizations like WHO also call for equity, patient safety and data protection. As the EU AI Act comes into force and international bodies publish Good Machine Learning Practice (GMLP) guidelines, researchers must ensure AI models respect privacy (e.g. GDPR/KVKK rules for health data) and maintain data security (15–17).

5. Translating Data into Decisions: Clinical and Public Health Applications

Effective translation of health data into action depends on strong surveillance, predictive risk models, and targeted intervention strategies for maximum impact. Advances in data science and AI enhance these functions in both clinical settings and public health. This section explores how modern analytics facilitate real-time outbreak detection and support decision-making (5.1), risk stratification for patient management and resource allocation (5.2), and the emerging concept of precision public health (PPH) (5.3) – emphasizing both opportunities and necessary cautions.

5.1. Surveillance and Early Warning Systems

Early detection of disease outbreaks depends on comprehensive surveillance and intelligent warning systems. Traditional methods, such as case reports, lab confirmations, and sentinel monitoring, often experience delays and fail to identify emerging threats promptly (34). AI and big data technologies can strengthen surveillance by integrating diverse data sources (such as electronic health records, laboratory feeds, social media, mobility and environmental sensors) for real-time monitoring (34). These tools can flag anomalies and forecast spread: for example, machine learning models have successfully used time-series clinic data and weather patterns to predict influenza peaks weeks in advance. During the COVID-19 pandemic, AI-driven dashboards and search-query analysis complemented official reports to forecast hotspots and healthcare demands.

Moreover, syndromic and event-based surveillance systems harness digital signals (e.g. symptom searches, tweets about illness) to provide early warnings before official case counts rise (34). These systems have contributed to recent epidemics by detecting unusual symptom clusters early. In healthcare environments, algorithmic early warning systems (EWS) that analyze live EHR data—such as vital signs and lab results—can alert clinicians to patient deterioration hours before manual checks. For instance, research on ML-based EWS for sepsis in hospitals showed that their use was linked to lower mortality rates compared to standard

care. Overall, AI-powered EWS utilize data integration and predictive analytics to enhance outbreak detection and patient monitoring. However, they require high-quality data, clear model explanations, and compatibility with existing reporting procedures (35).

Real-time decision support represents another key application of surveillance. Public health authorities now employ automated alert systems that assess risk across different regions—using indicators like test positivity rates or hospitalizations—to prompt actions such as increased testing or vaccination drives. Clinically, Early Warning System (EWS) feeds can activate bed allocation or contact-tracing processes. These systems demonstrate how data informs decisions in practice: they depend on predefined algorithms and business rules, but are progressively integrating machine learning models that continuously learn from new data. Overall, AI integration into surveillance enables earlier and more detailed detection of public health threats, aligning with WHO's call for comprehensive disease monitoring (34,35).

5.2. Risk Prediction and Stratification

Risk models convert data into personalized probabilities of adverse outcomes. In healthcare, predictive algorithms assess a patient's chances of experiencing morbidity or death based on factors such as age, comorbidities, and biomarkers. These models aid in triage and resource allocation: for instance, during COVID-19, risk scores helped hospitals determine which patients most likely needed intensive care or mechanical ventilation. An example is the QCOVID model, which utilized nationwide UK primary-care data (6 million adults) to predict COVID-19 mortality and hospitalization risk. This model demonstrated excellent discrimination (Harrell's C ≈0.93) and found that the top 20% of individuals predicted to be at highest risk accounted for 94% of actual deaths (36). Such stratification allows health systems to prioritize high-risk individuals for interventions (e.g. earlier therapy, prophylaxis or follow-up) and optimize allocation of scarce resources.

Risk stratification at the population level helps guide public health strategies. For example, region-specific COVID mortality predictions influence the distribution of ventilation and ICU beds. In managing chronic diseases, risk models can assess patients' chances of hospitalization, such as for heart failure flare-ups, allowing for proactive outpatient care. Triage protocols also incorporate prediction; during epidemics, ICU triage guidelines use clinical severity scores to prioritize bed allocation when demand exceeds supply. AI improves these processes by analyzing more extensive data and identifying complex patterns. Nonetheless, models need validation and recalibration as circumstances evolve; as noted by COVID researchers, their absolute risk estimates would change with infection rates and intervention (36). They recommend updating the model over time.

AI extends beyond prediction to prescriptive analytics, transforming risk estimates into actionable decisions. For instance, a high predicted sepsis mortality could prompt the application of advanced life support or initiate palliative care discussions. Public health agencies also leverage risk outputs to trigger interventions, such as lockdowns when forecasted ICU demand surpasses capacity. Importantly, any decision-support system should display risk with confidence intervals and be used alongside clinical judgment. Reporting

standards like TRIPOD+AI emphasize that developers must clearly report discrimination, calibration, and decision thresholds (28). In practice, even a well-performing algorithm (e.g. C-statistic >0.9) must demonstrate that acting on its predictions improves outcomes in a randomized or at least quasi-experimental evaluation.

5.3. Precision Public Health

PPH leverages tools at a population level to enhance the precision of targeted interventions. Unlike generic approaches, PPH analyzes detailed data to customize strategies for specific subgroups. For instance, health departments can identify neighborhoods with elevated diabetes risks and concentrate mobile screening clinics there. Combining genetic and clinical information helps direct vaccination or screening efforts toward vulnerable groups. As Muin Khoury states, while precision medicine focuses on individuals, PPH is fundamentally about delivering the correct intervention at the optimal moment, to the appropriate population (37). This approach combines efficiency and fairness by focusing resources on high-need groups to enhance overall health and decrease disparities. For example, one study found that targeting just 14% of regions with the highest risk for mosquito-borne diseases could address 90% of the global burden of these infections. AI and machine learning support PPH by analyzing large datasets—including genomics, mobility, and behavior—to categorize populations into risk levels. Predictive models, for example, can pinpoint pregnant women at the greatest risk of complications, allowing for customized prenatal care. At the policy level, AI-based analysis of socio-demographic data can identify underserved communities for priority interventions, such as public health messaging or infrastructure development.

However, experts caution that hype and ambiguity surround PPH (38). Terms and definitions vary, and technology alone does not guarantee better outcomes. Two main risks are inequity and privacy. Algorithms can inadvertently reinforce existing disparities if they use biased data (for example, if under-resourced communities have poorer health records) (34,38). Data-rich approaches often focus on biomedical factors but may overlook social determinants. Additionally, extensive data collection methods, such as wearables and genetic screening, raise concerns about consent and confidentiality. Effective governance is essential to ensure PPH promotes health equity. International experts suggest establishing clear definitions and involving community stakeholders to ensure interventions benefit the public without compromising ethical standards trust (37,38).

6. Scientific and Methodological Limits of Algorithmic Epidemiology

6.1. Causality and Interpretability

A fundamental scientific limit is that predictive AI models are associational, not causal. They excel at finding patterns in data, but cannot by themselves establish that an exposure causes an outcome. For example, a model might find that umbrellas and hot chocolate sales rise

together and predict snow (correctly), but the causal link is not umbrella+chocolate → snow; a confounding variable (cold weather) drives both (30). In epidemiology, acting on such spurious associations can lead to ineffective or harmful interventions. Hernán and Robins emphasize that without embedding causal assumptions or target trial design into analysis, big data can yield misleading causal inferences (18). Simply feeding data to a complex model (no matter how high its accuracy) does not guarantee valid causal insights.

This problem is worsened by black box models (e.g., deep neural networks or random forests) that make decisions in opaque ways. As Cynthia Rudin and colleagues warn, complex explainers often mislead: post hoc explanations of black-boxes can be unstable and untrustworthy (30). In clinical practice, if an AI system doesn't offer clear explanations for its risk scores or alerts, clinicians might mistrust it or overlook errors. For example, a sepsis prediction model could identify a patient as high-risk without indicating whether this conclusion was based on fever, lab results, or institutional patterns. Lack of interpretability allows hidden flaws or biases to go unnoticed.

To mitigate this, there is a push for inherently interpretable models in epidemiology (e.g. rule lists, sparse linear scores) wherever stakes are high (30). Such models trade some performance for clarity. Moreover, integrating causal inference methods (e.g. using directed acyclic graphs or counterfactual reasoning) into AI pipelines can help distinguish mere correlation from causation. In short, causality should be carefully considered during study design rather than presupposed, and explainable AI is essential to allow experts to critically assess and trust the models.

6.2. Bias, Data Quality, Data Reliability and Representativeness

AI systems are only as good as their data, and real-world health data often contain systematic errors. EHR and claims data were not collected for research: entries may be missing, mis-coded, or influenced by billing practices (30). For example, a diagnosis field may be left blank if it doesn't impact reimbursement, or two different codes might be used for the same condition across different hospitals. This kind of misclassification causes an AI model to learn from noisy and biased labels. Weiskopf & Weng describe five dimensions of EHR data quality: completeness, correctness, concordance, plausibility, and currency (5). Violations in any dimension (e.g., labs missing for healthier patients) can skew machine learning results.

Beyond data errors, algorithmic bias occurs when models reinforce societal biases in training data. Obermeyer et al. famously demonstrated that a popular risk algorithm underestimated the health needs of Black patients because it relied on healthcare costs as a proxy for risk (27,30). In short, causality should be carefully considered during study design rather than presupposed, and explainable AI is essential to allow experts to critically assess and trust the models.

Moreover, representativeness is a concern. Many AI studies use convenience samples or data from wealthy settings. Digital traces tend to over-represent younger, urban, or higher-SES people (19). As a result, the model's performance and predictions might not extend well to underrepresented groups, such as rural, uninsured, or older populations.

For instance, an influenza model trained solely on Twitter posts could overlook disease patterns in non-users. To improve this, it is important to use targeted strategies like gathering diverse datasets, incorporating fairness metrics during development, and considering the socio-economic background behind the data.

6.3. Reproducibility and External Validity

Reproducibility and transportability remain ongoing challenges. A model that performs well on one dataset or population does not necessarily work in another. Model portability is often hindered by differences in case mix, measurement methods, and healthcare practices. For example, a COVID-19 risk model created in one country might not perform well in another with different demographics or virus variants. As a result, external validation with independent cohorts is crucial. In fact, a systematic review revealed that most published ML health models are never externally validated, which reduces confidence in their ability to generalize (19).

Even in the same environment, dataset shift over time can reduce model performance. Variations in population behavior, interventions, or disease prevalence can render the model's knowledge outdated. Calibration—the alignment of predicted and observed risk—can significantly drift. As Van Calster et al. observe, calibration is the Achilles' heel of predictive models (19,24). A model with excellent discrimination (high AUC) may still produce miscalibrated and misleading predictions, consistently underestimating or overestimating risk. Without recalibration or updating, relying on these models can result in incorrect decisions.

Table 3. Shows the key methodological challenges in algorithmic epidemiology.

Methodological Domain	Core Technical Challenge	Strategic & Clinical Implications
Causal Foundation	Conflation of statistical association with causal pathways.	High predictive performance does not validate interventional efficacy; risk of spurious correlations leading to failed policy.
Model Transparency	Structural opacity of high-dimensional black-box architectures.	Difficulty in clinical auditing; clinicians may struggle to justify decision-making based on uninterpretable model outputs.
Data Integrity	Systematic misclassification and billing-driven data entry in EHRs.	Algorithmic amplification of existing noise, potentially skewing epidemiological estimates and resource allocation.
Algorithmic Equity	Encoding of historical or systemic biases within training datasets.	Risk of reinforcing health disparities; models may inadvertently under-prioritize marginalized or underinsured populations.
Generalizability	Selection bias and underrepresentation of specific sub-cohorts.	Limited transportability; findings derived from digital footprints may not reflect the broader, non-digital population.
Stability & Transfer	Performance decay across different clinical settings (data drift).	Necessity for continuous local validation; a model optimized for one healthcare system often requires recalibration elsewhere.

Reproducibility also relates to analysis choices. Even minor variations in data preprocessing or coding can alter model results, making it essential to share code and data and provide detailed methods. Guidelines like TRIPOD for ML models emphasize transparent reporting, and platforms such as GitHub or model cards assist in replication.

Finally, population differences lead to variability in performance. A chronic disease risk score might overpredict risk in populations with generally better health at baseline. Therefore, multi-center collaborations and federated learning (which trains models across multiple sites without sharing raw data) can enhance model robustness. In practice, AI epidemiology should always incorporate validation plans within the target setting, along with updates or retraining as necessary.

7. Ethical, Legal, and Social Implications

Algorithmic models depend on large-scale data, which is often initially gathered for care purposes rather than research. Regulations such as the EU's GDPR and Turkey's KVKK designate health data as sensitive, thereby necessitating explicit consent or legal authorization for secondary uses, such as research (14). De-identification and anonymization assist in safeguarding privacy; however, connecting multiple datasets or genomic data increases the risk of re-identification (14,39). Emerging frameworks, including the EU's upcoming European Health Data Space, aim to enable secure data sharing for research. Institutions should enforce strict data governance measures, such as obtaining ethics approval, applying pseudonymization, restricting data access, and considering privacy-preserving methods like federated learning. Federated learning allows models to be trained across different institutions without moving data to a central location, which can lower privacy risks. However, it still needs careful oversight concerning data quality and model updates (39). In all cases, clear patient consent processes (or lawful exceptions for public health) and comprehensive audit trails are essential.

AI tools serve as decision-support, not decision-makers. Clinicians hold final responsibility for patient care. Despite their accuracy, models can make mistakes or be misused, making human oversight essential. Relying too heavily on automation can lead to automation bias, where clinicians may accept machine suggestions without question (40). To avoid this, clinical workflows should integrate AI recommendations with opportunities for the physician's judgment and override. Training and guidelines should emphasize that AI complements, not replaces, medical expertise. Legally, the treating physician or institution often remains responsible for adverse outcomes, highlighting the importance of understanding an AI system's limitations. Providers should document how algorithms are used and assessed to ensure accountability and ongoing oversight.

Multiple regulatory frameworks guide AI in health. The WHO's ethics and governance guidance (2021) outlines principles like transparency, equity, and accountability for AI in medicine (14). The EU's AI Act (2024) categorizes diagnostic or treatment AI as high-risk, requiring stringent conformity assessment and post-market surveillance. In the U.S., the

FDA (together with international bodies via IMDRF) has published GMLP principles, emphasizing safety, effectiveness, and lifecycle management (40). These guidelines collectively call for thorough clinical validation, bias evaluation, and continuous performance monitoring of AI systems. Researchers should adhere to reporting standards like CONSORT-AI and TRIPOD-AI, and consult legal professionals to ensure compliance with data protection laws and medical device regulations. Practically, this involves planning independent validation studies, securing necessary approvals such as IRB or regulatory reviews, and setting up post-deployment oversight, including monitoring for model drift or adverse events.

Finally, trust and communication are essential. Patients usually prefer decisions made with human clinicians. If AI is involved, this must be disclosed, and models should be comprehensible at a high level. Providing explanations, even simple ones, helps doctors and patients understand why a recommendation was made. Research indicates that patients appreciate transparency about algorithmic help and are usually comfortable with it as long as they understand the reasoning, with the physician maintaining responsibility (14). Clinicians should explain AI's role in care—highlighting that algorithms offer risk assessments and pattern detection, not absolute decisions—and should communicate any uncertainty. This approach supports informed consent and upholds patient autonomy. To preserve the patient–doctor relationship, avoid presenting AI as flawless; instead, emphasize it as a tool with inputs like data quality and assumptions, and outputs that are probabilistic predictions, requiring human interpretation.

8. Human-in-the-Loop: Integrating AI into Clinical Decision-Making

Clinicians should view AI recommendations as supportive information, not as definitive answers. Studies consistently show that AI tools, especially in complex tasks like image interpretation or risk scoring, perform best in conjunction with expert review (41). In practice, this involves incorporating AI outputs into the clinical workflow as just one input among many, with physicians remaining the final decision-makers. For example, an automated sepsis alert should trigger prompt clinical assessment rather than automatic treatment, allowing clinicians to confirm, modify, or ignore the AI recommendation. This collaborative approach—often called human-in-the-loop—combines AI's speed and pattern recognition with human judgment in nuanced decisions. As a recent review states, AI is meant to support, not replace, clinicians. (41).

Automation bias occurs when users overtrust AI outputs and neglect contradictory evidence (41). For example, in simulated diagnostic tasks, clinicians sometimes accept incorrect AI suggestions, especially when under time pressure. This can directly harm patients if errors go unchecked. To prevent this, training and interface design should explicitly address bias. Practical measures include training clinicians to recognize common AI failure modes; designing AI interfaces that show confidence levels or explanations (explainable AI); offering regular feedback on AI performance; and using checklists or

second-review systems for critical decisions. Research indicates that highlighting uncertainty, such as emphasizing high risk over a definitive diagnosis, encourages clinicians to verify results more carefully (41,42). Ensuring easy access to alternative information (e.g. patient history, guidelines) can counteract blind reliance. In sum, workflows should embed critical oversight of AI: clinicians should routinely ask "Does this match what I see clinically?" and cross-check with independent data sources. Over time, this cultivates appropriate trust: clinicians learn where the AI is strong and where it needs scrutiny.

For AI to truly enhance care, it must be carefully integrated into clinical systems. This involves embedding algorithms within existing EHR platforms or imaging software and designing alerts that align with clinical workflows. Training clinicians is essential: they need to understand the function of AI tools, their validated performance metrics (such as sensitivity and false-positive rates), and their limitations. Regulatory and scientific standards emphasize these points. The FDA and IMDRF's GMLP principles advise documenting intended use, training procedures, and real-world performance (40). Similarly, reporting standards such as CONSORT-AI and TRIPOD-AI ask researchers to specify how models were integrated, validated, and how they communicated uncertainty (13,28). In practice, teams should perform silent trials or shadow testing—using the AI without acting on its results—before deployment to verify accuracy. After deployment, ongoing monitoring (post-market surveillance) is essential to detect performance drift, similar to drug safety monitoring.

Implementing human-in-the-loop involves establishing feedback loops where clinicians record their agreement or disagreement and patient outcomes when AI flags a patient. This information can be used to further improve the model. Interdisciplinary governance bodies, such as informatics committees and clinical champions, are important for oversight. Additionally, patient interactions should be taken into account, with clinicians possibly disclosing AI-assisted decisions to promote transparency and trust.

AI in clinical decision-making functions optimally as a collaborator. There is no evidence to suggest that AI will completely replace physicians; rather, data indicates that doctors working with AI outperform both unassisted doctors and AI alone. By leveraging the strengths of each, the human–algorithm team can enhance diagnostic accuracy, efficiency, and patient outcomes. Essential to this is careful implementation: establishing clear protocols for AI tool use, thorough validation in each clinical setting, and continuous monitoring. With these safeguards, AI supports human care while maintaining human responsibility.

9. Future Directions and Research Priorities

Bridging the gap between correlation and causation remains a critical goal. While traditional AI is strong at making predictions, it falls short in understanding causality. Techniques such as target trial emulation (Hernán & Robins, 2016) treat observational data as if derived from randomized trials (11,18). Causal graphs and doubly robust estimators

can be integrated with machine learning to estimate effects based on certain assumptions. For instance, neural networks can be used to flexibly model risk, combined with inverse probability weighting for treatment assignment, resulting in doubly-robust causal estimates. Practical applications include assessing treatment effects from electronic health record (EHR) cohorts by precisely defining eligibility criteria and follow-up procedures, similar to a hypothetical trial (11). A practical recommendation for researchers is to adopt hybrid designs: clearly specify causal estimands, use a combination of ML and traditional methods to adjust for confounding, and report assumptions transparently. As Pearl (2019) highlights, graph-based frameworks can help guide variable selection and specify the assumptions necessary for valid inference (43). Ultimately, developing causal AI will enable us to answer "why" questions, such as "Would statins reduce heart attacks in this population?", rather than only identifying "what patterns" emerge.

Ensuring AI model interpretability remains crucial for building trust and safety. Ideally, models should be designed to be interpretable from the start, such as simple scoring systems or decision trees. For complex models, post-hoc techniques like SHAP and LIME can help explain feature importance. Nevertheless, experts warn that these explanations can be misleading if misused. Recent standards, such as the TRIPOD-AI and PROBAST-AI extensions (2024–2025), mandate detailed reporting on model functionality, influential variables, and uncertainty measures. Practically, researchers should include a model card with summaries of the model's purpose, inputs, performance, and limitations in publications. Examples include calibration plots, confusion matrices, and subgroup analyses. Clinicians should insist that AI tools provide explanations—such as highlighting key lab results influencing risk scores—and recognize that no explanation method is flawless. Transparency extends to data sources too: clearly documenting data collection methods and applying rigorous validation can reveal biases before deployment. In summary, enhancing explainability and following reporting standards like TRIPOD-AI and PROBAST-AI are ongoing research objectives that will increase the trustworthiness and clinical utility of AI models.

Digital twins are detailed virtual representations that replicate real-world systems. In epidemiology, this involves creating agent-based or mechanistic simulations of populations to test interventions digitally. For instance, Barat et al. developed an agent-based digital twin of an Indian city to model COVID-19 spread and assess lockdown strategies (44). These models combine demographic, mobility, and disease biology data to enable what-if analyses, such as testing vaccination strategies before real-world trials. But they face significant challenges: creating accurate digital twins demands extensive data and calibration, and their reliability depends on many assumptions. Validation is essential, requiring comparison of model predictions with historical outbreak data to ensure accuracy. Ethical and privacy concerns also emerge when using detailed personal or mobility information. Moving forward, research should aim to standardize the development of digital twins—covering calibration and uncertainty quantification—and establish frameworks for ethical data use in simulations. Practically, researchers should begin with simple models, like influenza transmission, for validation before expanding, and involve stakeholders, such as public health officials and ethicists, early in the process.

Integrating AI into routine care involves more than just developing algorithms. Key priorities include comprehensive external validation and prospective impact evaluations. These models should be tested across multiple hospitals and populations to identify performance issues in different settings. Funding agencies and journals are increasingly demanding such validation efforts. Additionally, prospective trials or pilot studies are essential to assess real-world outcomes, such as whether an AI-based triage system truly shortens waiting times or reduces mortality. Implementation research should focus on workflow integration, examining how clinicians use these tools and how alerts can be timed to prevent overload. Governance and equity are also critical: monitoring systems must be put in place to detect bias or performance drift, and diverse teams should be involved to ensure tools benefit all patient groups.

The shift of AI from research to clinical use requires a clear validation process that includes retrospective studies, prospective assessments, and gold-standard clinical trials. Key to this is ongoing collaboration between technical developers and clinicians on the front lines, along with active patient involvement to promote transparency in how algorithms make decisions. Additionally, scaling these technologies depends on updating data infrastructure and ensuring compliance with international regulatory standards. By focusing on these critical methodological and structural elements, the healthcare field can ensure AI tools are safe, reliable, and suitable for high-stakes clinical settings.

10. Conclusion

The development of algorithmic epidemiology extends existing methodologies rather than breaking away from core principles of population health science. It responds intentionally to a changed data landscape—incorporating electronic health records, complex omics data, and digital traces to facilitate predictive analysis and real-time monitoring on an unprecedented scale. Although these advances improve early warning systems and risk assessment, their effectiveness is still limited by the quality of the data used. Recognizing complex patterns, no matter how advanced the computation, cannot replace a well-defined research question or the careful management of systematic bias. Moving forward, the field's progress depends on balancing rapid algorithmic processing with the foundational principles of traditional epidemiological research.

The core of this development is the important difference between explanation and prediction. Classical epidemiology offers the essential foundation for causal inference, focusing on comparability, measurement validity, and clear assumptions. Algorithmic approaches build on this by improving decision support but still rely on causal reasoning. Moving toward models driven by algorithms creates a tension between achieving high predictive accuracy and maintaining explanatory clarity, and this balance needs to be handled transparently. Bridging this gap requires a commitment to scientific anchors—such as the rigorous application of target trial emulation and adherence to reporting standards like TRIPOD-AI. Without these safeguards, algorithmic outputs could turn into black-

box heuristics that, although efficient in operation, do not hold the causal validity necessary for critical clinical decisions or effective public health policies.

The move from data analysis to decision-making is as much a sociotechnical challenge as it is a computational one. Scientific rigor and ethical oversight are essential parts of responsible implementation, not just additional constraints. The future impact of algorithmic epidemiology relies more on adhering to core scientific principles—such as clear assumptions, representativeness, and human oversight—than on processing speed alone. By integrating values like equity, privacy, and accountability into the technical process, AI can act as a supportive tool. This approach guarantees that the advantages of the data revolution are achieved through transparent methods and accountable systems, upholding the vision of a PPH that is both scientifically credible and ethically responsible.

5. References

1. FDA. Real-World Evidence | FDA [Internet]. 2026 [cited 2026 Mar 3]. Available from: https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence
2. Lash TL, VanderWeele TJ, Haneuse S, Rothman KJ. Modern Epidemiology, 4th edition. Wolters Kluwer; 2021. doi:10.1007/s10654-021-00778-w
3. Celentano DD, Szklo M (Moyses), Farag YMK, Preceded by (work): Gordis L. Gordis epidemiology: Chapter 14 - From association to causation: Deriving inferences from epidemiologic studies - Gordis Epidemiology [Internet]. Vol. 7. 2024 [cited 2026 Mar 3];7:268–87. Available from: https://www.us.elsevierhealth.com/gordis-epidemiology-9780323877756.html
4. Beam AL, Kohane IS. Big Data and Machine Learning in Health Care. JAMA. 2018 Apr 3;319(13):1317–8. doi:10.1001/JAMA.2017.18391 PubMed PMID: 29532063.
5. Weiskopf NG, Weng C. Methods and dimensions of electronic health record data quality assessment: enabling reuse for clinical research. Journal of the American Medical Informatics Association. 2013 Jan 1;20(1):144–51. doi:10.1136/AMIAJNL-2011-000681 PubMed PMID: 22733976.
6. Real-World Data: Assessing Electronic Health Records and Medical Claims Data To Support Regulatory Decision-Making for Drug and Biological Products | FDA [Internet]. 2024 [cited 2026 Mar 3]. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/real-world-data-assessing-electronic-health-records-and-medical-claims-data-support-regulatory
7. Topol EJ. High-performance medicine: the convergence of human and artificial intelligence. Nature Medicine 2019 25:1. 2019 Jan 7;25(1):44–56. doi:10.1038/s41591-018-0300-7 PubMed PMID: 30617339.
8. Wong A, Otles E, Donnelly JP, Krumm A, McCullough J, DeTroyer-Cooley O, et al. External Validation of a Widely Implemented Proprietary Sepsis Prediction Model in Hospitalized Patients. JAMA Intern Med. 2021 Aug 1;181(8):1065–70. doi:10.1001/JAMAINTERNMED.2021.2626 PubMed PMID: 34152373.
9. Perez M V., Mahaffey KW, Hedlin H, Rumsfeld JS, Garcia A, Ferris T, et al. Large-Scale Assessment of a Smartwatch to Identify Atrial Fibrillation. New England Journal of Medicine. 2019 Nov 14;381(20):1909–17. doi:10.1056/NEJMOA1901183/SUPPL_FILE/NEJMOA1901183_DATA-SHARING.PDF PubMed PMID: 31722151.
10. Wiemken TL, Kelley RR. Machine Learning in Epidemiology and Health Outcomes Research. Annu Rev Public Health. 2020 Apr 1;41:21–36. doi:10.1146/ANNUREV-PUBLHEALTH-040119-094437 PubMed PMID: 31577910.
11. Collins GS, Reitsma JB, Altman DG, Moons KGM. Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD): the TRIPOD Statement. Br J Surg. 2015 Feb 1;102(3):148–58. doi:10.1002/BJS.9736 PubMed PMID: 25627261.
12. Wolff RF, Moons KGM, Riley RD, Whiting PF, Westwood M, Collins GS, et al. PROBAST: A Tool to Assess the Risk of Bias and Applicability of Prediction Model Studies. Ann Intern Med. 2019 Jan 1;170(1):51–8. doi:10.7326/M18-1376 PubMed PMID: 30596875.
13. Liu X, Rivera SC, Moher D, Calvert MJ, Denniston AK, SPIRIT-AI and CONSORT-AI Working Group. Reporting guidelines for clinical trial reports for interventions involving artificial intelligence: the CONSORT-AI Extension. BMJ. 2020 Sep 9;370(9):m3164. doi:10.1136/bmj.m3164 PubMed PMID: 32909959.
14. WHO. Ethics and Governance of Artificial Intelligence for Health : WHO Guidance. WHO, editor. World Health Organization; 2021.
15. European Union. AI Act enters into force - European Commission [Internet]. 2024 [cited 2026 Mar 3]. Available from: https://commission.europa.eu/news-and-media/news/ai-act-enters-force-2024-08-01_en

16. European Parliament. Regulation (EU) 2016/679 of the European Parliament and of the Council [Internet]. Brussels: THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION; 2016 Apr 27. Available from: https://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:32016R0679&from=EN#d1e1489-1-1
17. Kişisel Verileri Koruma Kurumu. "Sağlık verilerini Kanunun 6 ncı maddesinde yer alan işleme şartlarından birine dayanmadan üçüncü bir kişiye aktaran veri sorumlusu hakkında" Kişisel Verileri Koruma Kurulunun 05/12/2018 Tarihli ve 2018/143 Sayılı Karar Özeti | Kişisel Verileri Koruma Kurumu [Internet]. Ankara: Kişisel Verileri Koruma Kurumu; 2019 Feb 18. Available from: https://www.kvkk.gov.tr/Icerik/5364/2018-143
18. Hernán MA, Robins JM. Practice of Epidemiology Using Big Data to Emulate a Target Trial When a Randomized Trial Is Not Available. Am J Epidemiol. 2016;183(8):758–64. doi:10.1093/aje/kwv254
19. Salathé M, Bengtsson L, Bodnar TJ, Brewer DD, Brownstein JS, Buckee C, et al. Digital Epidemiology. PLoS Comput Biol. 2012;8(7):e1002616. doi:10.1371/JOURNAL.PCBI.1002616 PubMed PMID: 22844241.
20. Bayın Donar G, Üniversitesi H, ve İdari Bilimler Fakültesi İ, Yönetimi Bölümü S, Bayın Donar AraşGör G. Dijital epidemiyoloji. Turkish Journal of Public Health. 2020 Aug 31;18(2):192–203. doi:10.20518/TJPH.656035
21. Shmueli G. To Explain or to Predict? https://doi.org/101214/10-STS330. 2010 Aug 1;25(3):289–310. doi:10.1214/10-STS330
22. Lazer D, Kennedy R, King G, Vespignani A. The Parable of Google Flu: Traps in Big Data Analysis. Science (1979). 2014 Mar 14;343(6176):1203–5. doi:10.1126/science.1248506
23. de Hond AAH, Shah VB, Kant IMJ, Van Calster B, Steyerberg EW, Hernandez-Boussard T. Perspectives on validation of clinical predictive algorithms. npj Digital Medicine 2023 6:1. 2023 May 6;6(1):86-. doi:10.1038/s41746-023-00832-9
24. Van Calster B, McLernon DJ, Van Smeden M, Wynants L, Steyerberg EW, Bossuyt P, et al. Calibration: the Achilles heel of predictive analytics. BMC Med. 2019 Dec 16;17(1):230. doi:10.1186/S12916-019-1466-7 PubMed PMID: 31842878.
25. Guo LL, Pfohl SR, Fries J, Posada J, Fleming SL, Aftandilian C, et al. Systematic Review of Approaches to Preserve Machine Learning Performance in the Presence of Temporal Dataset Shift in Clinical Medicine. Appl Clin Inform. 2021 Aug 1;12(4):808. doi:10.1055/S-0041-1735184 PubMed PMID: 34470057.
26. Rudin C. Stop explaining black box machine learning models for high stakes decisions and use interpretable models instead. Nature Machine Intelligence 2019 1:5. 2019 May 13;1(5):206–15. doi:10.1038/s42256-019-0048-x
27. Obermeyer Z, Powers B, Vogeli C, Mullainathan S. Dissecting racial bias in an algorithm used to manage the health of populations. Science (1979). 2019 Oct 25;366(6464):447–53. doi:10.1126/SCIENCE.AAX2342/SUPPL_FILE/AAX2342_OBERMEYER_SM.PDF PubMed PMID: 31649194.
28. Collins GS, Moons KGM, Dhiman P, Riley RD, Beam AL, Van Calster B, et al. TRIPOD+AI statement: updated guidance for reporting clinical prediction models that use regression or machine learning methods. BMJ. 2024 Apr 16;385. doi:10.1136/BMJ-2023-078378 PubMed PMID: 38626948.
29. Cber Oce C. Assessing Electronic Health Records and Medical Claims Data to Support Regulatory Decision-Making for Drug and Biological Products Guidance for Industry Real-World Data/Real-World Evidence (RWD/RWE) Contains Nonbinding Recommendations [Internet]. 2024 [cited 2026 Mar 3]. Available from: https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugsand/or
30. Hripcsak G, Albers DJ. Next-generation phenotyping of electronic health records. J Am Med Inform Assoc. 2012;20(1):117. doi:10.1136/AMIAJNL-2012-001145 PubMed PMID: 22955496.
31. Torkamani A, Wineinger NE, Topol EJ. The personal and clinical utility of polygenic risk scores. Nature Reviews Genetics 2018 19:9. 2018 May 22;19(9):581–90. doi:10.1038/s41576-018-0018-x PubMed PMID: 29789686.
32. Lewis CM, Vassos E. Polygenic risk scores: from research tools to clinical instruments. Genome Med. 2020 May 18;12(1). doi:10.1186/S13073-020-00742-5 PubMed PMID: 32423490.
33. Litjens G, Kooi T, Bejnordi BE, Setio AAA, Ciompi F, Ghafoorian M, et al. A survey on deep learning in medical image analysis. Med Image Anal. 2017 Dec 1;42:60–88. doi:10.1016/J.MEDIA.2017.07.005 PubMed PMID: 28778026.
34. Idahor CO, Esomu EJO, Ogbonna N, Momoh Z, Ogbeide OA, Ikhu-Omoregbe O, et al. Infectious Disease Surveillance in the Era of Big Data and AI: Opportunities and Pitfalls. Cureus. 2025 Oct 6;17(10):e93929. doi:10.7759/CUREUS.93929 PubMed PMID: 41200593.
35. Villanueva-Miranda I, Xiao G, Xie Y. Artificial intelligence in early warning systems for infectious disease surveillance: a systematic review. Front Public Health. 2025;13:1609615. doi:10.3389/FPUBH.2025.1609615/FULL PubMed PMID: 40626156.
36. Clift AK, Coupland CAC, Keogh RH, Diaz-Ordaz K, Williamson E, Harrison EM, et al. Living risk prediction algorithm (QCOVID) for risk of hospital admission and mortality from coronavirus 19 in adults: national derivation and validation cohort study. BMJ. 2020 Oct 20;371. doi:10.1136/BMJ.M3731 PubMed PMID: 33082154.
37. Weeramanthri TS, Dawkins HJS, Baynam G, Bellgard M, Gudes O, Semmens JB. Editorial: Precision Public Health. Front Public Health. 2018 Apr 30;6. doi:10.3389/FPUBH.2018.00121/FULL
38. Bosward MR, Braunack-Mayer A, Frost ME, Carter S. The emergence and future of precision public health: a scoping review. Health Policy Technol. 2025 Sep 1;14(5):101056. doi:10.1016/J.HLPT.2025.101056
39. Lieftink N, dos Ribeiro CS, Kroon M, Haringhuizen GB, Wong A, van de Burgwal LHM. The potential of federated learning for public health purposes: a qualitative analysis of GDPR compliance, Europe, 2021. Eurosurveillance. 2024 Sep 19;29(38):2300695. doi:10.2807/1560-7917.ES.2024.29.38.2300695 PubMed PMID: 39301744.
40. FDA. Good Machine Learning Practice for Medical Device Development: Guiding Principles | FDA [Internet]. 2025 [cited 2026 Mar 4]. Available from: https://www.fda.gov/medical-devices/software-medical-device-samd/good-machine-learning-practice-medical-device-development-guiding-principles

41. Sezgin E. Artificial intelligence in healthcare: Complementing, not replacing, doctors and healthcare providers. Digit Health. 2023 Jan 1;9:20552076231186520. doi:10.1177/20552076231186520 PubMed PMID: 37426593.
42. Cai CJ, Winter S, Steiner D, Wilcox L, Terry M. "Hello AI": Uncovering the Onboarding Needs of Medical Practitioners for Human-AI Collaborative Decision-Making. Proc ACM Hum Comput Interact. 2019 Nov 7;3(CSCW). doi:10.1145/3359206
43. Pearl Judea. Causality : models, reasoning, and inference. Pearl J, editor. Cambridge University Press; 2021. 465 p.
44. Barat S, Parchure R, Darak S, Kulkarni V, Paranjape A, Gajrani M, et al. An Agent-Based Digital Twin for Exploring Localized Non-pharmaceutical Interventions to Control COVID-19 Pandemic. Transactions of the Indian National Academy of Engineering. 2021 Jun;6(2):323. doi:10.1007/S41403-020-00197-5 PubMed PMID: 35837574.

CHAPTER 14

Is Emergency Room Triage Using ChatGPT More Successful Than Physicians in Early Diagnosis?

Assoc. Prof. Dr. Hatice Seyma Akca

1. Introduction

According to the European Union Artificial Intelligence Act, it must be transparent, accountable, and prevent bias. According to the United Nations Educational, Scientific and Cultural Organization (UNESCO) and the WHO, artificial intelligence must be fair, transparent, and ethical. However, the requirement to consider patient autonomy is frequently raised in the literature (1,2). In the United States, the production of more than 1000 AI-powered medical devices, primarily related to medical specialties such as radiology and gastroenterology, was approved in early 2025 (3).

Looking at meta-analyses, it was seen that approximately 5 years ago, studies evaluating the effectiveness of AI (Artificial Intelligence) in diagnosis and treatment in the emergency department were mostly retrospective, and studies improving diagnosis and diagnostic imaging did not exceed approximately 20% of the total studies. While studies predicting diagnosis were prominent, studies on effective decision-making and triage were less frequent (4). It is seen that developments, especially in emergency departments, will gain momentum with LLMs (large language models) including models such as ChatGPT, Gemini, Deepseek, OpenAI, GPT3.5, and GPT4.0. It is thought that data accumulation, training time, and financial resources are needed for artificial intelligence systems to be effective in the health system (5).

AI systems can be useful for hospitals in predicting bed occupancy rates in intensive care units and wards. Studies show that they can be used effectively in emergency departments for managing limited time, in triage systems, and in patient circulation. The aim is to reduce the workload of the emergency department by admitting high-risk patients early (6-9). However, different models tend to lead to misdiagnosis, differences in treat-

ment, and offer different treatment protocols in matters where we need to make urgent decisions, as there is no model that predicts uncertainty (10).

Machine learning (ML) applications, which have come to the fore with the use of artificial intelligence, can assist in emergency departments with issues such as referral, triage, patient management, image interpretation (especially in small-scale emergencies where specialist doctors are not available), intervention, and emergency department waiting times. In fact, machine learning is a branch of artificial intelligence that can evolve. It is divided into branches such as supervised, unsupervised, and reinforcement learning. Reinforcement or deep learning is structurally similar to nested neurons. It has high computational power and can work with a large amount of data. Its training may take a little longer than traditional machine learning. Convolutional neural networks, a sub-branch of deep learning, are preferred in medical imaging. Deep learning also contributes to Natural Language Processing (NLP). NLP is important in patient monitoring in emergency medicine. It is also useful in the retrospective screening of some diseases. Deep learning is also effectively used in image interpretations where emergency diagnoses can be made. Despite all the conveniences in the emergency department, machine learning (ML) applications require appropriate and accurate data input. Therefore, having data input by specialist doctors in the field will also reduce the possibility of incorrect calculations (11).

Furthermore, artificial intelligence needs large amounts of data to perform its function optimally. This poses a problem in terms of patient information confidentiality and privacy (12). Instead of artificial intelligence, the term augmented intelligence should be used in medicine. Because it should not be influenced by different fields such as science fiction and media (12). The condition that artificial intelligence is supported by clinical trials (13) and is free from bias (14) seems to always be on the agenda. A frequently used method in algorithm classification is the decision tree (15).

Emergency physicians may have difficulty making the right decision and diagnosis due to both the chaotic environment of the emergency department and changes in their own circadian rhythm. The ability of AI to make accurate diagnoses by improving existing information, synthesizing information with clinical decision support, and improving quality has been investigated. CDS (clinical decision support) applications have examined a wide range of differential diagnoses. While it can evaluate very large datasets, it can ensure a common diagnosis among emergency department staff and can diagnose diseases that might be overlooked due to circadian rhythm. It was also noted that intuition and feedback systems, especially with Q1, can increase the accuracy of existing diagnoses in emergency departments. However, to avoid errors, the data must undergo quality planning (diagnosis codes, symptom-disease history analyses, etc.) (16).

Two methods have been mentioned in the literature that enable faster intuitive and slower analytical thinking in the diagnostic process in the emergency department (17). As emergency department staff, we are expected to make quick decisions and provide effective treatment when we have very little data. Systematic meta-analyses were needed in terms of AI. Pre-hospital AI support was considered important in terms of speeding up hospital referral procedures and application procedures to the relevant department. In ad-

dition, emergency departments were the subject of studies in terms of increasing patient satisfaction and reducing waiting time (4).

Triage wasn't just about determining which rooms the patient would be examined and treated in. A patient might present to the emergency department with various complaints initially. Or, healthcare professionals might assess a stable trauma patient with mild bleeding as requiring urgent intervention. The clinical picture might also become clearer during the patient's observation in the hospital. Therefore, triage involves not only the initial assessment upon arrival, but also the evaluation of symptoms, diagnosis, differential diagnosis, and radiological diagnosis.

2. Artificial Intelligence in Diagnosis

Chat GPT has been shown to communicate effectively with patients online (18). It also saved physicians time in documenting, but emergency physicians may need to reinterpret documentation. Issues such as creating templates or libraries have arisen. While there may be difficulties in understanding discharge instructions due to language use, some studies, albeit limited, suggest that this problem can be solved by Chat GPT's readability correction feature (19). Chat GPT's responses to patient complaints have been evaluated as positive and empathetic (20).

3. Artificial Intelligence in Triage

Although there are studies using simulated or real patients in triage studies; it has been stated in the literature that chat GPT is as effective as doctors in determining triage, and also that it is not. In general, at high urgency levels, the accuracy of chat GPT in predicting triage was found to be significantly higher (19). In one triage study, the triage of the emergency department was statistically significantly more accurate than that of artificial intelligence (21). It should also be noted that there are improvements in each new version. It has been reported that LLMs can also be used in triage protocols, and the GPT-4 and GPT-3.5 turbo models have been found to have a significant accuracy rate according to the Emergency Severity Index (22). It has also been reported that the Chat GPT-4 performance is the closest model to human standards (23). In another triage study, sub-models were examined and GPT-4.0 showed higher accuracy and consistency compared to GPT-4-Turbo (24).

A retrospective triage study included over 1000 patients. In this study comparing LLMs, Google Gemini 2.5 flash was the fastest and showed the highest accuracy. The same study highlighted that the OpenAI GPT-4.1 model also provided high accuracy (25).

We will soon see the chat GPT 5 version. Using chat GPT as a decision support system is still controversial. It is not sufficient for patient management, and radiology readings do not yet save time for emergency physicians. However, high accuracy rates in fracture detection

may benefit orthopedic patients in terms of requesting consultations. While it is foreseen that it may have benefits in terms of differential diagnosis and time saving in infectious diseases, gastroenterology, and psychiatry consultations, the number of studies is small (19).

4. Artificial Intelligence in Differential Diagnosis

Although it has been shown that chat gpt may have similar or superior characteristics to non-specialist or resident physicians in differential diagnosis, no significant difference was found between specialist physicians and resident physicians (26,27). Similarly, in a study using simulated patients, the methods of taking and managing anamnesis were performed by real doctors and chat gpt, and patients were asked to rate them. In the study using twelve simulated patients, while no significant difference was found in terms of clinical accuracy; chat gpt scored higher than doctors in empathy and taking anamnesis (28).

In a study evaluating the ability to diagnose various diseases, primarily pneumonia, gastrointestinal system diseases, and cardiovascular diseases, the GPT-3.5 model had higher accuracy than newly developed versions. While asking for and adding comments did not change the diagnostic ability in this model, it was observed that asking for comments and adding explanations improved the diagnostic ability in the new versions. However, the accuracy rate of the versions was quite low in difficult cases where doctors could not correctly evaluate the preliminary diagnosis (29). AI was able to predict mortality in pneumonia and risk factors for syncope (30,31). The ability of AI to diagnose or not miss possible fractures in radiological examinations varies according to studies. It was shown to be more sensitive than clinician readings in the interpretation of CT images in the diagnosis of intracranial hemorrhage (32).

Environmental contamination in antimicrobial therapy was also considered by Chat-GPT, and it was observed that resistant infections were also active in improving the diagnosis of cerebrovascular and cardiovascular disease (33). While Chat-GPT is practical in terms of preparing discharge summaries; in a study on sudden cardiac arrest, responses related to CPR were found to be insufficient (34). In the models used for the postgraduate exam of emergency medicine residents in Canada, GPT-4 was found to be superior to other models in generating different and accurate scenarios (35).

5. Artificial Intelligence in Radiological Diagnosis

There are a limited number of studies on ECG reading, and these studies included emergency medicine and cardiology physicians. The literature shows that Chat GPT is sometimes better than physicians at ECG reading, and sometimes it isn't (36,37). In one study evaluating ECG findings, many of the cases that Chat GPT indicated as urgent and requiring intervention were not considered urgent by physicians. Chat GPT had low specificity and sensitivity in identifying both healthy and pathological cases (38). In another study, while emergency department specialists were superior to GPT in average ECG reading accuracy, a decrease in the

diagnostic rate for difficult-to-diagnose ECGs was observed in both groups (39). In a study evaluating radiographs of trauma patients, the probability of emergency medicine specialists and orthopedists making the correct diagnosis was found to be significantly superior to GPT-40. However, the accuracy of GPT-40 in evaluating normal radiographs was superior to that of pathological radiographs (40). Robotic or different artificial intelligence applications were developed for e-Fast (extended focused assessment with sonography for trauma) applications. In the guidance model, the kidneys received the highest IOU score. False positives were detected in the bladder. In M mode, it showed a tendency towards positive predictions. In thoracic M mode, the effectiveness was found to be lower compared to others (41).

6. Conclusion

Artificial intelligence is rapidly developing and improving in the field of medicine, as it is in all other fields. The assessment of patients based on their arrival at the emergency department, symptoms, triage, diagnosis, and treatment is crucial for providing higher quality service, reducing hospital costs, and lowering mortality, especially for healthcare professionals in emergency departments. By the time this article is published, improved GPT (Global Perceptron Testing) models will have been developed. More effective systems will be available for symptom assessment, triage, differential diagnosis, and radiological diagnoses. As a result, emergency departments will experience further improvements in the efficient use of time and quality patient care.

7. References

1. Porsdam Mann, S., Cohen, I.G., Minssen, T. (2024). The EU AI Act: implications for U.S. health care. *NEJM AI.* 1(11):AIp2400449.
2. Regulation - EU - 2024/1689 - EN. EUR-Lex. URL: http://data.europa.eu/eli/reg/2024/1689/oj/eng.
3. United States Food and Drug Administration. Artificial Intelligence and Machine Learning (AI/ML)-Enabled Medical Devices. [cited 2025 Feb 12]; (2024). Available from: https://www.fda.gov/medical-devices/software-medical-device-samd/artificial-intelligence-and-machine-learning-aiml-enabled-medical-devices.
4. Kirubarajan, A.T., Khan, S., Masood, S.(2020). Artificial intelligence in emergency medicine: A scoping review, *JACEP Open,* 1(6):1691-1702. https://doi.org/10.1002/emp2.12277.
5. Amiot, F., Potier, B. (2025). Artificial Intelligence (AI) and Emergency Medicine: Balancing Opportunities and Challenges *JMIR Med Inform.* 13:e70903. doi:10.2196/70903.
6. Tyler, S., Olis, M., Aust, N., et al.(2024). Use of artificial intelligence in triage in hospital emergency departments: a scoping review. *Cureus.* 16(5):e59906.
7. Zaboli, A., Brigo, F., Sibilio, S., Mian, M., Turcato, G.(2024). Human intelligence versus Chat-GPT: who performs better in correctly classifying patients in triage? *Am J Emerg Med.* 79:44-7.
8. Levin, S., Toerper, M., Hamrock, E., et al.(2018). machine-learning-based electronic triage more accurately differentiates patients with respect to clinical outcomes compared with the Emergency Severity Index. *Ann Emerg Med.* 71(5):565-74.
9. Frost, D.W., Vembu, S., Wang, J., Tu, K., Morris, Q., Abrams, H.B.(2017). Using the electronic medical record to identify patients at high risk for frequent emergency department visits and high system costs. *Am J Med.* 130(5):601.
10. Amiot, F., Potier, B. (2025). Artificial Intelligence (AI) and Emergency Medicine: Balancing Opportunities and Challenges. *JMIR Med Inform.* 13:e70903. doi:10.2196/70903. PMID: 40802997.
11. Mueller, B., Kinoshita, T., Peebles, A., Mark, A.(2022). Graber, Sangil Lee. Artificial intelligence and machine learning in emergency medicine: a narrative review. *Acute Medicine and Surgery.* 9(1) :2022. e740. https://doi.org/10.1002/ams2.740.
12. Vearrier, L., Derse, A.R., Basford, J.B., Larkin, G.L. (2022). Artificial Intelligence in Emergency Medicine: Benefits, Risks, and Recommendations. *The Journal of Emergency Medicine*. 62(4): 492-9. https://doi.org/10.1016/j.jemermed.2022.01.001.

13. McCradden, M.D., Stephenson, E.A., Anderson, J.A. (2020). Clinical research underlies ethical integration of healthcare artificial intelligence. Nat Med. 26:1325-1326.
14. Israni, S.T., Verghese, A. (2019). Humanizing artificial intelligence. *JAMA*. 321:29-30.
15. Mueller, B., Kinoshita, T., Peebles, A., Graber, M.A., Lee, S. (2022). Artificial intelligence and machine learning in emergency medicine: a narrative review. *Acute Medicine and Surgery*. 9(1):e740. https://doi.org/10.1002/ams2.740.
16. Taylor, R.A., Sangal, R.B., Smith, M.E., (2025). Leveraging artificial intelligence to reduce diagnostic errors in emergency medicine: Challenges, opportunities, and future directions. *Academic Emergency Medicine.* 32(3): 327-39. https://doi.org/10.1111/acem.15066.
17. Pelaccia, T., Sherbino, J., Wyer P. (2025). Diagnostic reasoning and cognitive error in emergency medicine: Implications for teaching and learning. *Academic Emergency Medicine.* 32(3): 320-6. https://doi.org/10.1111/acem.14968.
18. Ayers, J.W., Poliak, A., Dredze, M., et al. (2023). Comparing physician and artificial intelligence chatbot responses to patient questions posted to a public social media forum. *JAMA Intern Med.* 183(6):589–96. doi: 10.1001/jamainternmed.2023.1838. doi. Medline.
19. Meyer, N.S., Meyer, J.W. (2025). A Practical Guide to the Utilization of ChatGPT in the Emergency Department: A Systematic Review of Current Applications, Future Directions, and Limitations. *Cureus.* 17(4): e81802. doi: 10.7759/cureus.81802.
20. Yong, L.P., Tung, J.Y., Lee, Z.Y., Kuan, W.S., Chua, M.T. (2024). Performance of large language models in patient complaint resolution: web-based cross-sectional survey. J Med *Internet Res.* 26:0. doi: 10.2196/56413.
21. Zaboli, A., Brigo, F., Brigiari, G. (2025). Chat-GPT in triage: Still far from surpassing human expertise - An observational study. *The American Journal of Emergency Medicine*. 92:165-71. https://doi.org/10.1016/j.ajem.2025.03.028.
22. Williams C.Y., Zack T., Miao, B.Y., et al. (2024) Use of a large language model to assess clinical acuity of adults in the emergency department. *JAMA* Netw Open: e248895-e248895.
23. Hwai, H., Ho Y., Wang C., Huang, C. (2025). Large language model application in emergency medicine and critical care. *Journal of the Formosan Medical Association.* 124(8) :696-9. https://doi.org/10.1016/j.jfma.2024.08.032.
24. Wang, C., Wang, F., Li, S., et al. (2025). Patient Triage and Guidance in Emergency Departments Using Large Language Models: Multimetric Study. *J Med Internet Res.* 27:e71613. doi: 10.2196/71613.
25. Lee, S., Jung, S., Park, JH. et al. (2025). Performance of ChatGPT, Gemini and DeepSeek for non-critical triage support using real-world conversations in emergency department. *BMC Emerg Med.* 25:176 https://doi.org/10.1186/s12873-025-01337-2.
26. Hoppe, J.M., Auer, M.K., Strüven, A., Massberg, S., Stremmel, C. (2024). ChatGPT with GPT-4 outperforms emergency department physicians in diagnostic accuracy: retrospective analysis. *J Med Internet Res.* 26:0. doi: 10.2196/56110.
27. Berg, H.T., van Bakel, B., van de Wouw, L., et al. (2024). ChatGPT and generating a differential diagnosis early in an emergency department presentation. *Ann Emerg Med.*83:83-6. doi: 10.1016/j.annemergmed.2023.08.003.
28. Park, C., An, M.H., Hwang, G., Park, R.W., An J. (2025). Clinical Performance and Communication Skills of ChatGPT Versus Physicians in Emergency Medicine: Simulated Patient Study. *JMIR Med Inform*. 13:e68409. doi: 10.2196/68409.
29. Wang, J., Shue, K., Liu, L. et al. (2025). Preliminary evaluation of ChatGPT model iterations in emergency department diagnostics. *Sci Rep.* 15:10426. https://doi.org/10.1038/s41598-025-95233-1.
30. Bae, Y., Moon, H.K., Kim, S.H. (2018). Predicting the mortality of pneumonia patients visiting the emergency department through machine learning. *J Korean Soc Emerg Med.* 29(5): 455-64.
31. Costantino, G., Falavigna, G., Solbiati, M., et al. (2016). Neural networks as a tool to predict syncope risk in the Emergency Department. *Ep Europace.* 19(11): 1891-5.
32. Sinha, M., Kennedy, C.S., Ramundo, M.L. (2001). Artificial neural network predicts CT scan abnormalities in pediatric patients with closed head injury. *J Trauma Acute Care Surg.* 50(2): 308-12.
33. Chlorogiannis, D.D., Apostolos, A., Chlorogiannis, A., et al. (2023). The role of ChatGPT in the advancement of diagnosis, management, and prognosis of cardiovascular and cerebrovascular disease. *Healthcare.* 11.
34. Scquizzato, T., Semeraro F., Swindell P., et al. (2024). Testing ChatGPT ability to answer laypeople questions about cardiac arrest and cardiopulmonary resuscitation. *Resuscitation.* 194: Article 110077.
35. Almehairi, N., Clark, G. & Davis, S. (2025). How well does GPT-4 perform on an emergency medicine board exam? A comparative assessment. *Can J Emerg Med*. 27:969–973 https://doi.org/10.1007/s43678-025-00951-0.
36. Günay, S., Öztürk, A., Özerol, H., Yiğit, Y., Erenler, A.K. Comparison of emergency medicine specialist, cardiologist, and Chat-GPT in electrocardiography assessment. *Am J Emerg Med.* 80:51–60. doi: 10.1016/j.ajem.2024.03.017.
37. Günay, S., Öztürk, A., Yiğit, Y. (2024). The accuracy of Gemini, GPT-4, and GPT-4o in ECG analysis: a comparison with cardiologists and emergency medicine specialists. *Am J Emerg Med.* 84:68–73. doi: 10.1016/j.ajem.2024.07.043.
38. Zaboli, A., Brigo, F., Ziller M., et.al. (2025). Exploring ChatGPT's potential in ECG interpretation and outcome prediction in emergency department. *The American Journal of Emergency Medicine.* 88:7-11. https://doi.org/10.1016/j.ajem.2024.11.023.
39. Umit, T.B., Arslan, M., Inan, G. et al. (2026). Can ChatGPT compete with emergency medicine specialists? A two-stage assessment of ECG interpretation supported by clinical information. *BMC Emerg Med.* https://doi.org/10.1186/s12873-026-01486-y.
40. Öztürk, A., Günay, S., Ateş, S., Yiğit, Y. (2025). Can Gpt-4o Accurately Diagnose Trauma X-Rays? A Comparative Study with Expert Evaluations. *The Journal of Emergency Medicine.* 73: 71-9, https://doi.org/10.1016/j.jemermed.2024.12.010.
41. Hernandez Torres, S.I., Holland, L., Winter, T. et al. (2025). Real-Time Deployment of Ultrasound Image Interpretation AI Models for Emergency Medicine Triage Using a Swine Model. *Technologies.* 13(1):29. https://doi.org/10.3390/technologies13

CHAPTER 15

Artificial Intelligence in Pathology: Principles, Applications, and Future Perspectives

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1. Introduction

Pathology is central to modern medical practice, providing the definitive diagnoses that guide patient management, prognosis, and therapeutic decisions. Over the past decades, the field has evolved from a predominantly morphology-based discipline to an integrative science incorporating immunohistochemistry, molecular diagnostics, and genomic profiling. While these advances have significantly improved diagnostic precision, they have also increased the complexity and volume of data that pathologists must interpret in routine practice (1–3).

At the same time, pathology services are facing substantial global challenges, including increasing workload, growing diagnostic demands, and a shortage of trained pathologists. These pressures highlight the need for innovative approaches that can enhance efficiency, improve reproducibility, and support decision-making. Artificial intelligence (AI) has emerged as a promising solution, offering computational tools capable of analyzing large and complex datasets beyond the limits of human cognition (4–6).

The integration of AI into pathology has been enabled by the widespread adoption of digital pathology, particularly whole slide imaging (WSI), which converts glass slides into high-resolution digital data. This digital transformation provides the essential infrastructure for applying machine learning algorithms to histopathological images. Early AI applications have focused on tasks such as image classification, segmentation, and quantification, demonstrating improved consistency and scalability, while more recent developments have expanded toward multimodal data integration and predictive modeling (7–9).

More recently, the emergence of generative AI and foundation models has introduced new capabilities, including automated report generation, decision support, and advanced

data synthesis. Despite these advances, significant challenges remain, including issues related to validation, interpretability, bias, and clinical implementation. This chapter provides a concise overview of the principles of AI in pathology, its current applications, and future directions, with particular emphasis on its role as an augmentative tool that enhances, rather than replaces, the expertise of the practicing pathologist (10).

2. Historical Evolution of Artificial Intelligence in Pathology

The evolution of artificial intelligence (AI) in pathology reflects broader advances in computational sciences, data availability, and imaging technologies. Early conceptual foundations of AI date back to the mid-20th century, with the emergence of machine learning principles and initial attempts to apply computational methods to biomedical data. In pathology, early developments focused primarily on image analysis and pattern recognition, aiming to assist in the interpretation of microscopic structures. These early systems were limited by computational power and data accessibility but established the groundwork for subsequent advancements in digital and computational pathology (8–9).

The introduction and widespread adoption of whole slide imaging (WSI) marked a pivotal turning point in the field, enabling the digitization of glass slides into high-resolution images suitable for computational analysis. This technological shift facilitated the application of more advanced machine learning algorithms and enabled large-scale data-driven approaches. During this period, deep learning—particularly convolutional neural networks (CNNs)—emerged as a transformative methodology, allowing automated feature extraction directly from image data. These developments significantly improved the performance of AI systems in tasks such as classification, segmentation, and tumor detection, bringing computational pathology closer to clinical applicability (9–10).

More recently, the evolution of AI in pathology has been characterized by the transition from task-specific algorithms to more generalized and scalable models. Traditional machine learning approaches have been complemented by increasingly sophisticated deep learning frameworks, while the integration of AI into laboratory medicine and pathology workflows has gained momentum. Contemporary efforts focus not only on improving diagnostic accuracy but also on achieving seamless clinical integration, reproducibility, and scalability. This ongoing evolution continues to shape the role of AI as a supportive and augmentative tool in modern pathology practice (10–12).

3. Basic Concepts and Terminology

Artificial intelligence (AI) is a broad field encompassing computational methods designed to simulate human cognitive processes, including learning, reasoning, and problem-solving. Within this domain, machine learning (ML) represents a subset of AI that enables systems to learn patterns from data without being explicitly programmed. ML approaches

are commonly divided into supervised, unsupervised, and reinforcement learning, depending on how the models are trained and how they interact with data. In pathology, these approaches are used to analyze complex datasets derived from histopathological images, molecular profiles, and clinical information, forming the foundation for computational diagnostics and decision support systems (1,12).

A major advancement in AI has been the development of deep learning (DL), a subset of machine learning based on artificial neural networks with multiple hidden layers. Convolutional neural networks (CNNs), in particular, have become the dominant architecture for image analysis tasks in pathology due to their ability to automatically extract hierarchical features directly from raw image data. Unlike traditional algorithms that rely on handcrafted features, deep learning models learn relevant patterns from large annotated datasets, enabling improved performance in tasks such as tumor detection, classification, and grading. These capabilities have significantly contributed to the rapid expansion of AI applications in digital pathology (9,10).

More recently, the field has expanded to include generative artificial intelligence and foundation models, which represent a shift from predictive analytics to content generation and multimodal integration. Generative AI systems, including large language models (LLMs) and generative adversarial networks (GANs), are capable of producing new data such as text, images, or synthetic histopathological patterns. Foundation models, trained on large and diverse datasets, offer flexible architectures that can be adapted to multiple downstream tasks with minimal additional training. While these emerging approaches hold great promise for advancing diagnostic workflows, education, and research, they also introduce challenges related to interpretability, reliability, and ethical use in clinical settings (13-18).

4. Digital Pathology as the Infrastructure for AI

The successful integration of artificial intelligence (AI) into pathology is fundamentally dependent on the digital transformation of the field. The introduction of whole slide imaging (WSI) has enabled the conversion of traditional glass slides into high-resolution digital images, creating a robust data infrastructure suitable for computational analysis. These digital slides capture complex morphological details at multiple magnifications and generate vast amounts of data, providing a rich substrate for machine learning algorithms. As a result, digital pathology has become the essential foundation upon which modern AI applications in pathology are built (2,10).

Beyond image digitization, digital pathology facilitates data storage, sharing, and interoperability, which are critical for large-scale AI model development and validation. The ability to archive and access digitized slides enables the creation of annotated datasets required for training supervised learning models, while also supporting collaborative research and telepathology practices. Advances in computational power, data storage solutions, and network infrastructure have further accelerated the adoption of digital

workflows, allowing pathologists to integrate AI tools into routine diagnostic practice. These developments have transformed pathology from a purely microscope-based discipline into a data-driven environment (14,15,19).

Despite these advances, several challenges remain in fully leveraging digital pathology for AI applications. Variability in slide preparation, staining techniques, and scanner technologies can introduce inconsistencies that affect model performance and generalizability. Additionally, the need for high-quality annotations and standardized datasets continues to be a major bottleneck in developing reliable AI systems. Addressing these challenges requires coordinated efforts in standardization, quality control, and validation to ensure that AI tools can be safely and effectively integrated into clinical workflows (14).

5. Non-Generative AI in Pathology

Non-generative artificial intelligence, often referred to as traditional or predictive AI, forms the backbone of most clinically validated applications in pathology. These approaches primarily rely on supervised and unsupervised machine learning algorithms designed to identify patterns within existing datasets and generate predictions or classifications. In digital pathology, non-generative AI is widely used for tasks such as image classification, tumor detection, segmentation, grading, and quantification of histopathological features. By leveraging labeled datasets, supervised learning models can distinguish between benign and malignant lesions, while unsupervised approaches can reveal hidden structures and patterns within complex data (8,12,20).

A major advancement in this domain has been the adoption of deep learning, particularly convolutional neural networks (CNNs), which enable automated feature extraction directly from histopathological images. These models have demonstrated high performance in a variety of diagnostic tasks, often approaching or exceeding human-level accuracy in controlled settings. Furthermore, non-generative AI systems contribute to improved workflow efficiency by automating repetitive tasks, highlighting regions of interest, and supporting quantitative analysis. Despite these advantages, challenges remain regarding generalizability, data quality, and integration into routine clinical workflows, necessitating careful validation and standardization (5,17,21).

6. Generative AI in Anatomic and Clinical Pathology

Generative artificial intelligence represents a significant paradigm shift from traditional predictive models by enabling the creation of new data rather than solely analyzing existing information. These systems, including large language models (LLMs) and generative adversarial networks (GANs), can generate text, images, and synthetic datasets based on learned patterns from large-scale training data. In pathology, generative AI has introduced novel applications such as automated report generation, clinical decision support, synthetic image creation, and virtual staining. These capabilities have the potential to en-

hance efficiency, improve accessibility to expert-level insights, and support both clinical and educational activities (18,22).

In addition to content generation, generative AI is increasingly being integrated into multimodal frameworks that combine textual, imaging, and molecular data. Such approaches enable more comprehensive analyses and open new avenues for personalized medicine and research. However, the adoption of generative AI in pathology also raises important concerns, including the risk of hallucinated outputs, lack of transparency, and challenges in validation and regulatory oversight. Ensuring reliable and ethical use of these technologies requires human-in-the-loop systems, robust evaluation frameworks, and clear guidelines for clinical implementation (22-24).

7. AI Applications Across Pathology Subspecialties

Artificial intelligence has demonstrated broad applicability across multiple pathology subspecialties, reflecting its versatility in analyzing complex histopathological data (25-34). In genitourinary pathology, AI has been extensively studied for prostate cancer detection, grading, and risk stratification, showing strong potential to improve diagnostic consistency and reduce interobserver variability (19). Similarly, in dermatopathology and cytopathology, AI-assisted image analysis has been used to enhance lesion classification and screening accuracy, particularly in high-throughput settings where rapid and reproducible assessment is essential (25,27). In thoracic pathology, AI models have been applied to lung tumor classification and prognostic prediction, while in gastrointestinal pathology, they assist in identifying dysplastic changes and supporting biopsy evaluation, thereby contributing to more efficient diagnostic workflows (17,30).

Beyond these commonly studied areas, AI applications are rapidly expanding into other subspecialties, including neuropathology, pediatric pathology, and head and neck pathology. In central nervous system tumors, AI models have shown promise in tumor classification and outcome prediction by integrating imaging and histopathological data (21). In pediatric and perinatal pathology, digital pathology combined with AI offers opportunities for improved diagnostic support and education, particularly in rare and complex cases (31,32). Additionally, in oral and head and neck pathology, AI-based approaches are increasingly used for lesion detection and prognostic assessment, highlighting the growing role of computational tools across diverse diagnostic contexts (20,33). Collectively, these developments underscore the expanding integration of AI into routine pathology practice, with the potential to enhance diagnostic accuracy, efficiency, and reproducibility across subspecialties.

8. AI in Cancer Pathology and Precision Oncology

Artificial intelligence has emerged as a transformative tool in cancer pathology, significantly enhancing diagnostic accuracy, prognostic assessment, and therapeutic decision-

making. By leveraging large-scale histopathological datasets, AI models can identify subtle morphological patterns associated with tumor biology that may not be readily apparent through conventional microscopic evaluation. In particular, AI-assisted systems have demonstrated strong performance in tumor detection, classification, and grading across multiple cancer types, contributing to improved diagnostic reproducibility and efficiency (34,35).

Beyond traditional histopathological assessment, AI plays a critical role in advancing precision oncology by integrating multimodal data, including imaging, molecular, and clinical information. These approaches enable more refined risk stratification and personalized treatment planning by linking morphological features with underlying genomic alterations and clinical outcomes. In gastrointestinal, head and neck, and other malignancies, AI-based models have been used to predict disease progression, treatment response, and survival outcomes, highlighting their potential in guiding individualized patient management (36,37).

In addition, AI applications in genitourinary and prostate pathology have demonstrated particular promise, with models capable of improving tumor grading consistency and predicting clinically relevant endpoints. These advances support the growing integration of AI into precision oncology frameworks, where data-driven insights can complement pathologist expertise. Despite these encouraging developments, challenges remain regarding data standardization, external validation, and clinical implementation, underscoring the need for robust evaluation before widespread adoption (38,39).

9. Foundation Models and AI Copilots in Pathology

Recent developments in artificial intelligence have led to the emergence of foundation models, which represent a new generation of large-scale, highly adaptable systems trained on diverse datasets. Unlike traditional task-specific models, foundation models are designed to perform multiple downstream tasks with minimal additional training, enabling applications across a wide range of pathology workflows. These models often rely on self-supervised learning techniques and can process multimodal data, including histopathological images, genomic information, and clinical text, thereby offering a more comprehensive understanding of disease processes (40).

Building on these advances, AI "copilots" have been introduced as interactive systems capable of assisting pathologists in real-time decision-making. These tools integrate large language models with image analysis capabilities, allowing users to query data, generate reports, and receive context-aware insights. Such systems have the potential to streamline diagnostic workflows, reduce cognitive burden, and enhance efficiency by providing on-demand support during routine practice. Importantly, AI copilots are designed to augment rather than replace human expertise, reinforcing the central role of the pathologist in clinical decision-making (40,41).

However, despite their transformative potential, foundation models and AI copilots present several challenges that must be addressed before widespread clinical adoption. Issues related to generalizability, data bias, interpretability, and reliability remain significant concerns, particularly when models are applied across diverse populations and laboratory settings. Furthermore, the risk of generating inaccurate or misleading outputs necessitates the implementation of human-in-the-loop systems and rigorous validation frameworks. Addressing these challenges will be essential to ensure the safe and effective integration of these advanced AI systems into pathology practice (41).

10. AI in Pathology Education and Training

Artificial intelligence is increasingly being incorporated into pathology education and training, offering new opportunities to enhance learning experiences and improve accessibility to educational resources. Generative AI systems, particularly large language models, enable the creation of personalized educational content, interactive case discussions, and adaptive learning platforms tailored to individual needs. These tools can assist trainees in understanding complex diagnostic concepts, providing explanations and feedback in a dynamic and scalable manner (23).

In addition to content generation, AI-driven tools facilitate simulation-based learning and virtual case training, allowing learners to engage with a wide range of histopathological scenarios. Digital pathology platforms integrated with AI can provide annotated slides, automated assessments, and performance tracking, supporting competency-based education. Such approaches are particularly valuable in subspecialty training and in settings where access to expert mentorship or diverse case material may be limited (18,23).

Despite these advantages, the integration of AI into pathology education requires careful consideration of potential limitations and ethical implications. Overreliance on AI-generated content may reduce critical thinking and independent diagnostic reasoning if not appropriately supervised. Furthermore, concerns related to accuracy, bias, and transparency must be addressed to ensure the reliability of educational tools. As such, AI should be viewed as a complementary resource that enhances, rather than replaces, traditional educational methods and human mentorship (18,24).

11. Implementation in Routine Pathology Practice

The implementation of artificial intelligence in routine pathology practice represents a critical step in translating research advancements into clinical impact. Integrating AI tools into laboratory workflows requires compatibility with existing digital pathology systems, including laboratory information systems (LIS) and whole slide imaging platforms. AI applications are increasingly being used to assist in tasks such as case triage, region-of-interest detection, and quantitative analysis, contributing to improved workflow efficiency and diagnostic consistency (14,15).

Successful implementation also depends on robust validation and quality assurance processes to ensure that AI systems perform reliably across diverse clinical settings. Variability in tissue preparation, staining, and scanning protocols can affect model performance, highlighting the need for standardized datasets and external validation studies. Additionally, continuous monitoring and updating of AI models are necessary to maintain accuracy and address issues such as data drift over time (17,42).

Beyond technical considerations, the adoption of AI in routine practice requires addressing practical, regulatory, and user-related challenges. Pathologists must be adequately trained to interpret AI outputs and understand their limitations, while institutions must establish clear guidelines for accountability and clinical responsibility. Acceptance of AI tools also depends on user trust and perceived utility, emphasizing the importance of transparency and explainability. Ultimately, the successful integration of AI into routine pathology practice will depend on a balanced approach that combines technological innovation with clinical expertise and oversight (24,41).

12. Ethical, Legal, and Regulatory Considerations

The integration of artificial intelligence into pathology raises important ethical and regulatory challenges that must be carefully addressed to ensure safe and responsible use. Issues such as data privacy, patient confidentiality, and informed consent are central to the development and deployment of AI systems, particularly given the large-scale datasets required for model training. Furthermore, concerns regarding algorithmic bias and fairness are increasingly recognized, as models trained on non-representative datasets may produce unequal performance across different populations (24).

Another critical aspect involves the interpretability and transparency of AI systems, often referred to as the "black-box" problem. Many advanced models, particularly deep learning algorithms, lack explainability, making it difficult for clinicians to understand how decisions are generated. This limitation raises questions regarding accountability, especially in cases where AI-assisted decisions influence patient management. As a result, regulatory frameworks are evolving to emphasize the importance of explainable AI, validation standards, and clear documentation of model performance (24,41).

In addition to technical and ethical considerations, legal and regulatory challenges play a crucial role in shaping the adoption of AI in pathology. Regulatory agencies are increasingly developing guidelines for the approval and monitoring of AI-based medical devices, while institutions must establish policies regarding clinical responsibility and liability. Ensuring compliance with these frameworks requires collaboration among pathologists, data scientists, policymakers, and industry stakeholders. Ultimately, the responsible implementation of AI will depend on balancing innovation with patient safety, ethical integrity, and regulatory oversight (41).

13. Current Limitations and Practical Challenges

Despite significant advancements, several limitations continue to hinder the widespread adoption of artificial intelligence in pathology. One of the most prominent challenges is the issue of generalizability, as AI models often perform well in controlled research settings but may fail when applied to external datasets with different characteristics. Variability in staining protocols, slide preparation, and scanner technologies can introduce inconsistencies that negatively impact model performance, highlighting the need for robust external validation (41).

Another major limitation is the dependence on high-quality annotated data for training supervised learning models. The process of generating accurate annotations is time-consuming and requires expert input, which can limit the scalability of AI development. Additionally, many AI systems rely on large datasets that may not be readily available in all institutions, creating disparities in access to advanced technologies. These challenges underscore the importance of data standardization, collaborative data sharing, and the development of annotation-efficient approaches (14).

Furthermore, practical challenges related to workflow integration and user acceptance remain significant barriers. Pathologists may be hesitant to adopt AI tools due to concerns about reliability, transparency, and potential disruption of established diagnostic processes. The risk of overreliance on AI outputs, particularly in the presence of model errors or "hallucinations," also raises concerns regarding patient safety. Addressing these issues requires ongoing education, validation, and the development of systems that support human oversight rather than replacing clinical expertise (18,41).

14. Future Perspectives

The future of artificial intelligence in pathology is expected to be shaped by continued advancements in computational methods, data integration, and collaborative research efforts. Emerging technologies such as multimodal AI, which combine histopathological, molecular, and clinical data, have the potential to provide a more comprehensive understanding of disease processes and improve precision medicine approaches. These developments will enable more accurate risk stratification, treatment selection, and outcome prediction across a wide range of diseases (34).

In addition, the development of foundation models and scalable AI architectures is likely to play a central role in the next phase of innovation. These models offer the ability to generalize across multiple tasks and datasets, reducing the need for extensive retraining and enabling broader clinical applicability. Advances in federated learning and distributed data analysis may also facilitate collaboration across institutions while preserving data privacy, thereby accelerating the development of robust and generalizable AI systems (40,41).

Importantly, the future of AI in pathology will depend not only on technological progress but also on successful integration into clinical workflows and acceptance by the

medical community. Efforts to improve model explainability, transparency, and user trust will be essential to ensure that AI tools are effectively adopted in practice. Ultimately, AI is expected to function as a collaborative partner that enhances the capabilities of pathologists, supporting more efficient, accurate, and personalized patient care (7,41).

15. Conclusion

Artificial intelligence has rapidly emerged as a transformative force in pathology, offering powerful tools for improving diagnostic accuracy, efficiency, and reproducibility. From traditional machine learning approaches to advanced deep learning and generative models, AI technologies have demonstrated significant potential across a wide range of applications, including tumor detection, prognostic assessment, and workflow optimization. These advancements highlight the growing role of AI as an integral component of modern pathology practice (1,7).

Despite these promising developments, the successful integration of AI into clinical practice requires careful consideration of technical, ethical, and regulatory challenges. Issues related to data quality, model validation, interpretability, and accountability must be addressed to ensure safe and reliable use. Furthermore, the importance of maintaining human oversight and clinical judgment remains paramount, as AI tools are designed to augment, rather than replace, the expertise of pathologists.

Looking forward, the continued evolution of AI in pathology will depend on interdisciplinary collaboration, robust validation frameworks, and the development of transparent and trustworthy systems. As these challenges are addressed, AI is poised to play an increasingly central role in advancing precision medicine and improving patient outcomes. By integrating technological innovation with clinical expertise, the future of pathology will be defined by a synergistic partnership between humans and intelligent systems.

16. References

1. Rashidi, H. H., Pantanowitz, J., Hanna, M. G., Tafti, A. P., Sanghani, P., Buchinsky, A., Fennell, B., Deebajah, M., Wheeler, S., Pearce, T., Abukhiran, I., Robertson, S., Palmer, O., Gur, M., Tran, N. K., & Pantanowitz, L. (2025). Introduction to Artificial Intelligence and Machine Learning in Pathology and Medicine: Generative and Nongenerative Artificial Intelligence Basics. Modern pathology: an official journal of the United States and Canadian Academy of Pathology, Inc, 38(4), 100688. https://doi.org/10.1016/j.modpat.2024.100688
2. Niazi, M. K. K., Parwani, A. V., & Gurcan, M. N. (2019). Digital pathology and artificial intelligence. The Lancet. Oncology, 20(5), e253–e261. https://doi.org/10.1016/S1470-2045(19)30154-8
3. Cohen, S., Levenson, R., & Pantanowitz, L. (2021). Artificial Intelligence in Pathology. The American journal of pathology, 191(10), 1670–1672. https://doi.org/10.1016/j.ajpath.2021.07.011
4. Usta, U., & Taştekin, E. (2024). Present and Future of Artificial Intelligence in Pathology. Balkan medical journal, 41(3), 157–158. https://doi.org/10.4274/balkanmedj.galenos.2024.2024.060324
5. Bera, K., Schalper, K. A., Rimm, D. L., Velcheti, V., & Madabhushi, A. (2019). Artificial intelligence in digital pathology - new tools for diagnosis and precision oncology. Nature reviews. Clinical oncology, 16(11), 703–715. https://doi.org/10.1038/s41571-019-0252-y
6. Sagiv, C., Hadar, O., Najjar, A., & Pahnke, J. (2025). Artificial intelligence in surgical pathology - Where do we stand, where do we go?. European journal of surgical oncology: the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology, 51(7), 109541. https://doi.org/10.1016/j.ejso.2024.109541

7. Hanna, M. G., Pantanowitz, L., Dash, R., Harrison, J. H., Deebajah, M., Pantanowitz, J., & Rashidi, H. H. (2025). Future of Artificial Intelligence-Machine Learning Trends in Pathology and Medicine. Modern pathology: an official journal of the United States and Canadian Academy of Pathology, Inc, 38(4), 100705. https://doi.org/10.1016/j.modpat.2025.100705
8. Shafi, S., & Parwani, A. V. (2023). Artificial intelligence in diagnostic pathology. Diagnostic pathology, 18(1), 109. https://doi.org/10.1186/s13000-023-01375-z
9. Jiang, Y., Yang, M., Wang, S., Li, X., & Sun, Y. (2020). Emerging role of deep learning-based artificial intelligence in tumor pathology. Cancer communications (London, England), 40(4), 154–166. https://doi.org/10.1002/cac2.12012
10. Colling, R., Pitman, H., Oien, K., Rajpoot, N., Macklin, P., CM-Path AI in Histopathology Working Group, Snead, D., Sackville, T., & Verrill, C. (2019). Artificial intelligence in digital pathology: a roadmap to routine use in clinical practice. The Journal of pathology, 249(2), 143–150. https://doi.org/10.1002/path.5310
11. Pillay T. S. (2021). Artificial intelligence in pathology and laboratory medicine. Journal of clinical pathology, 74(7), 407–408. https://doi.org/10.1136/jclinpath-2021-207682
12. Pantanowitz, L., Pearce, T., Abukhiran, I., Hanna, M., Wheeler, S., Soong, T. R., Tafti, A. P., Pantanowitz, J., Lu, M. Y., Mahmood, F., Gu, Q., & Rashidi, H. H. (2025). Nongenerative Artificial Intelligence in Medicine: Advancements and Applications in Supervised and Unsupervised Machine Learning. Modern pathology: an official journal of the United States and Canadian Academy of Pathology, Inc, 38(3), 100680. https://doi.org/10.1016/j.modpat.2024.100680
13. Waqas, A., Bui, M. M., Glassy, E. F., El Naqa, I., Borkowski, P., Borkowski, A. A., & Rasool, G. (2023). Revolutionizing Digital Pathology With the Power of Generative Artificial Intelligence and Foundation Models. Laboratory investigation; a journal of technical methods and pathology, 103(11), 100255. https://doi.org/10.1016/j.labinv.2023.100255
14. Zhang, X. M., Gao, T. H., Cai, Q. Y., Xia, J. B., Sun, Y. N., Yang, J., Li, W. H., Zhang, S. X., Lou, H. R., Yu, X. T., Hu, K. W., Ye, J. W., Zhang, J. X., Lei, J., Cheng, L. C., Xu, L. J., Chen, Q., Wang, H. X., Gan, M. F., Lu, C., … Feng, Z. L. (2026). Artificial intelligence in digital pathology diagnosis and analysis: technologies, challenges, and future prospects. Military Medical Research, 12(1), 93. https://doi.org/10.1186/s40779-025-00680-6
15. Jariyapan, P., Pora, W., Kasamsumran, N., & Lekawanvijit, S. (2025). Digital pathology and artificial intelligence in diagnostic pathology. The Malaysian journal of pathology, 47(1), 3–12.
16. Zhang, X. M., Gao, T. H., Cai, Q. Y., Xia, J. B., Sun, Y. N., Yang, J., Li, W. H., Zhang, S. X., Lou, H. R., Yu, X. T., Hu, K. W., Ye, J. W., Zhang, J. X., Lei, J., Cheng, L. C., Xu, L. J., Chen, Q., Wang, H. X., Gan, M. F., Lu, C., … Feng, Z. L. (2026). Artificial intelligence in digital pathology diagnosis and analysis: technologies, challenges, and future prospects. Military Medical Research, 12(1), 93. https://doi.org/10.1186/s40779-025-00680-6
17. Yilmaz, F., Brickman, A., Najdawi, F., Yakirevich, E., Egger, R., & Resnick, M. B. (2024). Advancing Artificial Intelligence Integration Into the Pathology Workflow: Exploring Opportunities in Gastrointestinal Tract Biopsies. Laboratory investigation; a journal of technical methods and pathology, 104(5), 102043. https://doi.org/10.1016/j.labinv.2024.102043
18. McCaffrey, P., Jackups, R., Seheult, J., Zaydman, M. A., Balis, U., Thaker, H. M., Rashidi, H., & Gullapalli, R. R. (2025). Evaluating Use of Generative Artificial Intelligence in Clinical Pathology Practice: Opportunities and the Way Forward. Archives of pathology & laboratory medicine, 149(2), 130–141. https://doi.org/10.5858/arpa.2024-0208-RA
19. Patel, A. U., Parwani, A. V., & Satturwar, S. (2026). Artificial intelligence in genitourinary pathology. Histopathology, 88(1), 353–373. https://doi.org/10.1111/his.70020
20. Petsiou, D. P., Spinos, D., Martinos, A., Muzaffar, J., Garas, G., & Georgalas, C. (2025). Effectiveness of Artificial Intelligence in detecting sinonasal pathology using clinical imaging modalities: a systematic review. Rhinology, 63(4), 448–462. https://doi.org/10.4193/Rhin25.044
21. Suero Molina, E., Azemi, G., Russo, C., Liu, S., & Di Ieva, A. (2024). Artificial Intelligence in Brain Tumors. Advances in experimental medicine and biology, 1462, 201–220. https://doi.org/10.1007/978-3-031-64892-2_12
22. Brodsky, V., Ullah, E., Bychkov, A., Song, A. H., Walk, E. E., Louis, P., Rasool, G., Singh, R. S., Mahmood, F., Bui, M. M., & Parwani, A. V. (2025). Generative Artificial Intelligence in Anatomic Pathology. Archives of pathology & laboratory medicine, 149(4), 298–318. https://doi.org/10.5858/arpa.2024-0215-RA
23. Cecchini, M. J., Borowitz, M. J., Glassy, E. F., Gullapalli, R. R., Hart, S. N., Hassell, L. A., Homer, R. J., Jackups, R., Jr, McNeal, J. L., & Anderson, S. R. (2025). Harnessing the Power of Generative Artificial Intelligence in Pathology Education: Opportunities, Challenges, and Future Directions. Archives of pathology & laboratory medicine, 149(2), 142–151. https://doi.org/10.5858/arpa.2024-0187-RA
24. Jackson, B. R., Rashidi, H. H., Lennerz, J. K., & de Baca, M. E. (2025). Ethical and Regulatory Perspectives on Generative Artificial Intelligence in Pathology. Archives of pathology & laboratory medicine, 149(2), 123–129. https://doi.org/10.5858/arpa.2024-0205-RA
25. Lalmalani, R. M., Lim, C. X. Y., & Oh, C. C. (2025). Artificial intelligence in dermatopathology: a systematic review. Clinical and experimental dermatology, 50(2), 251–259. https://doi.org/10.1093/ced/llae361
26. Alhatem, A., Wong, T., & Clark Lambert, W. (2024). Revolutionizing diagnostic pathology: The emergence and impact of artificial intelligence-what doesn't kill you makes you stronger?. Clinics in dermatology, 42(3), 268–274. https://doi.org/10.1016/j.clindermatol.2023.12.020
27. Harinath, L., Bai, X., Minkowitz, J., Zeng, X., Harrington, S., Zhao, C., & Pantanowitz, L. (2026). Artificial Intelligence in Gynecologic Cytology. Acta cytologica, 70(1), 52–71. https://doi.org/10.1159/000546182
28. Hanna M. G. (2025). Digital Pathology and Artificial Intelligence in Breast Pathology. Surgical pathology clinics, 18(4), 791–804. https://doi.org/10.1016/j.path.2025.07.002

29. Li, W., Ye, S., Jin, Z., Chen, L., Chao, Y., Wei, G., Huang, Q., Tu, H., & Wang, Q. (2025). Artificial Intelligence in digital pathology of breast cancer, new era of practice?. International journal of surgery (London, England), 111(11), 8270–8283. https://doi.org/10.1097/JS9.0000000000002953
30. Hartman D. J. (2024). Applications of Artificial Intelligence in Lung Pathology. Surgical pathology clinics, 17(2), 321–328. https://doi.org/10.1016/j.path.2023.11.013
31. Hutchinson, J. C., Picarsic, J., McGenity, C., Treanor, D., Williams, B., & Sebire, N. J. (2025). Whole Slide Imaging, Artificial Intelligence, and Machine Learning in Pediatric and Perinatal Pathology: Current Status and Future Directions. Pediatric and developmental pathology: the official journal of the Society for Pediatric Pathology and the Paediatric Pathology Society, 28(2), 91–98. https://doi.org/10.1177/10935266241299073
32. Shankar, N., Kreiger, P. A., Oldridge, D. A., Picarsic, J., & Arnold, M. A. (2025). Digital Pathology and Artificial Intelligence in Pediatric Pathology. Surgical pathology clinics, 18(2), 397–406. https://doi.org/10.1016/j.path.2024.11.006
33. Alsanie, I. S., Qannam, A., Bello, I. O., & Khurram, S. A. (2025). Exploring the Role of Artificial Intelligence in Oral Pathology: Diagnostic and Prognostic Implications. Journal of oral pathology & medicine: official publication of the International Association of Oral Pathologists and the American Academy of Oral Pathology, 54(7), 487–497. https://doi.org/10.1111/jop.70002
34. Yates, J., & Van Allen, E. M. (2025). New horizons at the interface of artificial intelligence and translational cancer research. Cancer cell, 43(4), 708–727. https://doi.org/10.1016/j.ccell.2025.03.018
35. Ni, H. M., Kouzy, R., Sabbagh, A., Rooney, M. K., Feng, J., Castillo, S. P., Gadoue, S. M., El Kouzi, Z., Hoffman, K., Yuan, Y., Madabhushi, A., & Mohamad, O. (2026). The state of the art in artificial intelligence and digital pathology in prostate cancer. Nature reviews. Urology, 23(1), 13–28. https://doi.org/10.1038/s41585-025-01070-2
36. Gao, Y., Wen, P., Liu, Y., Sun, Y., Qian, H., Zhang, X., Peng, H., Gao, Y., Li, C., Gu, Z., Zeng, H., Hong, Z., Wang, W., Yan, R., Hu, Z., & Fu, H. (2025). Application of artificial intelligence in the diagnosis of malignant digestive tract tumors: focusing on opportunities and challenges in endoscopy and pathology. Journal of translational medicine, 23(1), 412. https://doi.org/10.1186/s12967-025-06428-z
37. Wang, P., Tian, J., Zheng, G., Chen, Y., & Ren, X. (2026). Application of artificial intelligence in head and neck squamous cell carcinoma. Annals of medicine, 58(1), 2620191. https://doi.org/10.1080/07853890.2026.2620191
38. Egevad, L., Camilloni, A., Delahunt, B., Samaratunga, H., Eklund, M., & Kartasalo, K. (2025). The Role of Artificial Intelligence in the Evaluation of Prostate Pathology. Pathology international, 75(5), 213–220. https://doi.org/10.1111/pin.70015
39. Chan, G. J., & Ding, C. C. (2026). Advances in artificial intelligence in prostate cancer pathology. Seminars in diagnostic pathology, 43(2), 150995. https://doi.org/10.1016/j.semdp.2026.150995
40. Cheng, C. H., & Wong, C. C. (2025). The role of artificial intelligence-based foundation models and "copilots" in cancer pathology: potential and challenges. Journal of experimental & clinical cancer research: CR, 45(1), 2. https://doi.org/10.1186/s13046-025-03592-4
41. Aggarwal, A., Bharadwaj, S., Corredor, G., Pathak, T., Badve, S., & Madabhushi, A. (2025). Artificial intelligence in digital pathology - time for a reality check. Nature reviews. Clinical oncology, 22(4), 283–291. https://doi.org/10.1038/s41571-025-00991-6
42. Jariyapan, P., Pora, W., Kasamsumran, N., & Lekawanvijit, S. (2025). Digital pathology and artificial intelligence in diagnostic pathology. The Malaysian journal of pathology, 47(1), 3–12.

CHAPTER 16

The Use of Artificial Intelligence in Phytotherapy Research

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1. Introduction

1.1. Overview of Phytotherapy

Phytotherapy, defined as the science of using plant-derived extracts and natural compounds for the prevention and treatment of diseases, represents one of the oldest forms of medical practice known to humanity. Throughout history, diverse civilizations, from the ancient Sumerians and Egyptians to practitioners of Traditional Chinese Medicine and Ayurveda, have relied on the vast chemical repertoire of the botanical world to address human ailments. While once rooted in empirical observation and ethnobotanical tradition, modern phytotherapy has evolved into a rigorous scientific discipline that intersects with molecular biology, pharmacology, and clinical medicine (1).

At its core, the therapeutic efficacy of plants stems from their complex secondary metabolites, including alkaloids, flavonoids, terpenoids, and polyphenols. Unlike conventional monotherapy, where a single synthetic molecule targets a specific pathway, phytotherapeutic interventions often involve "polypharmacy by nature." This multi-component nature allows for synergistic interactions often termed the "entourage effect" in which multiple compounds work in concert to enhance efficacy or reduce adverse effects (2).

However, this inherent complexity also poses significant challenges for drug discovery and standardization. The variability in phytochemical profiles due to environmental factors, the difficulty in isolating active leads from dense matrices, and the sophisticated multi-target mechanisms of action have often limited the integration of herbal medicines into evidence-based clinical protocols. In the contemporary era, the transition from 'traditional use' to 'standardized therapeutic agent' requires a systemic understanding of these interactions. As we stand at the intersection of natural products and digital transforma-

tion, the need for advanced computational frameworks and multivariable precision approaches has never been more critical to unlock the full pharmacological potential of the plant kingdom (3).

1.2. The Complexity of Plant-Derived Compounds

The fundamental distinction between conventional pharmacology and phytotherapy lies in the molecular diversity of the therapeutic intervention. While modern drug discovery typically follows the "one drug, one target, one disease" model, phytotherapy operates on a "multi-compound, multi-target" paradigm. A single medicinal plant extract may contain hundreds of bioactive secondary metabolites, each contributing to the overall clinical outcome (4).

1.2.1. The Challenge of Multi-Target Mechanisms

Plant-derived compounds often exhibit pleiotropic effects, meaning they interact with multiple molecular targets such as enzymes, ion channels, and G protein-coupled receptors (GPCRs) simultaneously. Identifying which specific compound is responsible for which biological effect is a monumental task. This complexity is further compounded by the fact that many phytochemicals possess low individual potency but achieve significant therapeutic impact through collective action (4, 5). This multifaceted interactome between plant metabolites and human proteins is systematically visualized in Figure 1.

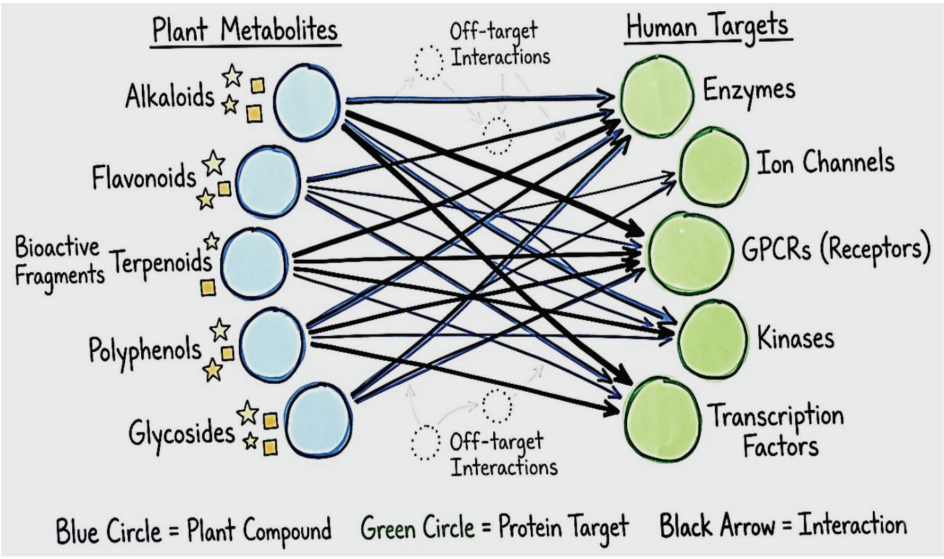


Figure 1. Network pharmacology architecture illustrating the multi-target interactome of botanical secondary metabolites

1.2.2. Synergy and the "Entourage Effect"

Synergy occurs when the combined effect of multiple compounds is greater than the sum of their individual effects. In phytotherapy, this is often described as the "entourage effect," in which secondary metabolites that may not be active on their own enhance the bioavailability or reduce the degradation of the primary active compounds. Identifying these synergistic pairs or groups using traditional "wet-lab" experiments is practically impossible due to the astronomical number of possible combinations (6). The inherent complexity of phytotherapeutic agents, characterized by their non-linear interactions and multi-target profiles, necessitates a departure from traditional reductionist models. While conventional pharmacology is built upon the "lock-and-key" hypothesis, focusing on a single ligand interacting with a specific receptor, botanical research demands a holistic, systems-biology approach (7). To illustrate this paradigm shift and the computational challenges that Artificial Intelligence (AI) is uniquely positioned to resolve, a comparative analysis is presented in Table 1.

Table 1. Comparative Analysis of Conventional Pharmacology and Complex Phytotherapeutic Systems.

Feature	Conventional Pharmacology	Phytotherapy (Complex Botanicals)
Active Ingredient	Single synthetic molecule	Multiple bioactive metabolites
Molecular Target	High specificity (Single target)	Low specificity (Multi-target)
Interaction Model	Linear (Additive)	Non-linear (Synergistic/Antagonistic)
Data Structure	Structured & predictable	High-dimensional & noisy
Research Approach	Reductionist	Holistic / Systems Biology
Discovery Barrier	Finding a new lead	Decoding complex interactions

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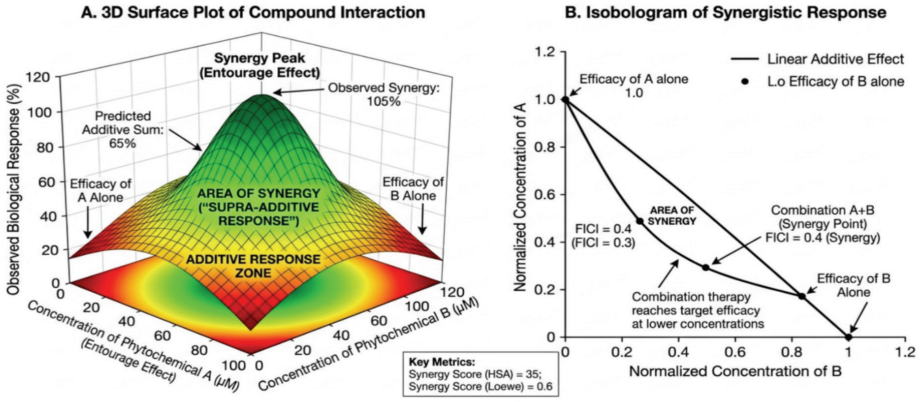


Figure 2. 3D synergy surface plot and isobologram demonstrating the supra-additive 'entourage effect' in complex plant extracts.

1.2.3. Computational Bottlenecks and the Combinatorial Explosion

The primary obstacle in elucidating the pharmacological mechanisms of plant extracts is the phenomenon known as "combinatorial explosion." In conventional drug discovery, testing a single agent is a linear process; however, evaluating a botanical extract with multiple constituents introduces an exponential increase in the number of experimental variables. For instance, mathematically, even a relatively simple extract consisting of only 20 discrete bioactive compounds presents 2^{20} - 1 possible combinations, which equates to over one million unique molecular interactions, excluding the additional complexity of varying concentration ratios (8).

Traditional pharmacodynamic models, which often rely on linear regression or basic dose-response curves, are inherently limited in their ability to account for these high-dimensional, non-linear relationships. This computational deficit creates a substantial knowledge gap regarding how phytochemicals collectively modulate biological systems. AI-driven network pharmacology and deep learning architectures are uniquely equipped to bridge this gap. By employing multivariate analysis and non-linear algorithms, AI can identify emergent properties within these complex mixtures that remain invisible to reductionist experimental designs. This transition from "observation-based" to "prediction-based" modeling is essential for the systematic deconvolution of phytotherapeutic synergy (8,9).

1.3. The Emergence of AI in Life Sciences

The landscape of biomedical research has undergone a seismic shift, evolving from a traditional, observation-based "trial-and-error" approach to a sophisticated "data-driven" paradigm. For decades, drug discovery was characterized by the serendipitous identification

of active molecules, followed by exhaustive in vitro and in vivo validation. This linear path was not only time-consuming and capital-intensive but also constrained by researchers' cognitive capacity to interpret multidimensional biological data (10).

The emergence of Artificial Intelligence (AI) and its subsets, such as Machine Learning (ML) and Deep Learning (DL), has fundamentally redefined this process. In the life sciences, the transition to data-driven discovery is powered by AI algorithms' ability to process "Big Data" ranging from genomic sequences and proteomic profiles to high-resolution imaging and electronic health records. Unlike traditional statistical methods, AI identifies complex, non-linear patterns within these vast datasets, enabling the prediction of molecular behaviors and biological outcomes with unprecedented accuracy. This computational evolution is particularly crucial for disciplines involving natural products, where the objective is no longer to find a "needle in a haystack" but to understand the "haystack" itself as a dynamic biological system (11).

1.4. Purpose of the Chapter

The primary objective of this chapter is to delineate the critical role of Artificial Intelligence as a bridge between the historical wisdom of ethnopharmacology and the modern imperatives of precision medicine. While ethnopharmacology provides a vast repository of traditional knowledge about the therapeutic potential of plants, it often lacks the molecular granularity required for contemporary clinical integration. Conversely, precision medicine seeks to tailor treatments to individual biological profiles, a goal that requires a deep understanding of the effects of multi-target drugs.

This chapter will evaluate how AI-driven tools such as virtual screening, network pharmacology, and predictive ADMET modeling can transform crude botanical data into standardized, evidence-based therapeutic interventions. By systematically deconstructing the "combinatorial explosion" of phytochemicals, AI enables a transition from a generalized herbal approach to a targeted, molecularly defined phytotherapy. Ultimately, we aim to demonstrate that integrating AI into phytotherapy research is not merely a technological upgrade but a foundational necessity to ensure that natural product discovery meets the rigorous standards of 21st-century healthcare (12).

2. AI-Driven Drug Discovery from Botanical Sources

2.1. Virtual Screening of Phytochemicals

The initial phase of drug discovery involves identifying "hits"—molecules that exhibit the desired biological activity against a specific target. Traditionally, this was achieved through High-Throughput Screening (HTS), a physical process involving automated robotic systems testing thousands of compounds in "wet-lab" assays. While effective, HTS is prohibitively expensive and time-consuming when applied to the vast chemical space of the plant kingdom (13).

In contrast, AI-powered *in silico* screening marks a computational revolution. Rather than physical testing, AI algorithms use molecular docking and quantitative structure-activity relationship (QSAR) models to simulate interactions between phytochemicals and target proteins. While traditional virtual screening relies on physics-based scoring functions that are computationally intensive, AI-driven approaches employ Machine Learning (ML) to "learn" from existing ligand-target data. This enables screening millions of phytochemicals in a fraction of the time, effectively prioritizing the most promising candidates for subsequent laboratory validation and significantly reducing the rate of experimental failure (13,14).

2.2. Predicting Bioactivity

Beyond simple target binding, the true challenge in phytotherapy is predicting the broad spectrum of biological responses elicited by complex extracts. Deep Learning (DL) architectures, such as Multi-layer Perceptrons and Convolutional Neural Networks (CNNs), excel at identifying patterns within high-dimensional biological data that characterize specific therapeutic properties (15).

DL models can be trained on chemical fingerprints to predict:

- **Antioxidant Activity:** By analyzing the electron-donating capacity and structural stability of polyphenolic compounds.
- **Anti-inflammatory Properties:** By simulating the inhibition of specific cytokine pathways (e.g., TNF-α, IL-6) or enzymatic activities (e.g., COX-2).
- **Anti-cancer Efficacy:** By predicting the cytotoxicity of compounds against specific tumor cell lines through the analysis of structure-based gene expression perturbations.

These DL models bypass the limitations of linear statistics, capturing the "hidden" features of phytochemicals that determine their multifaceted bioactivity, thus enabling a more targeted approach to herbal pharmacology (15).

2.3. De-orphaning Plant Metabolites

A significant number of plant metabolites are "orphans" compounds known to exist and perhaps even show clinical promise, but whose exact molecular targets remain unknown. De-orphaning is the process of identifying these missing links, which is essential for understanding the mechanism of action (MoA) and ensuring regulatory compliance. AI facilitates de-orphaning through Reverse Virtual Screening and Similarity-Based Profiling. Instead of screening many drugs against one target, AI screens a single orphan plant metabolite against an entire "proteome library" of thousands of human proteins. By identifying high-affinity "off-target" interactions, AI can uncover previously unknown therapeutic uses for established herbal medicines (drug repurposing) and clarify the molecular basis for traditional ethnobotanical claims (16).

3. Machine Learning in Ethnobotany and Taxonomy

3.1. Automated Plant Identification

The accurate taxonomic identification of medicinal plants is the cornerstone of phytotherapy. Traditionally, this required the expertise of trained botanists and the use of dichotomous keys, which can be subjective and prone to human error. Convolutional Neural Networks (CNNs), a specialized class of deep learning, have revolutionized this field by enabling high-precision image-based classification.CNNs automatically extract hierarchical features such as leaf venation, floral morphology, and stem texture from digital images. Beyond simple identification, this technology is critical for preventing adulteration. Adulteration with look-alike species is a significant safety concern in the herbal industry; AI models can now distinguish a therapeutic species from its toxic or inactive counterparts with accuracy that exceeds human capabilities. When integrated into mobile applications, CNNs enable researchers and quality control specialists to perform real-time botanical verification in the field or at the processing facility (17).

3.2. Mining Ethnobotanical Databases

Ethnopharmacology possesses an expansive, yet largely unstructured, repository of "pre-clinical" knowledge documented over millennia in diverse linguistic formats and historical manuscripts. The systematic conversion of this qualitative traditional knowledge into quantitative pharmacological data is now achievable through Natural Language Processing (NLP) (18).

NLP algorithms, specifically those using Named Entity Recognition (NER) and Latent Dirichlet Allocation (LDA), enable the automated extraction of therapeutic patterns from digitized historical archives. These computational linguistics tools can:

- **Deconvolve Archaic Nomenclature:** Standardize historical plant names to contemporary binomial nomenclature (e.g., International Plant Names Index standards).
- **Quantify Ethnobotanical Consensus:** Analyze the frequency of specific plant-indication pairs across disparate cultures to calculate "Informant Consensus Factors" (ICF), thereby prioritizing species for bioprospecting through a "reverse-pharmacology" pipeline.
- **Predict Novel Indications:** Identify latent correlations between traditional use narratives and modern physiological pathways using semantic embedding and sentiment analysis.

By synthesizing ethnographic heritage with modern computational frameworks, NLP transforms anecdotal evidence into structured datasets, facilitating the targeted discovery of novel bioactive leads (18).

4. Phytopharmacology and Network Pharmacology

4.1. The Synergy Problem

The hallmark of phytotherapy is the "entourage effect," in which the therapeutic outcome of a botanical extract exceeds the efficacy of its isolated constituents. Characterizing these

synergistic, additive, or antagonistic interactions poses a significant computational challenge because of the non-linear nature of biochemical networks. AI models, particularly those employing Ensemble Learning and Support Vector Machines (SVM), are now used to predict synergistic pairs by analyzing molecular descriptors and transcriptomic perturbations. These models help identify optimal concentration ratios that maximize therapeutic potency while minimizing dose-dependent toxicity, providing a mathematical basis for the holistic action of complex mixtures (7,19).

4.2. Pathway Analysis: Mapping Phytochemical-Protein-Disease Networks using Graph Neural Networks (GNNs)

The transition from reductionist pharmacology to systems medicine is facilitated by Graph Neural Networks (GNNs). Unlike traditional algorithms, GNNs are designed to process data structured as graphs, where phytochemicals, target proteins, and disease phenotypes are represented as nodes, and their interactions as edges. By modeling these complex topologies, GNNs can predict how a multi-component plant extract modulates entire signaling pathways rather than isolated receptors. This approach is essential for identifying the "nodes of vulnerability" in chronic diseases, allowing researchers to visualize the multi-target impact of secondary metabolites on cellular homeostasis (19,20).

4.3. ADMET Prediction: AI-Driven Pharmacokinetics of Herbal Extracts

The clinical translation of phytochemicals is often hindered by poor bioavailability or rapid metabolic clearance. AI-powered Predictive ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) modeling uses deep learning to forecast the pharmacokinetic profiles of plant compounds before entering in vivo trials. By integrating chemical structure data with physiological descriptors, these models predict intestinal permeability (e.g., Caco-2 models), blood-brain barrier (BBB) penetration, and cytochrome P450 inhibition. This computational pre-screening is vital for optimizing the delivery of phytotherapeutic agents and ensuring that their safety profiles meet regulatory standards (21).

5. Quality Control and Standardization

5.1. Metabolomics and Fingerprinting: AI in Analyzing HPLC, GC-MS, and NMR Data

Standardization remains the most critical barrier to the global acceptance of phytopharmaceuticals. Metabolomics-based fingerprinting, coupled with AI, addresses the inherent chemical variability of plant materials. Machine learning algorithms, such as Principal Component Analysis (PCA) and Partial Least Squares-Discriminant Analysis (PLS-DA), are used to analyze complex datasets generated by HPLC, GC-MS, and NMR. These AI tools can detect subtle variations in metabolite profiles, ensuring batch-to-batch consistency and identifying minute contaminants or biomarkers that define the extract's potency (22).

5.2. Prediction of Cultivation Variables for Maximal Secondary Metabolite Yield

The concentration of bioactive metabolites is highly sensitive to environmental stressors. AI models that use Reinforcement Learning and Bayesian Optimization are increasingly applied in precision agriculture to predict how "abiotic factors" such as light spectrum, soil composition, and hydration levels affect phytochemical biosynthesis. By optimizing these cultivation variables, AI enables the sustainable production of high-quality raw materials with standardized therapeutic yields (23). This proactive approach ensures that the "chemical blueprint" of the medicinal plant is optimized at the source, significantly reducing the downstream burden of post-harvest standardization.

6. Case Studies: AI in Specific Therapeutic Areas

6.1. Neuroprotective Agents: Discovery for Alzheimer's and Parkinson's

AI has accelerated the discovery of neuroprotective leads by screening botanical libraries against complex targets such as acetylcholinesterase (AChE) and pathways involved in amyloid-beta (Aβ) aggregation. Deep learning models have successfully identified polyphenolic scaffolds with multi-target activity in neurodegenerative models, effectively bridging ethnopharmacological tradition and modern neuropharmacology. Recent computational frameworks have enabled the identification of dual-target compounds from traditional medicinal plants, such as those used in Ayurvedic medicine, providing a more holistic approach to Alzheimer's therapy. By targeting both enzymatic activity and protein aggregation strategies, AI-driven platforms bypass the "one-drug-one-target" limitation, offering a sophisticated paradigm for multi-factorial neurodegenerative diseases (24, 25, 26).

6.2. Metabolic Disorders: Identifying Anti-Diabetic Phytochemicals

In the context of metabolic syndrome, AI-driven network analysis has been instrumental in identifying phytochemicals that simultaneously modulate insulin signaling, GLUT4-mediated glucose transport, and PPAR-g activation. These studies highlight AI's capacity to validate complex herbal formulations used in traditional diabetes management (27, 28).

By integrating deep learning with transcriptomic data, these platforms can simulate the systemic effects of multi-component extracts on metabolic homeostasis, providing a robust, evidence-based framework for the clinical integration of anti-diabetic botanical products.

7. Challenges and Future Directions

7.1. Data Quality and the "Small Data" Problem

Despite the "Big Data" era, specialized phytotherapy research often faces the "Small Data" problem, namely the scarcity of high-quality, labeled datasets for specific plant-disease interactions. Transfer Learning and Generative Adversarial Networks (GANs) are emerg-

ing as vital strategies for augmenting data and enhancing model robustness in data-scarce environments (29).

7.2. Interpretability (XAI): The "Black Box" Barrier

For AI to be integrated into clinical phytotherapy, models must move beyond the "black box" paradigm. Explainable AI (XAI) techniques are essential to provide clinicians with the biological rationale behind AI-generated predictions, ensuring that computational insights are transparent, trustworthy, and clinically actionable (30).

By employing XAI, such as attention maps or feature importance rankings, clinicians can visualize which specific phytochemical interactions or metabolic pathways led to a particular therapeutic recommendation. This transparency is crucial for high-stakes clinical decision-making, where understanding the "why" behind a prediction is as important as the prediction itself, particularly when integrating multimodal data from genomics, metabolomics, and traditional clinical records.

7.3. Ethical, Legal, and Regulatory Considerations

The use of AI in natural product discovery raises complex questions regarding the Intellectual Property (IP) of traditional knowledge. Protecting the rights of indigenous communities while navigating the patentability of AI-derived phytochemical leads remains a significant regulatory challenge (31).

8. Conclusion

The systematic integration of Artificial Intelligence (AI) into phytotherapy research marks a paradigm shift that requires a rigorous synthesis of Medical Biology and Medical Pharmacology. The historical challenge of translating complex botanical extracts into evidence-based therapeutic interventions is no longer a matter of empirical observation but a multidimensional computational problem that AI is uniquely equipped to solve.

From a mechanistic perspective, the synergy between these two disciplines enables a holistic deconvolution of plant-derived compounds. Medical Biology provides the foundational understanding of the cellular landscape using AI-driven omics data and molecular modeling to map the intricate perturbations in gene expression and protein-protein interaction networks induced by phytochemicals. Simultaneously, Medical Pharmacology uses these biological insights to refine the "multi-component, multi-target" paradigm. AI-powered predictive models for synergistic interactions and non-linear pharmacokinetic profiles (ADMET) ensure that the latent pharmacological potential of secondary metabolites is translated into standardized, clinically viable protocols.

Ultimately, the computational framework offered by AI serves as the bridge between these two domains, ensuring that the study of natural products meets the rigorous requirements of contemporary systems medicine. The ability of machine learning to de-

code the "entourage effect" and identify emergent biological properties within complex mixtures facilitates a transition from traditional ethnopharmacology to targeted precision medicine. As this interdisciplinary collaboration matures, the fusion of advanced biological insights with robust pharmacological validation will be the cornerstone for developing the next generation of safe, effective, and molecularly defined phytotherapeutic agents.

9. References

1. Atanasov, A. G., Zotchev, S. B., Dirsch, V. M., et al. (2021). Natural products in drug discovery: advances and opportunities. *Nature Reviews Drug Discovery*, *20*, 200–216. https://doi.org/10.1038/s41573-020-00114-z
2. Wagner, H., & Ulrich-Merzenich, G. (2009). Synergy research: approaching a new generation of phytopharmaceuticals. *Phytomedicine*, *16*(2-3), 97-110. https://doi.org/10.1016/j.phymed.2008.12.018
3. Srisittiratkul, P., Limsuvan, S., Pattanapholkornsakul, S., & Akarasereenont, P. (2025). Optimizing herbal drug use through multivariable standardization and precision approaches. *Phytomedicine Plus*, *5*(4), Article 100907. https://doi.org/10.1016/j.phyplu.2025.100907
4. Kumar, A., Tiwari, A., & Sharma, A. (2018). Changing paradigm from one target one ligand towards multi-target directed ligand design for key drug targets of Alzheimer disease: An important role of in silico methods in multi-target directed ligands design. *Current Neuropharmacology*, *16*(6), 726–739. https://doi.org/10.2174/1570159X16666180315141643
5. Gonçalves, A. C., Pinto, A. R., Cima, A., Olo-Fontinha, E., Martins, J. C. L., Garcia, J., Lemos, A., Saavedra, M. J., Pintado, M. M., & Alves, M. J. (2026). Plant-derived bioactive compounds: One health perspective. *Applied Sciences*, *16*(1), 327. https://doi.org/10.3390/app16010327
6. André, R., Gomes, A. P., Pereira-Leite, C., Marques-da-Costa, A., Monteiro Rodrigues, L., Sassano, M., Rijo, P., & Costa, M. D. C. (2024). The entourage effect in cannabis medicinal products: A comprehensive review. *Pharmaceuticals*, *17*(11), 1543. https://doi.org/10.3390/ph17111543
7. Wagner, H. (2011). Synergy research: Approaching a new generation of phytopharmaceuticals. *Fitoterapia*, *82*(1), 34–37. https://doi.org/10.1016/j.fitote.2010.11.016
8. Panossian, A. (2023). Challenges in phytotherapy research. *Frontiers in Pharmacology*, *14*, 1199516. https://doi.org/10.3389/fphar.2023.1199516
9. Yang, L., Wang, H., Zhu, Z., Yang, Y., Xiong, Y., Cui, X., & Liu, Y. (2025). Network pharmacology-driven sustainability: AI and multi-omics synergy for drug discovery in traditional Chinese medicine. *Pharmaceuticals*, *18*(7), 1074. https://doi.org/10.3390/ph18071074
10. Wang, X. Y., Chen, Y., Li, Y. F., Wei, C. Y., Liu, M. Y., Yuan, C. X., ... & Li, X. T. (2025). Advancing active compound discovery for novel drug targets: insights from AI-driven approaches. *Acta Pharmacologica Sinica*, *46*(11), 2865–2876. https://doi.org/10.1038/s41401-025-01591-x
11. Paul, I. (2026). Artificial Intelligence (AI) and Machine Learning (ML) in Personalized Medicine. In M. K. Ghosh & M. Basu (Eds.), *Personalized Cancer Therapy*. Springer, Singapore. https://doi.org/10.1007/978-981-95-6845-1_23
12. Tan, E. W., Low, L. H., Atanasov, A. G., & Goh, B. H. (2025). Bridging traditions and technology: The role of ethnopharmacology in shaping next-generation multidisciplinary researchers. *Pharmacological Research & Perspectives*, *13*(1), e70074. https://doi.org/10.1002/prp2.70074
13. Kansagra, J. J., Raval, K. Y., & Ganatra, T. H. (2022). A brief review of high-throughput screening in the drug discovery process. *Current Trends in Pharmaceutical and Pharmaceutical Chemistry*, *4*(3), 120–122. https://doi.org/10.18231/j.ctppc.2022.020
14. Koirala, M., Yan, L., Mohamed, Z., & DiPaola, M. (2025). AI-integrated QSAR modeling for enhanced drug discovery: From classical approaches to deep learning and structural insight. *International Journal of Molecular Sciences*, *26*(19), 9384. https://doi.org/10.3390/ijms26199384
15. Wijaya, S. H., Nasution, A. K., Batubara, I., Gao, P., Huang, M., Ono, N., Kanaya, S., & Altaf-Ul-Amin, M. (2023). Deep learning approach for predicting the therapeutic usages of Unani formulas towards finding essential compounds. *Life*, *13*(2), 439. https://doi.org/10.3390/life13020439
16. Prosser, G. A., Larrouy-Maumus, G., & de Carvalho, L. P. S. (2014). Metabolomic strategies for the identification of new enzyme functions and metabolic pathways. *EMBO Reports*, *15*(7), 657–669. https://doi.org/10.15252/embr.201338283
17. Mulugeta, A. K., Sharma, D. P., & Mesfin, A. H. (2024). Deep learning for medicinal plant species classification and recognition: a systematic review. *Frontiers in Plant Science*, *14*, 1286088. https://doi.org/10.3389/fpls.2023.1286088
18. Chele, K. H., Piater, L. A., van der Hooft, J. J. J., & Tugizimana, F. (2025). Bridging ethnobotanical knowledge and multi-omics approaches for plant-derived natural product discovery. *Metabolites*, *15* (6), 362. https://doi.org/10.3390/metabo15060362

19. Menezes, I. O., Scherf, J. R., Martins, A., Ramos, A. G. B., Quintans, J. S. S., Coutinho, H. D. M., Ribeiro-Filho, J., & de Menezes, I. R. A. (2020). Biological properties of terpinolene evidenced by *in silico*, *in vitro* and *in vivo* studies: A systematic review. *Phytomedicine*, *71*, 153230. https://doi.org/10.1016/j.phymed.2020.153230
20. Zhang, X. M., Liang, L., Liu, L., & Tang, M. J. (2021). Graph neural networks and their current applications in bioinformatics. *Frontiers in Genetics*, *12*, 690049. https://doi.org/10.3389/fgene.2021.690049
21. Pathan, I., Raza, A., Sahu, A., Joshi, M., Sahu, Y., Patil, Y., et al. (2025). Revolutionizing pharmacology: AI-powered approaches in molecular modeling and ADMET prediction. *Medical Drug Discovery*, *28*, 100223. https://doi.org/10.1016/j.mdd.2025.100223
22. Alum, E. U., et al. (2025). Metabolomics-driven standardization of herbal medicine: Advances, applications, and sustainability considerations. *Natural Product Communications*, *20*(8), 1–16. https://doi.org/10.1177/1934578X251367650
23. Ghanghas, S., Kumar, N., Kumar, S., & Singh, V. K. (2025). Advancement in measurement and AI-driven predictions of maturity indices in kinnow (*Citrus nobilis* x *Citrus deliciosa*): A comprehensive review. *Food Physics*, *2*, 100026. https://doi.org/10.1016/j.foodp.2024.100026
24. Fontanella, F., et al. (2026). Artificial Intelligence for natural products drug discovery in neurodegenerative therapies: A review. *Biomolecules*, *16*(1), 129. https://doi.org/10.3390/biom16010129
25. Grabowska, W., et al. (2025). Acetylcholinesterase as a multifunctional target in amyloid-driven neurodegeneration: From dual-site inhibitors to anti-aggregation strategies. *International Journal of Molecular Sciences*, *26*(17), 8726. https://doi.org/10.3390/ijms26178726
26. Shah, M., et al. (2025). Computer-aided discovery of dual-target compounds for Alzheimer's from ayurvedic medicinal plants. *PLOS ONE*, *20*(6), e0325441. https://doi.org/10.1371/journal.pone.0325441
27. Rosenzweig, T., & Sampson, S. R. (2021). Activation of insulin signaling by botanical products. *International Journal of Molecular Sciences*, *22*(8), 4193. https://doi.org/10.3390/ijms22084193
28. Martín, M. Á., & Ramos, S. (2024). Effects of phytochemicals on metabolic diseases and human health. *Nutrients*, *16*(24), 4323. https://doi.org/10.3390/nu16244323
29. Gangwal, A., Ansari, A., Ahmad, I., Azad, A. K., Kumarasamy, V., Subramaniyan, V., & Wong, L. S. (2024). Generative artificial intelligence in drug discovery: Basic framework, recent advances, challenges, and opportunities. *Frontiers in Pharmacology*, *15*, 1331062. https://doi.org/10.3389/fphar.2024.1331062
30. Lipkova, J., Chen, R. J., Chen, B., Lu, M. Y., Barbieri, M., Shao, D., ... & Mahmood, F. (2022). Artificial intelligence for multimodal data integration in oncology. *Cancer Cell*, *40*(10), 1095–1110. https://doi.org/10.1016/j.ccell.2022.09.012
31. Paerhati, Y., Aikebaier, A., Dilimulati, D., Baishan, A., Yusufujiang, N., Qiu, X., Wusiman, Y., & Zhou, W. (2026). Rethinking nature's pharmacy: AI era and natural product drug discovery. *Pharmaceuticals*, *19*(2), 301. https://doi.org/10.3390/ph19020301

CHAPTER 17

Distinguishing Asymptomatic Bacteriuria from True Urinary Tract Infection in Children: An AI-Based Risk Stratification Approach

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1. Introduction

Urinary tract infections (UTIs) are among the most prevalent bacterial infections in childhood and are a common cause of febrile illness, healthcare use, and antibiotic prescriptions in pediatric populations. Pediatric UTIs cause a substantial clinical burden, especially in infants and young children. In these groups, infections often present with nonspecific symptoms and may lead to complications such as renal scarring or recurrent infections if not promptly managed (1). Distinguishing between true *urinary tract infection (UTI)* and *asymptomatic bacteriuria (ASB)* is a significant clinical challenge. True UTI means bacteria in the urinary tract cause symptoms and an inflammatory response. In contrast, ASB occurs when bacteria are present in the urine, but there are no urinary symptoms or evidence of inflammation. Inadequate differentiation may delay treatment of significant infections or result in unnecessary antibiotic exposure in children who have bacterial colonization rather than true infection (2).

Overdiagnosis and overtreatment of bacteriuria are significant concerns in pediatric infectious disease. Studies show inappropriate antibiotic therapy for asymptomatic bacteriuria offers little clinical benefit but increases antimicrobial resistance and avoidable adverse events. Thus, current guidelines stress careful interpretation of laboratory findings when assessing possible UTI in children (3). Suspected UTI in pediatric patients is evaluated through clinical assessment, urinalysis, and urine culture. Each diagnostic step has its own limitations. Clinical symptoms vary by age; infants and young children may present with nonspecific signs such as fever, irritability, or poor feeding that are not specific to urinary infection (4).

Urinalysis is frequently used as a rapid screening tool to detect markers such as leukocyte esterase, nitrites, or pyuria. These findings can support suspicion of infection but do

not provide definitive diagnostic accuracy, as they may also appear in conditions unrelated to bacterial UTI. Thus, interpret urinalysis with caution and consider it alongside clinical presentation and microbiological findings (5). Urine culture is the reference standard for confirming UTI. It identifies the causative organism and quantifies bacterial growth. However, interpretation depends on the urine collection method and the bacterial count threshold set for diagnosis. Contamination during collection, especially in non–toilet-trained children, further complicates interpretation and increases diagnostic uncertainty (6). Despite these challenges, the clinical consequences of UTI in children highlight the need for precise diagnosis. UTIs can cause acute morbidity and, in some cases, long-term complications such as renal scarring, especially if the upper urinary tract is affected or infections recur (7). Conversely, unnecessary antibiotic therapy for ASB may expose children to adverse drug effects and worsen antimicrobial resistance (8).

Given these diagnostic challenges, clinicians must integrate multiple clinical and laboratory variables when evaluating children with suspected urinary infection. Traditional diagnostic frameworks, however, often rely on isolated parameters. This reliance limits the integration of patient-specific data. As a result, interest has grown in computational and data-driven approaches that synthesize complex clinical information to aid diagnostic decisions (9). Artificial intelligence (AI) and machine learning techniques are now frequently investigated as tools to support clinicians. These approaches analyze multiple clinical variables at once and generate probabilistic disease risk estimates from large clinical datasets. Recent advances in AI-based decision support systems have shown promising results across several areas of clinical medicine, especially in infectious disease diagnostics (10). In pediatric UTI, these AI-based models can increasingly integrate clinical symptoms, urinalysis parameters, microbiological data, and patient details into risk prediction frameworks. This integration helps clinicians better distinguish ASB from true infection, thereby improving diagnostic accuracy (11).

The development of AI-based risk-stratification strategies promises to enhance diagnostic accuracy and support antimicrobial stewardship. These models use multidimensional clinical and laboratory data to help clinicians distinguish colonization from clinically significant infection. This approach may reduce unnecessary antibiotic use while maintaining patient safety (12). Figure 1 illustrates a conceptual framework for how AI-based risk stratification can help clinicians distinguish asymptomatic bacteriuria from true urinary tract infection.

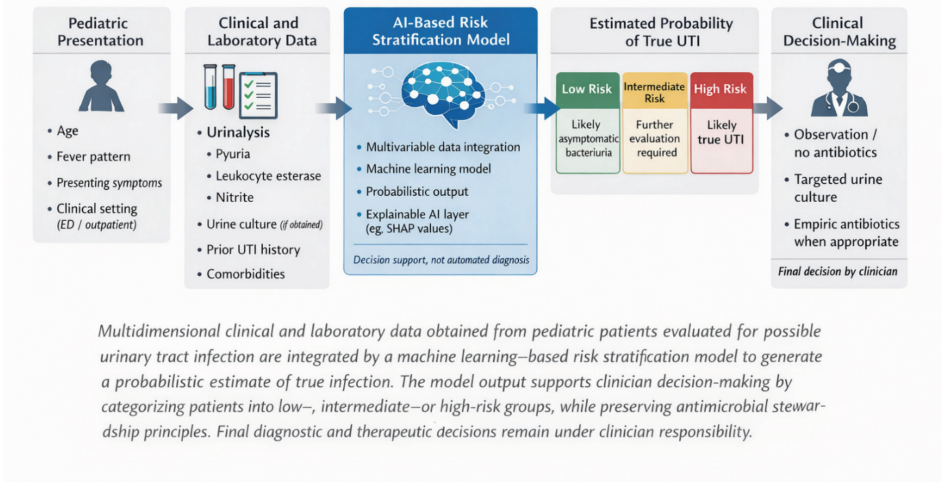


Figure 1. AI-Based Risk Stratification for Distinguishing Asymptomatic Bacteriuria from True Urinary Tract Infection in Children

2. Clinical Definitions and Diagnostic Challenges

Accurate differentiation between ASB and true UTI is essential for the appropriate management of pediatric patients presenting with bacteriuria. In children, the detection of bacteria in urine may represent either colonization without an inflammatory response or an active urinary tract infection requiring treatment. Misclassification between these two conditions may lead to delayed treatment of clinically significant infection or unnecessary antibiotic exposure in children who merely harbor bacterial colonization (13).

2.1. Definition of Asymptomatic Bacteriuria

Asymptomatic bacteriuria is defined as the presence of significant bacterial growth in urine in the absence of clinical signs or symptoms attributable to UTI. The diagnosis is primarily microbiological and relies on urine culture findings obtained from appropriately collected specimens. Importantly, the defining characteristic of ASB is the absence of urinary symptoms or systemic manifestations of infection despite bacteriuria (13).

In pediatric populations, ASB is often found incidentally during tests for unrelated conditions. In the past, finding bacteriuria on urine culture often led to antibiotics. However, evidence shows that treating asymptomatic bacteriuria rarely helps and may increase antibiotic resistance and exposure. For this reason, guidelines now advise against treating ASB routinely in most pediatric patients (13,14).

2.2. Definition of True Urinary Tract Infection

In contrast, a true urinary tract infection represents bacterial invasion of the urinary tract accompanied by an inflammatory response. UTIs may involve different anatomical struc-

tures of the urinary tract, including the bladder and kidneys, and their clinical presentation varies depending on the site of infection and the patient's age. The diagnosis of UTI in children generally requires the combination of clinical symptoms, laboratory evidence of inflammation, and microbiological confirmation (15).

Typical clinical manifestations may include fever, dysuria, urinary frequency, abdominal pain, or flank pain. In infants and young children, however, symptoms are frequently nonspecific and may include irritability, vomiting, or poor feeding. These age-related differences in clinical presentation complicate the diagnostic evaluation and often necessitate reliance on laboratory testing to support clinical suspicion (16).

Laboratory evaluation usually includes urinalysis and urine culture. The presence of pyuria or positive leukocyte esterase on urinalysis may suggest urinary tract inflammation, while urine culture allows identification of the causative pathogen and quantification of bacterial growth. Diagnostic guidelines generally require both pyuria and significant bacterial growth on urine culture for confirmation of UTI in children (15,16).

2.3. Age-Related Diagnostic Challenges

The clinical diagnosis of UTI in pediatric patients is complicated by several factors related to age. Infants and young children frequently present with nonspecific symptoms such as fever without a clear source, making clinical differentiation from other infections difficult. In such cases, clinicians often rely on urine testing to evaluate the possibility of UTI (17).

Another major challenge involves obtaining reliable urine specimens. In non–toilet-trained children, urine collection methods such as bag specimens may result in higher contamination rates. Contaminated urine samples can complicate the interpretation of culture results and may lead to false-positive diagnoses of urinary infection. For this reason, guidelines recommend careful interpretation of culture results and emphasize the importance of appropriate specimen collection methods (17).

2.4. Limitations of Conventional Diagnostic Criteria

Despite established diagnostic criteria, differentiating ASB from true UTI remains challenging in clinical practice. The presence of bacteriuria alone does not necessarily indicate infection, as colonization of the urinary tract may occur without an inflammatory response. Conversely, pyuria may occasionally occur in conditions other than bacterial infection, including viral illnesses or noninfectious inflammatory processes (18).

These diagnostic uncertainties highlight the limitations of conventional diagnostic approaches that rely on individual laboratory parameters or isolated clinical findings. As summarized in Figure 2, several clinical and microbiological features may help distinguish asymptomatic bacteriuria from true urinary tract infection; however, substantial overlap persists in real-world clinical settings. Taken together, these diagnostic ambiguities highlight the need for more integrative approaches that can simultaneously evaluate multiple clinical variables. A conceptual framework illustrating how AI–based risk stratification may assist clinicians in this process is illustrated in Figure 1.

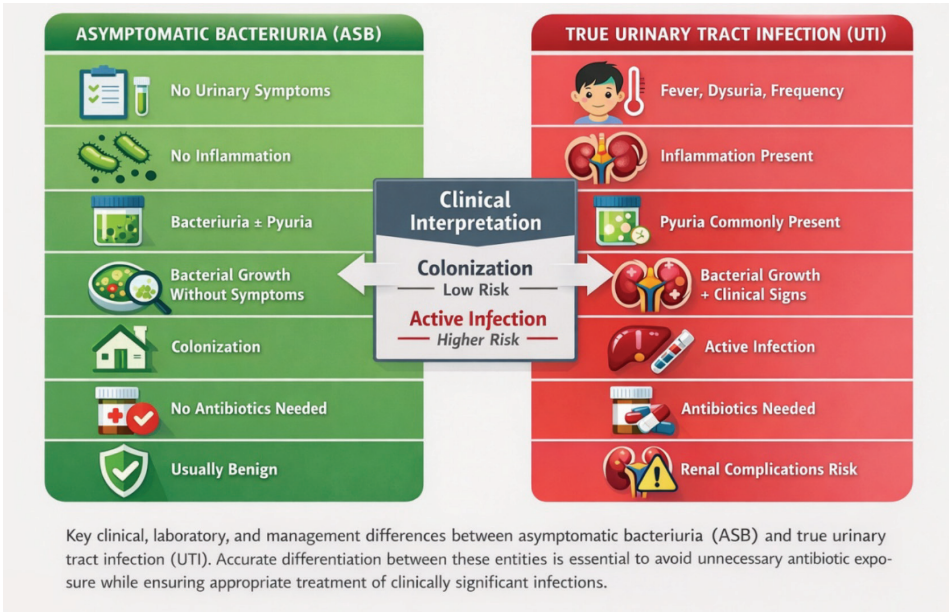


Figure 2. Visual Comparison of Asymptomatic Bacteriuria (ASB) and True Urinary Tract Infection (UTI) in Children

3. Current Diagnostic Approaches and Their Limitations

The diagnostic evaluation of suspected UTI in children relies on clinical assessment, urinalysis, urine culture, and, when indicated, imaging studies. These are the main tools for diagnosing pediatric UTIs. Yet each has limitations that make it hard to distinguish ASB from a true UTI. Symptoms vary, and tests are not always accurate. This can result in both overdiagnosis and missed infections in children (19).

3.1. Clinical Assessment

Clinical evaluation represents the first step in the diagnostic assessment of children with suspected UTI. Classic symptoms such as dysuria, urinary frequency, abdominal pain, and flank pain may suggest infection in older children. However, the clinical presentation of UTI in infants and young children is often nonspecific. Symptoms such as fever, irritability, vomiting, or poor feeding may occur in a wide variety of pediatric illnesses and are not specific to UTI (19).

Because of this nonspecific presentation, clinicians often rely on laboratory testing when evaluating febrile children without an obvious source of infection. However, no single clinical sign or symptom reliably confirms or excludes the diagnosis. This underscores the major limitation of clinical assessment: its lack of diagnostic reliability (20).

3.2. Urinalysis

Urinalysis serves as a rapid screening tool for children with suspected UTI. Dipstick testing typically assesses leukocyte esterase and nitrite, while microscopic analysis evaluates white blood cells and bacteria in urine. Pyuria or a positive leukocyte esterase result increases the likelihood of UTI. In contrast, a positive nitrite test is highly specific but less sensitive, as not all pathogens produce nitrite (21).

Despite its clinical usefulness, urinalysis has significant diagnostic limitations. False-negative results may occur when bacteria do not have sufficient time to convert nitrate to nitrite, or when infections are caused by organisms that do not produce nitrite. Conversely, pyuria may be observed in noninfectious inflammatory conditions, thereby reducing the specificity of urinalysis for diagnosing UTI (22).

3.3. Urine Culture

Urine culture remains the reference standard for confirming UTI in children because it allows identification of the causative pathogen and quantification of bacterial growth. Current clinical guidelines generally define UTI as the presence of pyuria combined with significant bacterial growth in urine culture obtained from an appropriately collected specimen (23).

However, urine culture also has several limitations. Results typically require 24 to 48 hours, which may delay definitive diagnosis and treatment decisions. Furthermore, contamination during specimen collection remains a common problem, particularly in non–toilet-trained children. Collection methods such as bag urine samples are associated with higher contamination rates, which may complicate the interpretation of culture results and lead to false-positive diagnoses (21).

3.4. Imaging Studies

Imaging studies may be performed in selected pediatric patients with UTI to evaluate underlying anatomical abnormalities or complications. Renal and bladder ultrasonography is commonly used to identify structural abnormalities, while voiding cystourethrography may be considered in cases of recurrent infection or suspected vesicoureteral reflux (23).

Although imaging studies are important for identifying anatomical risk factors for recurrent infections or renal damage, they do not directly distinguish ASB from true infection. Consequently, imaging is generally used as a complementary diagnostic tool rather than a primary method for confirming UTI (23).

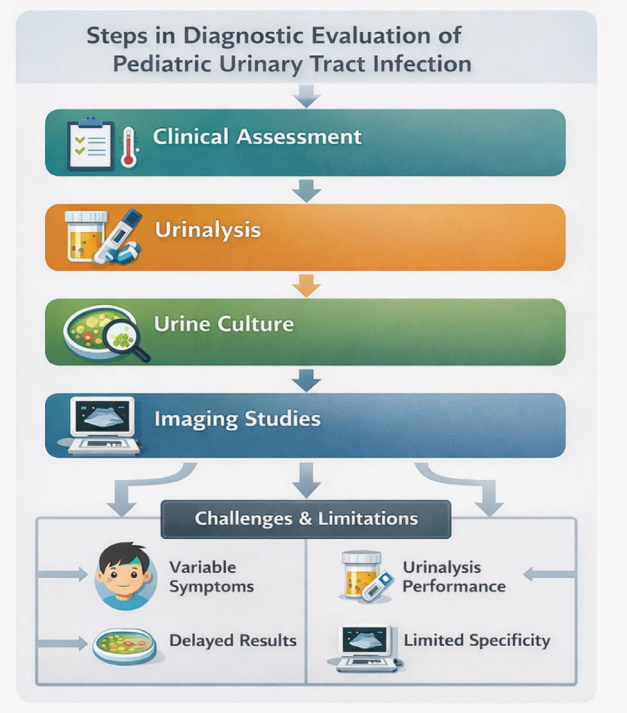
3.5. Limitations of Conventional Diagnostic Strategies

Despite the widespread use of these diagnostic methods, considerable uncertainty remains when differentiating ASB from true UTI. Clinical symptoms may be nonspecific, urinalysis lacks perfect sensitivity and specificity, and urine culture results may be influenced by contamination or collection technique. Furthermore, delays in obtaining culture results

may complicate early clinical decision-making (19). The clinical importance of accurate diagnosis is underscored by evidence demonstrating that untreated UTI may occasionally lead to complications such as renal scarring, particularly in young children with febrile infections (22). At the same time, unnecessary antibiotic treatment for asymptomatic bacteriuria contributes to antimicrobial resistance and avoidable medication exposure.

As illustrated in Figure 3, the conventional diagnostic pathway for pediatric UTI involves sequential evaluation using clinical assessment, urinalysis, urine culture, and imaging when indicated. While this approach provides valuable information, it often requires clinicians to interpret multiple imperfect diagnostic parameters simultaneously.

These limitations highlight the need for more integrative diagnostic frameworks that can synthesize diverse clinical and laboratory variables into unified risk assessments. Such limitations provide a strong rationale for exploring data-driven approaches, including AI–based risk-stratification models, which may help clinicians more accurately distinguish ASB from true UTI.



Sequential steps in the diagnostic evaluation of suspected urinary tract infection in children and the corresponding challenges or limitations of each diagnostic component. Accurate diagnosis requires an integrative approach considering the limitations of clinical symptoms, laboratory assessments and imaging findings.

Figure 3. Diagnostic Pathway for Evaluating Urinary Tract Infections in Children

4. Rationale for AI-Based Risk Stratification

The difficulty of distinguishing ASB from true UTI underscores the limitations of conventional decision-making. Clinicians must consider numerous clinical and laboratory factors when diagnosing pediatric UTI, including symptoms, urinalysis, urine culture results, age, and context. Integrating this data is particularly demanding in urgent settings (25). Building on this challenge, traditional diagnostic approaches often depend on rule-based criteria or single-lab thresholds. While helpful, these may overlook complex interactions among clinical variables. In the face of modern medicine's extensive patient data, analyzing such information with conventional methods can overwhelm clinicians (26).

Given these difficulties, machine learning and AI have emerged as promising tools for supporting clinical decision-making. Specifically, AI algorithms can identify patterns in large clinical datasets and integrate multiple variables simultaneously to generate probabilistic predictions. Rather than relying on single diagnostic markers, AI-based models synthesize complex combinations of clinical features to estimate the likelihood of a particular condition (26). This promise is reflected in the rapid expansion of machine learning techniques in healthcare. AI-driven clinical decision support systems have demonstrated potential in disease prediction, diagnostic classification, and risk stratification. By identifying patterns that are difficult to recognize through conventional clinical reasoning, these models may assist clinicians, particularly in high-diagnostic-uncertainty scenarios (27).

Against this background, UTI represents a clinical condition that may particularly benefit from such approaches. The diagnosis of pediatric UTI often requires integration of multiple imperfect diagnostic indicators, including clinical presentation, urinalysis findings, and microbiological data. Several recent studies have suggested that machine learning models may improve diagnostic accuracy by simultaneously analyzing these diverse data elements and generating individualized risk estimates for infection (28). In addition to integrating diverse data, another important advantage of AI-based risk prediction models is their ability to provide probabilistic outputs rather than binary diagnostic classifications. Instead of categorizing patients strictly as "infected" or "not infected," these models estimate the probability that a patient has a true infection based on available clinical data. Such probabilistic risk estimates may better support clinical decision-making by allowing physicians to incorporate algorithmic predictions into broader clinical judgment (29).

Despite their potential benefits, integrating artificial intelligence into clinical practice also requires careful consideration. Clinicians must understand how predictive models generate their outputs and must be able to interpret these results within the clinical context of individual patients. This requirement has led to increasing interest in explainable artificial intelligence, which aims to make complex predictive models more transparent and interpretable for clinical users (30). Explainability is particularly important in healthcare applications, where clinicians must justify diagnostic and therapeutic decisions. Methods such as feature attribution techniques allow researchers to identify which variables contribute most strongly to a model's prediction. These approaches help clinicians understand how algorithmic predictions are generated and ensure that AI systems function as decision-support tools rather than autonomous diagnostic systems (30).

Taken together, these arguments provide a strong rationale for exploring AI-based risk-stratification approaches in pediatric UTIs. By integrating multidimensional clinical and laboratory data, machine learning models can help clinicians more accurately differentiate ASB from true infection, while supporting antimicrobial stewardship and reducing unnecessary antibiotic exposure. The following section, therefore examines existing AI models developed to differentiate ASB from true UTI, as well as the methodological considerations relevant to their development and clinical implementation.

5. AI Models in Differentiating Asymptomatic Bacteriuria and True Urinary Tract Infection

Recent advances in machine learning—a form of artificial intelligence that enables computers to learn from data—have led to the development of predictive models. These models can assist clinicians in complex diagnostic scenarios. In healthcare, they analyze large volumes of structured clinical data to uncover patterns that are not readily apparent through traditional reasoning. Such approaches are increasingly explored for diagnostic support in infectious diseases, including urinary tract infection (31). Machine learning algorithms are well-suited to problems that require integrating many different variables. In pediatric UTIs, diagnostic decision-making often involves interpreting multiple clinical parameters at once. These include patient age, fever characteristics, urinalysis findings, microbiological results, and additional clinical risk factors. Predictive models combine these variables and generate probabilistic infection risk estimates. In this way, they assist clinicians in distinguishing ASB from true infection (32). Examples of clinical and laboratory variables commonly incorporated into machine learning models for predicting urinary tract infection are summarized in *Table 1*.

Table 1. Key clinical and laboratory variables incorporated into AI-based risk prediction models for differentiating asymptomatic bacteriuria from true urinary tract infection in children

Feature Category	Example Variables	Clinical Interpretation	Role in AI Prediction Models
Demographic variables	Age, sex	Younger children often present with nonspecific symptoms	Provide baseline risk stratification
Clinical symptoms	Fever, dysuria, urinary frequency, flank pain	Indicate presence of urinary or systemic symptoms	Increase probability of true UTI
Vital signs	Body temperature, heart rate	Reflect systemic inflammatory response	Contribute to infection probability estimation
Urinalysis parameters	Leukocyte esterase, nitrite, pyuria	Indicators of urinary tract inflammation	Strong predictive features in most models
Microbiological indicators	Urine culture growth, colony count	Confirm presence and magnitude of bacteriuria	Distinguish colonization from infection
Clinical history	Previous UTI, urinary tract anomalies	Identify structural or recurrent risk factors	Modify individualized risk estimates

Several machine learning techniques have been investigated for clinical prediction tasks. These include logistic regression, random forests, gradient boosting, and neural networks. Logistic regression is a statistical method for predicting outcomes. Random forests use multiple decision trees. Gradient boosting improves predictors step-wise. Neural networks are inspired by the human brain. These algorithms analyze complex relationships in clinical datasets and can identify nonlinear interactions. Their use can improve the accuracy of risk prediction compared with traditional rule-based decision systems (33). In addition, the increasing availability of electronic health record (EHR) data—digital versions of patients' medical histories—has further facilitated the development of such predictive models. Large clinical datasets offer opportunities to train machine learning algorithms on real-world patient data, enabling the development of models capable of estimating disease probability based on multiple patient-specific characteristics. These data-driven approaches may improve diagnostic precision by capturing complex patterns that are difficult to identify through conventional clinical analysis (34).

Recent studies have explored the application of machine learning models to predict bacteriuria and UTI using routinely collected clinical variables. These models often incorporate parameters such as age, temperature, urinalysis findings, previous medical history, and laboratory results to estimate the probability of infection. Early results suggest that such approaches may improve diagnostic discrimination compared with traditional decision rules alone (31). Despite their predictive potential, machine learning models must remain interpretable to ensure safe clinical use. Clinicians must understand the factors that contribute to algorithmic predictions to evaluate their clinical relevance and reliability. This requirement has led to increasing interest in explainable artificial intelligence, which aims to make complex predictive models more transparent and interpretable (35).

One widely used approach for model interpretability is the *SHapley Additive exPlanations (SHAP)* framework. SHAP values quantify the contribution of each variable to a model's prediction by decomposing the model's output into additive contributions from each feature. In clinical applications, this approach allows physicians to understand how variables such as fever, pyuria, age, or laboratory findings influence the predicted probability of infection for an individual patient (35). By providing feature-level explanations for individual predictions, SHAP analysis helps bridge the gap between complex machine learning models and clinical interpretability. Instead of presenting clinicians with a simple probability score, explainable AI methods can identify the specific factors driving each prediction. This transparency is particularly important in healthcare settings where clinicians must justify diagnostic and therapeutic decisions (36).

An example illustrating how individual clinical variables may contribute to model predictions can be conceptualized using SHAP-based feature attribution methods. Such explainable frameworks enable clinicians to interpret algorithmic predictions more effectively and to evaluate whether model outputs align with established clinical knowledge. Taken together, these developments suggest that machine learning models, when combined with explainable AI techniques, may provide valuable support for differentiating ASB from true UTI. By integrating multiple clinical variables into probabilistic risk pre-

diction models, AI-based approaches can improve diagnostic accuracy while maintaining transparency and supporting clinician decision-making.

6. Clinical Integration: From Algorithm to Bedside

Developing machine learning models to distinguish ASB from UTI is only the first step. For real clinical impact, these models must be integrated into routine workflows. AI tools moving from research to bedside require understanding how algorithms fit into clinical decisions and healthcare systems (38). AI in healthcare is best viewed as augmented intelligence that assists, not replaces, clinicians. In this role, AI adds analytics to support human judgment. Collaboration between clinicians and algorithms can improve diagnostic accuracy, and this maintains the physicians' vital role (37). Successful AI integration requires careful alignment with existing workflows. Predictive models should deliver outputs at key decision points during patient evaluation. For example, a model predicting UTI is most useful when urinalysis results are available or when clinicians are considering starting empiric antibiotic therapy. Delivering algorithmic outputs at these moments can enhance their usefulness in guiding decisions (38). An example of how AI-based risk stratification models may be incorporated into the clinical workflow of pediatric urinary tract infection evaluation is summarized in *Table 2.* Such workflow-oriented integration may enhance diagnostic consistency and support antimicrobial stewardship while preserving clinician oversight.

A common clinical use of AI is through *clinical decision support systems (CDSS)*. These systems embed predictive models in electronic health records or clinical platforms. They provide algorithm-based insights. For example, an AI model for UTI could review patient data in real time and estimate the probability of true infection to guide decisions (39). CDSS can enhance diagnostic consistency and reduce cognitive workload by synthesizing

Table 2. Potential clinical workflow integration of AI-based risk stratification for pediatric urinary tract infection

Clinical Step	Available Data	AI Model Function	Potential Clinical Impact
Initial patient assessment	Age, symptoms, vital signs	Estimate baseline probability of UTI	Support early diagnostic suspicion
Urinalysis evaluation	Leukocyte esterase, nitrite, pyuria	Integrate urinalysis parameters into prediction model	Improve interpretation of screening tests
Microbiological testing	Urine culture results, colony counts	Update probability of true infection vs colonization	Assist in confirming diagnosis
Risk stratification	Combined clinical and laboratory data	Generate individualized infection risk score	Guide antibiotic decision-making
Clinical decision	Model output + physician assessment	Provide decision-support recommendations	Reduce unnecessary antibiotic use

large amounts of clinical data. In situations of high diagnostic uncertainty, such systems may highlight patterns in patient data that clinicians might otherwise overlook. However, the responsibility for diagnosis and treatment stays with the clinician. Each clinician must interpret algorithmic predictions within each patient's broader clinical context (40).

Another important consideration is the reliability and safety of predictive models. Machine learning algorithms may be susceptible to biases from training data or differences between development and deployment environments. Ensuring fairness, transparency, and validation of AI systems is essential before implementation in routine clinical practice. Continuous monitoring of model performance is also necessary to maintain predictive accuracy over time (41). Explainability also plays a critical role in clinical adoption of AI tools. Clinicians are more likely to trust and use models when they understand how algorithms make predictions. Explainable AI techniques, like feature attribution methods, highlight which variables contribute to individual predictions. These approaches help clinicians assess if algorithmic outputs align with clinical reasoning and medical knowledge (42).

In pediatric UTI, integrating AI-based risk-stratification tools into clinical workflows may lead to more precise diagnostic decisions. These tools can also improve antimicrobial stewardship. By identifying patients with a higher probability of true infection, predictive models may help clinicians target antibiotic therapy more appropriately. They help avoid unnecessary treatment in children with asymptomatic bacteriuria. Successful clinical implementation of AI-based tools depends on developing accurate and interpretable systems that integrate seamlessly into routine health care. When designed and deployed appropriately, AI-driven support systems can enhance diagnostic precision. They maintain clinicians' central role in patient care. The following section discusses ethical and practical considerations for implementing artificial intelligence in clinical medicine. These include issues related to algorithmic bias, transparency, and responsible use of AI technologies in healthcare.

7. Ethical and Practical Considerations

The integration of artificial intelligence into clinical practice presents substantial opportunities to enhance diagnostic accuracy and decision-making. However, the adoption of AI-based tools in healthcare introduces significant ethical and practical considerations. Addressing these concerns is crucial for the responsible implementation of predictive models. Patient safety, fairness, and transparency must remain core elements of clinical practice (44). Algorithmic bias is a prominent concern in clinical AI applications. Machine learning models are often trained on historical clinical datasets. Any biases within these datasets can be inadvertently learned by the algorithms. When training data do not represent diverse patient populations, predictive models may perform differently across demographic groups. These biases can contribute to disparities in healthcare delivery. If unaddressed, they may exacerbate existing health inequalities (43).

A related challenge is ensuring data representativeness and generalizability. Many AI models are developed using data from a limited set of healthcare institutions or geograph-

ic regions. However, applying these models in different clinical environments introduces variations in patient populations, diagnostic practices, and healthcare infrastructure. These differences may affect model performance. Thus, external validation across multiple settings is essential before widespread clinical implementation (44). Interpretability of machine learning models is another critical consideration. Many advanced algorithms function as complex computational systems that clinicians may find difficult to interpret. This "black-box" problem raises concerns about the use of opaque decision-making tools in healthcare. Clinicians must justify diagnostic and therapeutic decisions to patients and regulatory authorities. Achieving an appropriate balance between predictive accuracy and interpretability remains a central challenge in developing clinically acceptable AI systems (45).

In response to these concerns, there is growing emphasis on the development of explainable AI. Explainable AI techniques seek to clarify how predictive models generate outputs. This enables clinicians to assess the contribution of individual variables to algorithmic predictions. Such transparency supports clinicians in evaluating whether model outputs align with established medical knowledge and clinical reasoning (48). Beyond all technical considerations, the use of AI in medicine raises broader ethical questions about responsibility and accountability. Clinical decisions directly impact patient outcomes. The assignment of responsibility for decisions influenced by algorithmic recommendations remains under debate. Most experts advocate for AI systems to serve as decision-support tools. Clinicians should maintain ultimate responsibility for patient care (46).

Ethical frameworks have been proposed to guide the responsible development and implementation of AI in healthcare. These frameworks emphasize fairness, transparency, accountability, and respect for patient autonomy. Following these principles supports AI systems that promote equitable and trustworthy healthcare delivery (47). These ethical considerations are especially pertinent in pediatric UTIs. AI-based risk prediction models can influence decisions about diagnostic testing and antibiotic prescribing. Ensuring that these systems are transparent, unbiased, and clinically interpretable is essential for maintaining trust among clinicians and patients. It also supports responsible antimicrobial stewardship.

In summary, ethical and practical considerations are central to the safe integration of artificial intelligence into clinical practice. Addressing bias, interpretability, and accountability is essential to ensure that AI-based diagnostic tools enhance, rather than compromise, patient care quality. The next section examines future perspectives and emerging directions in applying artificial intelligence for diagnostic decision-making in pediatric urinary tract infection.

8. Future Perspectives

The rapid evolution of AI technologies is expected to further transform diagnostic decision-making in clinical medicine. As computational methods advance and healthcare datasets become more comprehensive, AI-based tools will likely support clinicians in a

broader range of diagnostic scenarios. Machine learning models that integrate multidimensional clinical data may help address complex diagnostic problems. These are often difficult to resolve using traditional rule-based approaches (49). AI-based risk stratification may soon help clinicians distinguish ASB from true pediatric UTI. The wider availability of electronic health records, laboratory databases, and clinical registries enables the development of predictive models using large, diverse patient populations. Such data enables machine learning algorithms to identify subtle interactions among clinical variables and improve the accuracy of individual risk predictions (49).

Another promising direction is integrating predictive models into clinical information systems. Embedding AI-based decision-support tools within electronic health record platforms may help clinicians obtain real-time risk estimates during patient evaluation. This approach could improve diagnostic consistency and reduce unnecessary testing and inappropriate antibiotic prescribing. In turn, it supports antimicrobial stewardship initiatives (50). Advances in explainable AI are also likely to play a crucial role in future healthcare. Methods that provide transparent explanations for model predictions may increase clinician trust. They can also facilitate the responsible implementation of machine learning systems in clinical practice. By allowing clinicians to understand how specific variables influence model outputs, explainable AI approaches can help keep predictive algorithms interpretable and clinically meaningful (49). Despite these promising developments, several challenges remain. Future research must validate predictive models across various healthcare settings and patient populations. This is necessary to ensure generalizability and reliability. In addition, regulatory frameworks, ethical guidelines, and clinical governance structures will be essential. These elements will help guide the responsible use of AI in healthcare environments (50).

Ultimately, the future of AI in diagnosing pediatric UTI will likely use a collaborative model. In this model, machine learning tools support, rather than replace, clinical expertise. Integrating computational methods with physician judgment, AI-based risk stratification systems may offer more precise diagnostics, better patient outcomes, and more responsible antimicrobial use.

9. Conclusion

Differentiating ASB from UTI presents a central challenge in pediatric care. Overlapping presentations, diagnostic limitations, and difficulties in specimen collection make accurate diagnosis difficult and highlight the urgent need for better diagnostic tools. AI using machine learning integrates clinical and lab data for improved pattern recognition. AI provides risk estimates to support decisions but depends on data quality, is subject to algorithmic biases, and requires clinical interpretation. It augments, rather than replaces, the clinical expertise with explainable AI ensuring transparency. Incorporating AI-based risk stratification helps clinicians improve diagnostic accuracy, reduce unnecessary antibiotics, and support stewardship. Clinicians should note that AI depends on data and context,

and clinical judgment guides decisions. The future of pediatric UTI diagnosis may combine AI analysis with clinical expertise for individualized, ethical care.

10. References

1. Nelson, Z., Aslan, A. T., Beahm, N. P., Blyth, M., Cappiello, M., Casaus, D., ... & Mena Lora, A. J. (2024). Guidelines for the prevention, diagnosis, and management of urinary tract infections in pediatrics and adults: a WikiGuidelines group consensus statement. JAMA Network Open, 7(11), e2444495.
2. Nicolle, L. E., Gupta, K., Bradley, S. F., Colgan, R., DeMuri, G. P., Drekonja, D., ... & Siemieniuk, R. (2019). Clinical practice guideline for the management of asymptomatic bacteriuria: 2019 update by the Infectious Diseases Society of America. Clinical infectious diseases, 68(10), e83-e110.
3. Dahiya, A., & Goldman, R. D. (2018). Management of asymptomatic bacteriuria in children. Canadian Family Physician, 64(11), 821-824.
4. Hari, P., Meena, J., Kumar, M., Sinha, A., Thergaonkar, R. W., Iyengar, A., ... & Bagga, A. (2024). Evidence-based clinical practice guideline for management of urinary tract infection and primary vesicoureteric reflux. Pediatric Nephrology, 39(5), 1639-1668.
5. Maringhini, S., Alaygut, D., & Corrado, C. (2024). Urinary tract infection in children: an up-to-date study. Biomedicines, 12(11), 2582.
6. Barola S, Kliegman RM, St Geme JW **(2024)**. Urinary tract infections in children. In: StatPearls. Treasure Island (FL): StatPearls Publishing.
7. Doern, C. D., & Richardson, S. E. (2016). Diagnosis of urinary tract infections in children. Journal of clinical microbiology, 54(9), 2233-2242.
8. Ventola, C. L. (2015). The antibiotic resistance crisis: part 1: causes and threats. Pharmacy and therapeutics, 40(4), 277-283.
9. Naik, N., Talyshinskii, A., Shetty, D. K., Hameed, B. Z., Zhankina, R., & Somani, B. K. (2024). Smart diagnosis of urinary tract infections: is artificial intelligence the fast-lane solution?. Current Urology Reports, 25(1), 37-47.
10. Topol, E. J. (2019). High-performance medicine: the convergence of human and artificial intelligence. Nature medicine, 25(1), 44-56.
11. Sheele, J. M., Campbell, R. L., & Jones, D. D. Machine learning to predict bacteriuria in the emergency.
12. Brigadoi, G., Liberati, C., Gres, E., Barbieri, E., Boreggio, E., Rossin, S., ... & Donà, D. (2024). Impact of an antibiotic stewardship program on adherence to antibiotic prescription in children admitted with urinary tract infection. Therapeutic Advances in Infectious Disease, 11, 20499361241282824.
13. Bryant, P. A., Bitsori, M., Vardaki, K., Vaezipour, N., Khan, M., & Buettcher, M. (2025). Guidelines for complicated urinary tract infections in children: a review by the European Society for Pediatric Infectious Diseases. The Pediatric Infectious Disease Journal, 44(6), e211-e223.
14. Nicolle, L. E. (2016). The paradigm shift to non-treatment of asymptomatic bacteriuria.
15. Shaikh, N., Osio, V. A., Wessel, C. B., & Jeong, J. H. (2020). Prevalence of asymptomatic bacteriuria in children: a meta-analysis. The Journal of Pediatrics, 217, 110-117.
16. Tullus, K., & Shaikh, N. (2020). Urinary tract infections in children. The Lancet, 395(10237), 1659-1668.
17. Holden, J. G., Wallace, S., Chang, P. W., Davis-Rodriguez, S., Hamdy, R. F., Morrison, J. M., ... & Forster, C. S. (2025). Diagnostic evaluation and treatment of UTIs in children with neurogenic bladder. Journal of pediatric urology, 22, 105602.
18. Bryant, P. A., Bitsori, M., Vardaki, K., Vaezipour, N., Khan, M., & Buettcher, M. (2025). Guidelines for complicated urinary tract infections in children: a review by the European Society for Pediatric Infectious Diseases. The Pediatric Infectious Disease Journal, 44(6), e211-e223.
19. Olson, P., Dudley, A. G., & Rowe, C. K. (2022). Contemporary management of urinary tract infections in children. Current Treatment Options in Pediatrics, 8(3), 192-210.
20. Kawalec, A., Józefiak, J., & Kiliś-Pstrusińska, K. (2023). Urinary tract infection and antimicrobial resistance patterns: 5-year experience in a tertiary pediatric nephrology center in the southwestern region of Poland. Antibiotics, 12(9), 1454.
21. Kaufman, J., Temple-Smith, M., & Sanci, L. (2019). Urinary tract infections in children: an overview of diagnosis and management. BMJ paediatrics open, 3(1), e000487.
22. Sameer, S. K., Taha, M. J., Alrubasy, W. A., Abozenah, A. T., Alkiswani, M. Y., Elhakim, A. A., ... & Alshami, A. (2025). A systematic review of the accuracy and reliability of pyuria in diagnosing pediatric urinary tract infections. Cureus, 17(2).
23. Ahmed, S. M., & Swedlund, S. K. (1998). Evaluation and treatment of urinary tract infections in children. American family physician, 57(7), 1573-1580.
24. Okarska-Napierała, M., Wasilewska, A., & Kuchar, E. (2017). Urinary tract infection in children: Diagnosis, treatment, imaging–Comparison of current guidelines. Journal of pediatric urology, 13(6), 567-573.
25. von Knebel Doeberitz, M. (2022). Human and Artificial Intelligence in Medicine. In Intelligence-Theories and Applications (pp. 273-282). Cham: Springer International Publishing.

26. Rajkomar, A., Dean, J., & Kohane, I. (2019). Machine learning in medicine. New England Journal of Medicine, 380(14), 1347-1358.
27. Sendak, M., Gao, M., Nichols, M., Lin, A., & Balu, S. (2019). Machine learning in health care: a critical appraisal of challenges and opportunities. EGEMs, 7(1), 1.
28. Rezaei, M., Rahmani, E., Khouzani, S. J., Rahmannia, M., Ghadirzadeh, E., Bashghareh, P., ... & Taheri, F. (2023). Role of artificial intelligence in the diagnosis and treatment of diseases. Kindle, 3(1), 1-160.
29. Obermeyer, Z., Powers, B., Vogeli, C., & Mullainathan, S. (2019). Dissecting racial bias in an algorithm used to manage the health of populations. Science, 366(6464), 447-453.
30. Lundberg, S. M., & Lee, S. I. (2017). A unified approach to interpreting model predictions. Advances in neural information processing systems, 30.
31. Taylor, R. A., Moore, C. L., Cheung, K. H., & Brandt, C. (2018). Predicting urinary tract infections in the emergency department with machine learning. PloS one, 13(3), e0194085.
32. Khan, I. U. (2022). Explainable Artificial Intelligence (XAI) Model for the Diagnosis of Urinary Tract Infections in Emergency Care Patients. *Mathematical Modelling of Engineering Problems*, *9*(4).
33. Khalilia, M., Chakraborty, S., & Popescu, M. (2011). Predicting disease risks from highly imbalanced data using random forest. BMC medical informatics and decision making, 11(1), 51.
34. Sendak, M. P., Balu, S., & Schulman, K. A. (2017). Barriers to achieving economies of scale in analysis of EHR data. Applied clinical informatics, 8(03), 826-831.
35. Lundberg, S. M., Erion, G., Chen, H., DeGrave, A., Prutkin, J. M., Nair, B., ... & Lee, S. I. (2020). From local explanations to global understanding with explainable AI for trees. Nature machine intelligence, 2(1), 56-67.
36. Molnar, C. (2020). Interpretable machine learning. Lulu. com.
37. Smith, A., van Wagoner, H. P., Keplinger, K., & Celebi, C. (2025). Navigating AI convergence in human–artificial intelligence teams: A signaling theory approach. Journal of Organizational Behavior.
38. Sendak, M. P., D'Arcy, J., Kashyap, S., Gao, M., Nichols, M., Corey, K., ... & Balu, S. (2020). A path for translation of machine learning products into healthcare delivery. EMJ Innov, 10, 19-00172.
39. Sutton, R. T., Pincock, D., Baumgart, D. C., Sadowski, D. C., Fedorak, R. N., & Kroeker, K. I. (2020). An overview of clinical decision support systems: benefits, risks, and strategies for success. NPJ digital medicine, 3(1), 17.
40. Shortliffe, E. H., & Sepúlveda, M. J. (2018). Clinical decision support in the era of artificial intelligence. Jama, 320(21), 2199-2200.
41. Rajkomar, A., Hardt, M., Howell, M. D., Corrado, G., & Chin, M. H. (2018). Ensuring fairness in machine learning to advance health equity. Annals of internal medicine, 169(12), 866-872.
42. Amann, J., Blasimme, A., Vayena, E., Frey, D., Madai, V. I., & Precise4Q Consortium. (2020). Explainability for artificial intelligence in healthcare: a multidisciplinary perspective. BMC medical informatics and decision making, 20(1), 310.
43. Chin, M. H., Afsar-Manesh, N., Bierman, A. S., Chang, C., Colón-Rodríguez, C. J., Dullabh, P., ... & Ohno-Machado, L. (2023). Guiding principles to address the impact of algorithm bias on racial and ethnic disparities in health and health care. JAMA Network Open, 6(12), e2345050.
44. Kelly, C. J., Karthikesalingam, A., Suleyman, M., Corrado, G., & King, D. (2019). Key challenges for delivering clinical impact with artificial intelligence. BMC medicine, 17(1), 195.
45. London, A. J. (2019). Artificial intelligence and black-box medical decisions: accuracy versus explainability. Hastings Center Report, 49(1), 15-21.
46. Vayena, E., Blasimme, A., & Cohen, I. G. (2018). Machine learning in medicine: addressing ethical challenges. PLoS medicine, 15(11), e1002689.
47. Floridi, L., Cowls, J., Beltrametti, M., Chatila, R., Chazerand, P., Dignum, V., ... & Vayena, E. (2018). AI4People—An ethical framework for a good AI society: Opportunities, risks, principles, and recommendations. Minds and machines, 28(4), 689-707.
48. Amann, J., Blasimme, A., Vayena, E., Frey, D., Madai, V. I., & Precise4Q Consortium. (2020). Explainability for artificial intelligence in healthcare: a multidisciplinary perspective. BMC medical informatics and decision making, 20(1), 310.
49. Zybailov, B. L., Kosovsky, G. Y., Glazko, G. V., Glazko, V. I., & Skobel, O. I. (2024). Evolutionary Perspectives on Human-Artificial Intelligence Convergence. Acta Naturae (англоязычная версия), 16(3), 4-17.
50. Goździkiewicz, N., Zwolińska, D., & Polak-Jonkisz, D. (2022). The use of artificial intelligence algorithms in the diagnosis of urinary tract infections—a literature review. Journal of Clinical Medicine, 11(10), 2734.

CHAPTER 18

Predictive Analytics in Urology: AI-Driven Risk Stratification and Clinical Decision Support

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1. Introduction

1.1. From Clinical Intuition to Predictive Models: A Historical Arc

Considering the evolution of medical science to the present day, decision-making processes have long relied on experience-based clinical reasoning, grounded in observational practice and the accumulation and transmission of expertise within an apprenticeship-based paradigm (1). Within this framework, mnemonics used as memory-supporting cognitive tools may be regarded as foundational elements underlying early examples of clinical prediction. With the second half of the twentieth century, more objective and quantitative models for risk estimation began to emerge. The transition from traditional risk categorization approaches (low-, intermediate-, and high-risk) to models generating individualized risk predictions based on multivariable statistical modeling, in an era characterized by increasing data diversity, has formed the basis of modern predictive analytics.

From a urological perspective, the Kattan nomograms and the CAPRA scoring system, developed to predict recurrence following radical prostatectomy, can be considered historical precursors of predictive analytics, as they are based on multivariable regression-based prognostic modeling (2,3).

1.2. Ars Longa, Vita brevis

Contemporary urological clinical guidelines represent one of the most important tools supporting decision-making processes in diagnosis, treatment, and follow-up. These guidelines provide a systematic synthesis of the available evidence, current literature, and

multidisciplinary consensus, extending well beyond the limits of individual clinical experience and enabling clinicians to access and apply a comprehensive body of knowledge within a single framework.

Within the context of the European Association of Urology (EAU) guidelines, these documents systematically compile a volume of literature that would be impractical for an individual clinician to review independently, integrate multidisciplinary expert perspectives into a unified decision-making structure, and transparently grade the quality of evidence. Taking the prostate cancer guideline as an example, which is updated annually, it represents a collaborative effort involving six international associations and experts from urology, radiation oncology, medical oncology, radiology, pathology, and geriatric oncology. The guideline incorporates 3,060 references.

A key aspect to emphasize is the methodological rigor underlying the decision-making process. Recommendations are updated only when supported by high-quality evidence, including systematic reviews, meta-analyses, randomized controlled trials, and prospective comparative studies. Clinical recommendations are formulated through the integration of the Oxford Levels of Evidence with the GRADE system for recommendation strength. Accordingly, strong recommendations within the EAU framework are predominantly supported by Level of Evidence (LE) 1a–1b, corresponding to randomized controlled trials and meta-analyses. However, in real-world clinical practice, not all decisions are supported by evidence of this level, resulting in areas where guidelines may not provide definitive guidance (67).

Machine learning (ML) has emerged as a powerful approach due to its ability to identify, learn, and integrate complex and nonlinear relationships among variables and across diverse data types within a unified modeling framework (4,5). For example, a linear relationship may be described as an increase in serum levels of a given variable with advancing age. In contrast, a nonlinear pattern may involve a gradual increase up to a certain age, followed by a rapid rise and subsequent plateau.

Such complex and nonlinear relationships may include interactions between imaging-derived parameters such as tumor size on MRI, contrast enhancement patterns, and standardized uptake values (SUV) on PET and clinical outcomes, including survival or treatment response. For instance, prognosis may be favorable in the presence of small tumor volume, whereas combinations of necrosis and increased vascularization may be associated with poorer outcomes, or risk may increase beyond specific tumor size thresholds.

Since 2015, advances in deep learning have enabled its application across a wide range of domains, from image interpretation to prediction of clinical outcomes (4). More recently, the emergence of large language models since 2023 has markedly accelerated the rate of scientific output in the field of artificial intelligence in urology (6).

This study aims to evaluate the current and future role of artificial intelligence within urology an evidence-based discipline supported by high-level scientific data based on the available literature. It is anticipated that these technologies will become increasingly integrated into both daily life and clinical practice in the near future.

1.3. From Reactive to Predictive Medicine

The classical medical paradigm follows a predominantly reactive sequence of "symptom, diagnosis, and treatment." In contrast, AI-supported predictive medicine introduces a fundamentally different approach to clinical decision-making. By enabling the estimation of individualized risk profiles prior to overt clinical manifestation, predictive models have the potential to inform therapeutic strategies earlier in the disease course. For example, models capable of estimating the biochemical probability of recurrence before surgery may support decisions regarding adjuvant treatment without the need to await radiological evidence. Similarly, preoperative prediction of muscle invasion risk in bladder cancer may facilitate earlier consideration of radical cystectomy and has the potential to influence existing treatment algorithms (7).

1.4. Oncological Dominance in Urological AI Research

The urology-focused artificial intelligence literature demonstrates a thematic distribution that does not fully reflect the clinical burden of disease. While prostate cancer accounts for approximately one-third of total publications, conditions such as benign prostatic hyperplasia (BPH) and urolithiasis despite constituting a substantial proportion of outpatient workload remain comparatively underrepresented. This imbalance appears to be driven, in part, by differences in data infrastructure. Prostate cancer research benefits from the availability of large, well-structured, and longitudinal cohort datasets accumulated over decades. In contrast, benign urological conditions often lack similarly standardized and comprehensive data resources. Furthermore, heterogeneity in outcome definitions and the absence of widely accepted standard criteria limit the generation of high-quality datasets, thereby constraining research output in these domains (8).

1.5. Scope and Objectives of the Chapter

This chapter aims to critically examine the impact of artificial intelligence–based predictive modeling and risk stratification on clinical decision-making in urology, as well as the existing barriers to their implementation and the current level of evidence.

Three primary objectives are defined: (i) to synthesize current evidence on AI applications across prostate, bladder, and kidney cancers, as well as urolithiasis and benign prostatic hyperplasia/lower urinary tract symptoms (BPH/LUTS); (ii) to introduce and critically appraise methodological frameworks including PROBAST, TRIPOD, and STREAM-URO for the evaluation of study quality; and (iii) to explore the factors underlying the limited translation of statistically high-performing models into routine clinical practice.

The analysis is based on a systematically constructed dataset derived from searches conducted in PubMed, Google Scholar, and Embase. An initial pool of 604 records was identified, and through additional targeted searches and screening procedures, approximately 240 studies were included in the final evaluation.

2. Methodological Foundations

2.1. Basic Concepts

2.1.1. Predictive Analytics and Risk Stratification

Predictive analytics refers to methods that estimate the probability of future clinical events based on existing data (9). This approach corresponds to the third stage within a three-tier analytical framework: descriptive (what happened?), explanatory or causal (why did it happen?), and predictive (what is likely to happen?). In urology, predictive analytics addresses clinically relevant questions such as the risk of disease recurrence following treatment, the prediction of tumor histopathological characteristics without tissue sampling, and the likelihood of response to a given therapeutic regimen (5,9).

Risk stratification, in turn, is defined as the process of evaluating a heterogeneous patient population and classifying it into distinct subgroups to guide differential treatment and follow-up strategies (9). The clinical relevance of such stratification becomes evident only when it leads to meaningful changes in management, such as variation in treatment modalities or monitoring intensity across subgroups (see Section 3.3, ADT exclusion).

Established tools such as the CAPRA score and EORTC risk tables represent well-validated reference models based on regression-based and predominantly linear statistical methods (2,3,11). In contrast, machine learning–based approaches offer the capacity to identify complex patterns that may not be captured by traditional linear models, by integrating heterogeneous data sources including laboratory, imaging, and pathological variables within a unified analytical framework (5,7). When supported by robust validation studies and prospective data, this capability may position predictive analytics as a complementary component of evidence-based clinical decision-making.

2.1.2. Artificial Intelligence, Machine Learning, and Deep Learning

Although often used interchangeably in the literature, artificial intelligence (AI), machine learning (ML), and deep learning (DL) represent distinct conceptual domains. AI is an overarching field aimed at enabling computers to emulate aspects of human cognitive function. ML, as a subset of AI, focuses on algorithms that learn patterns from data without relying on explicitly programmed rules. DL, a subfield of ML, is based on multilayer artificial neural networks and has been widely applied in domains such as medical image analysis and genomic data interpretation (4,5).

Commonly used algorithms in urological research include random forest, support vector machines, and gradient boosting methods such as XGBoost and LightGBM. Radiomics represents a hybrid analytical approach in which high-dimensional quantitative features are extracted from medical imaging data and subsequently utilized within ML pipelines (12).

2.1.3. Clinical Decision Support Systems

A clinical decision support system (CDSS) is an information infrastructure designed to process patient-specific data and generate recommendations related to diagnosis, prognosis, or treatment selection (9). It serves as the interface between the quantitative output of predictive models and their translation into actionable clinical decisions.

Regardless of a model's discriminatory performance, its clinical utility depends on the ability of the clinician to interpret and operationalize its outputs. In this context, defining actionable threshold values at which model predictions are translated into clinical decisions is critical; without such thresholds, even high-performing models may fail to produce meaningful clinical impact (9,13).

2.2. Methodological Evaluation Frameworks

The majority of studies in the current urological AI literature are reported using technical performance metrics such as area under the curve (AUC), sensitivity, and specificity (7). When interpreting these metrics particularly in disease-specific sections beginning from Chapter 3 it is important to recognize that they primarily reflect the statistical discriminatory performance of a model. These measures should not be equated with clinical effectiveness. On their own, they do not determine whether a model will perform reliably across different patient populations or under real-world clinical conditions.

To address this limitation, several structured evaluation frameworks have been developed. Before discussing performance metrics in detail, it is therefore essential to briefly introduce the principal tools used for methodological assessment:

TRIPOD: An international reporting guideline designed to ensure transparency and reproducibility in studies of predictive models (10). Although adherence rates remain suboptimal in urological research, this limitation is not unique to the field and has been widely reported across the broader medical literature (63).

PROBAST: A structured tool for assessing risk of bias across four domains: participant selection, predictors, outcome definition, and analysis (14). A high risk of bias in any single domain results in an overall high-risk classification. In urological AI studies, the analysis domain is most frequently identified as problematic (7).

APPRAISE-AI: A composite scoring system (0–100) that evaluates the readiness of a model for clinical implementation (13). Notably, high discriminatory performance (e.g., AUC) does not necessarily correspond to high clinical readiness.

STREAM-URO: A reporting quality assessment scale developed specifically for machine learning studies in urology and endourology (8). Current literature reports mean scores of approximately 13–14 out of 26, with substantial deficiencies particularly in transparency and external validation domains.

DECISION CURVE ANALYSIS (DCA): A method used to evaluate the clinical utility of a model by quantifying net benefit across a range of decision thresholds (15). Importantly,

Table 1. Methodological Evaluation Frameworks

Tool	Type	Scope and function	Critical finding in urology AI	Ref
TRIPOD / TRIPOD+AI	Reporting	22-item checklist for transparent and reproducible reporting of prediction model studies. TRIPOD+AI (2024) covers regression and ML models.	Compliance rates in urology are low. Similar gaps documented across general medical AI literature.	(10)
PROBAST	Bias risk	Assesses risk of bias across 4 domains: participant selection, predictors, outcome measurement, and analysis. High risk in any domain = overall high risk.	Most problematic domain: analysis. Up to 84% of oncology ML studies carry high bias risk.	(14)
APPRAISE-AI	Clinical readiness	Quantifies readiness for clinical use on a 0-100 composite score across 6 domains: clinical relevance, data quality, methodology, robustness, reporting, and reproducibility.	High AUC does not guarantee high readiness. In NMIBC studies, no model reached the threshold for routine clinical integration.	(13)
STREAM-URO	Reporting quality	26-item quality scale specific to urology and endourology ML studies. Includes external validation, calibration, and clinical utility items.	Literature average: ~13-14/26. Notable gaps in transparency and external validation.	(8)
DCA	Clinical utility	Shows whether using a model at a given threshold provides greater net benefit than treating all or no patients.	A model with high AUC can yield negative net benefit. Reporting rate in urological AI: ~6%.	(15)
Calibration	Performance metric	Degree to which predicted probabilities match observed event rates. Assessed via calibration plots, slope, and intercept.	Reporting rate in oncology ML reviews: 11-19%. Only 11% of studies report both discrimination and calibration.	(9, 64)

models with high AUC values may still demonstrate limited or even negative net benefit when assessed using DCA.

CALIBRATION: The degree to which predicted probabilities correspond to observed event frequencies (9). In oncological machine learning studies, calibration reporting remains limited, with rates ranging from 11% to 19% in systematic reviews (64).

2.3. Explainable Artificial Intelligence: SHAP and LIME

Explainable artificial intelligence (XAI) methods aim to enhance the transparency of predictive models by enabling clinicians to interrogate, interpret, and, when necessary, challenge model outputs. By providing insight into the factors driving a given prediction, these approaches address the longstanding "black box" criticism associated with machine learning models.

Among these methods, SHAP (SHapley Additive Explanations) is one of the most frequently applied techniques in urological oncology studies. SHAP quantifies the contribution of each input feature to a specific prediction using Shapley values derived from cooperative game theory. These contributions can be evaluated at both the global level (across the entire cohort) and the local level (for an individual patient), thereby providing a comprehensive interpretation of model behavior (16).

LIME (Local Interpretable Model-Agnostic Explanations), in contrast, is a model-agnostic interpretability method that generates locally faithful, human-interpretable explanations for individual predictions by approximating the model's behavior in the vicinity of a specific data point (17).

3. Artificial Intelligence in Prostate Cancer

Prostate cancer, the second most common malignancy in men, represents a substantial global disease burden, with approximately 1.47 million new diagnoses reported worldwide in 2022 (18). A central challenge in clinical management is the marked biological heterogeneity of the disease, as patients within the same Gleason grade group may exhibit markedly divergent clinical trajectories. In the literature, this variability has been attributed to factors such as tissue-level architectural subpatterns, molecular markers of aggressiveness, and genomic profiles (66). Machine learning (ML)–based models are particularly suited to address this complexity due to their capacity to systematically integrate and analyze such multidimensional data (3,7). Traditional risk calculators developed for prostate cancer detection have been systematically reviewed and represent well-established clinical benchmarks against which the added value of AI-based approaches is evaluated (26).

3.1. Biochemical Recurrence Prediction

In prostate cancer management, biochemical recurrence (BCR) defined as a confirmed rise in PSA levels exceeding 0.2 ng/mL following radical prostatectomy, or an increase of

more than 2 ng/mL above nadir after radiotherapy serves as an early indicator of disease progression (66,67).

Current evidence suggests that ML-based models achieve discriminatory performance in the range of 0.82–0.83 for BCR prediction, with the highest performance observed when deep learning approaches are combined with imaging data (19,20). Notably, short-term predictive models focusing on the first postoperative year (AUC 0.86) demonstrate greater predictive stability compared to long-term models (AUC 0.80–0.82), underscoring the clinical importance of early follow-up (19). Among individual models, XGBoost (AUC 0.91) and LightGBM (AUC 0.88) outperform traditional risk calculators such as CAPRA-S in terms of discriminatory ability. Feature importance analyses indicate that pathological T stage, positive surgical margins, and PSA-related variables represent key determinants of recurrence risk (21,22). The reported consistency of XGBoost performance (AUC 0.89) further supports the potential clinical robustness of these approaches (22).

3.2. Extraprostatic Extension and Lymph Node Metastasis

In surgical planning for prostate cancer, accurate preoperative assessment of extracapsular extension (ECE) and lymph node metastasis (LNM) is critical, as it directly influences decisions regarding nerve-sparing techniques and the extent of pelvic lymph node dissection (PLND) (67).

Current evidence indicates that models integrating preoperative multiparametric MRI (mpMRI) with clinical variables achieve superior predictive performance for ECE, with pooled AUC values of approximately 0.89 (95% CI: 0.86–0.92) (23–25). Compared to MRI alone, radiomic–clinical models demonstrate improved diagnostic accuracy (sensitivity 0.83, specificity 0.82), thereby providing meaningful added value in surgical decision-making, particularly in the context of nerve-sparing approaches (23).

Furthermore, deep learning–based models have been reported to achieve higher diagnostic odds ratios (DOR: 24.6 vs. 17.3) compared to conventional machine learning methods (23).

3.3. Genomic Classifiers and Digital Pathology

Prospectively validated RNA-based genomic classifiers including Decipher, Prolaris, and Oncotype DX play an established role in prostate cancer management, offering independent prognostic value in risk stratification (67,27,28).

In the domain of digital pathology, a methodologically robust study demonstrated that an AI model achieved performance comparable to expert pathologists in Gleason grading, with reported values of 0.862 and 0.868 (68). Multimodal deep learning models that integrate preoperative biopsy imaging with clinical parameters offer a promising approach for refining treatment intensity decisions. Among these, ArteraAI represents one of the most clinically advanced platforms, having been incorporated into NCCN guidelines based on evidence derived from randomized controlled trials (58,61). Large-scale analyses have

demonstrated its ability to identify patient subgroups in whom short-term androgen deprivation therapy (ADT) may be safely omitted (7).

3.4. PSMA PET Integration and Clinical Decision Support

PSMA-targeted PET-CT, which has become a standard imaging modality in prostate cancer staging and recurrence localization, significantly enhances diagnostic accuracy when integrated with AI-based models (29). AI algorithms have also demonstrated strong performance in predicting treatment-related toxicities, including bowel, bladder, and sexual dysfunction following radiotherapy (30). Within the framework of clinical decision support systems (CDSS), the integration of AI-driven predictive tools into prostate cancer management is increasingly emphasized in the contemporary literature, highlighting their potential to support individualized, data-driven clinical decision-making (31).

4. Artificial Intelligence in Bladder Cancer

Approximately three-quarters of bladder cancer cases are diagnosed as non–muscle-invasive bladder cancer (NMIBC), while the remaining cases present with muscle-invasive disease (MIBC) or metastatic involvement at initial diagnosis (18,32). The therapeutic approaches and follow-up strategies for these groups differ substantially, as reflected in guideline-based management frameworks. Due to the high recurrence rate (70–80%) and a progression risk of approximately 20% in NMIBC, intensive surveillance is required (33). Consequently, bladder cancer represents one of the most resource-intensive malignancies in terms of per-patient healthcare costs.

4.1. Detection of Muscle Invasion

Accurate preoperative identification of muscle invasion is a critical determinant of treatment strategy in bladder cancer. The MRI-based VI-RADS scoring system has significantly improved standardization; however, interobserver variability remains an important limitation (34).

Meta-analytic evidence indicates that the incorporation of AI-based models into this diagnostic pathway improves discriminatory performance, increasing AUC from 0.82 to 0.94 (35). While standalone AI models demonstrate high performance (AUC 0.92), their combined use with VI-RADS (AUC 0.94) suggests that AI functions as a complementary tool that enhances, rather than replaces, established diagnostic frameworks (35).

4.2. NMIBC Recurrence and Progression Prediction

EORTC risk tables and the CUETO model remain the primary reference tools in NMIBC management. However, the biological and clinical heterogeneity observed among patients

within the same risk category highlights the limitations of these models in individualized risk prediction (32,33).

Machine learning and deep learning approaches developed to address these limitations have demonstrated improved predictive performance compared to traditional models (33). In particular, ML-based models have shown superior performance in survival prediction, and the number of real-world cohort studies in this domain is steadily increasing (37).

4.3. Neoadjuvant Chemotherapy Response Prediction

Cisplatin-based neoadjuvant chemotherapy administered prior to surgery is considered standard of care in muscle-invasive bladder cancer. However, pathological complete response (pCR) rates are limited to approximately one-third of patients, underscoring the need for reliable predictive biomarkers (32). Meta-analytic data indicate that radiomics-based models achieve a specificity of approximately 82% in predicting pCR (38). This level of specificity provides clinically meaningful value by facilitating the identification of patients most likely to benefit from treatment, while potentially reducing exposure to unnecessary toxicity.

4.4. BCG Response Prediction and Computational Histology

In high-risk NMIBC, the development of resistance to intravesical BCG therapy may necessitate radical cystectomy, representing a major treatment escalation. Artificial intelligence–assisted computational histology (CHAI) approaches have shown promise in informing decision-making at this critical juncture.

Evidence from multicenter studies with prospective validation cohorts demonstrates the clinical utility of AI-based biomarkers in predicting BCG response (39). Moreover, CHAI-based analyses have been shown to identify biological differences in high-grade Ta NMIBC that are not captured by conventional risk stratification systems, thereby addressing an important gap in personalized treatment approaches (40).

4.5. Upper Urinary Tract Urothelial Carcinoma

Although relatively rare, upper urinary tract urothelial carcinoma (UTUC) is characterized by aggressive biological behavior, contributing to diagnostic and therapeutic uncertainty. Radiomics-based models have demonstrated promising performance in predicting tumor-related characteristics, and research activity in this area continues to expand (41).

5. Artificial Intelligence in Renal Cell Carcinoma

Renal cell carcinoma (RCC), accounting for approximately 90% of adult kidney tumors, is increasingly detected incidentally due to the widespread use of imaging modalities (18). Established prognostic tools such as SSIGN, Leibovich, and UCLA SANI provide moder-

ate predictive performance; however, they remain limited in their ability to guide adjuvant treatment decisions and to individualize follow-up strategies (42,43).

5.1. Recurrence and Survival Prediction

Radiomics-based models developed for predicting recurrence and survival in localized RCC demonstrate high predictive performance, particularly when integrated with clinical variables (44). Among these, UroPredict stands out due to the maturity of its evidence base, supported by multicenter prospective data. This model has been shown to significantly outperform established prognostic systems and offers clinically relevant advantages in selecting candidates for adjuvant therapy and tailoring follow-up protocols (45).

5.2. Digital Pathology and Histopathological Classification

Histopathological grading, which plays a central role in determining treatment strategies in RCC, is subject to interobserver variability, even among experienced pathologists. Convolutional neural network (CNN)–based deep learning models have demonstrated the ability to reduce this variability by achieving classification performance comparable to expert pathologists in digital pathology image analysis (46).

The transformative potential of digital pathology lies in its capacity to integrate molecular-level information with morphological features. However, current evidence suggests that models incorporating such multimodal integration have not yet reached sufficient maturity for routine clinical implementation (62).

5.3. Renal Function Prediction After Nephrectomy

In the surgical management of renal masses, balancing oncological control with preservation of renal function represents a key clinical challenge. Machine learning models developed to improve prediction of postoperative renal function have demonstrated superior performance compared to traditional equations such as CKD-EPI and MDRD (47).

6. Artificial Intelligence in Benign Urological Diseases

The main focus of urological AI literature is concentrated in oncological fields, and urolithiasis and BPH/LUTS, despite their comparable prevalence to oncological diseases in clinical practice, are significantly underrepresented in the literature (8).

6.1. Urolithiasis

Urolithiasis poses a serious burden on public health due to its high prevalence and tendency to recur (48). In the current literature, AI solutions are structured around the axes of stone detection, treatment outcome prediction, urosepsis prediction, and recurrence monitoring (49, 8).

In the field of urinary system stone diagnosis, deep learning models have achieved >97% accuracy rates in CUB radiographs; models trained on endoscopic videos have shown 88% accuracy in intraoperative stone composition prediction, allowing for intraoperative - instantaneous adjustment of holmium laser parameters used in stone crushing (69). In the field of stone detection, AI-supported CT imaging models can perform stone localization with high sensitivity (50). Multicenter prospective models evaluating stone-free success after ESWL (51) demonstrate how artificial intelligence can be reliably incorporated into clinical decision support processes. Intraoperative real-time guidance in endoscopic lithotripsy (52) and urosepsis risk prediction (53) constitute research focuses in this area.

6.2. Benign Prostatic Hyperplasia and Lower Urinary Tract Symptoms

Despite its clinical prevalence affecting more than half of the male population over 60 years of age (54,55), the need for personalized predictive models is increasing due to heterogeneous responses to treatment. In the diagnostic field, ML models that process uroflowmetry data offer a non-invasive urodynamic alternative by increasing AUROC values to 0.826 and 0.819, respectively, in differentiating bladder outlet obstruction (BOO) and detrusor underactivity (DU) (70). This can prevent unnecessary urodynamic studies.

ML models demonstrate performance that surpasses traditional clinical parameters in predicting treatment response in cases of refractory overactive bladder. In one study, an ML model predicted onabotulinum toxin A (OBTX-A) treatment response with an AUC of 0.95 and sacral neuromodulation (SNM) with an AUC of 0.88 in 386 women unresponsive to drug treatment, exceeding human expert predictions (56). Subsequent analyses confirmed that neural networks also outperformed expert performance in predicting subjective improvement on a patient-by-patient basis (71).

7. Explainability, Application, and Future Trends

7.1. Explainable AI in Clinical Practice

A fundamental barrier to the integration of artificial intelligence into clinical decision-making is the lack of trust arising from the “black box” nature of many models, which do not provide interpretable justification for their predictions (5,65). In this context, model transparency is no longer a technical preference but a prerequisite for clinical adoption.

When a model cannot explain the basis of a risk estimate, clinicians have a legitimate rationale to disregard its recommendation. Such opacity renders decisions difficult to justify both to patients and within the framework of professional accountability (65).

7.2. Methodological Limitations

From a methodological perspective, the urological AI literature demonstrates consistent deficiencies in key quality indicators. Reporting rates for external validation, calibration,

and decision curve analysis (DCA) remain strikingly low approximately 5%, 4%, and 6%, respectively suggesting that many models are published without adequate evaluation of their real-world clinical impact (63,64).

Additional limitations include predominantly monocentric study designs, small sample sizes, and a lack of external validation, all of which are well-documented across the literature (72). These structural shortcomings are consistent across prostate, bladder, and kidney cancer studies, the majority of which are characterized by retrospective designs, limited standardization, and restricted cohort sizes (19,36,44).

Evaluation of NMIBC studies using the APPRAISE-AI framework further highlights this issue, indicating that very few models have reached the level of methodological maturity required for integration into routine clinical workflows (36). In radiomics-based studies, the combination of high specificity with relatively lower sensitivity introduces a clinically relevant asymmetry, raising the risk of incorrectly excluding patients who may benefit from treatment (38). Similarly, STREAM-URO assessments have identified comparable methodological limitations in studies focusing on urolithiasis and BPH (8).

Data dependency and performance bias represent additional critical concerns. The frequent use of overlapping public datasets such as SEER and TCGA may create an artificial sense of robustness by generating methodologically interdependent findings (63). Furthermore, the predominance of data derived from high-volume academic centers in North America, Europe, and East Asia limits the global generalizability of these models (6).

Taken together, these observations underscore a fundamental paradox: while the majority of studies lack external validation, fail to report calibration, and do not achieve sufficient methodological maturity, structured evaluation frameworks remain essential. Rather than accelerating clinical adoption, these tools function as critical filters distinguishing robust, clinically meaningful studies from those with a high risk of bias. Their value lies not in promoting rapid implementation, but in preventing premature or misleading clinical integration.

7.3. Future Trends

7.3.1. Performance Paradox and Structural Inflection Point

The urological AI literature is approaching a critical inflection point in terms of technical maturity. Pooled AUC values of approximately 0.82 for biochemical recurrence prediction, 0.89 for extracapsular extension, and 0.94 for bladder muscle invasion detection suggest that performance gains from isolated models are nearing a plateau.

However, this technical maturity introduces a paradox: despite continuous improvements in model performance, the number of prospectively validated AI-based clinical decision support tools remains extremely limited, and few trials are designed to directly influence clinical practice (73). This divergence between technical advancement and stagnation in clinical evidence generation reflects a structural imbalance rather than a coincidental trend.

Academic incentive structures prioritize publication output, while journal policies often reward technical novelty. In contrast, prospective implementation studies requiring longer timelines and involving greater uncertainty are systematically deprioritized. Without addressing this structural constraint, the gap between technological innovation and patient-centered care will persist.

7.3.2 Multimodal Integration and the Digital Twin Paradigm

The apparent saturation in predictive performance of models based on isolated data sources highlights the need for multidimensional modeling paradigms in urology. The integration of clinical parameters with imaging, digital pathology, molecular imaging, and genomic profiles represents an emerging standard for improving diagnostic accuracy.

Digital twin models offer a promising paradigm by simulating organ behavior and predicting treatment responses through the integration of clinical, genomic, imaging, and histopathological data. Uro-oncology constitutes a particularly strong application domain for this approach (74,59).

A critical and underemphasized observation is that urological oncology possesses a structural advantage for digital twin implementation compared to other oncological subfields. PSA kinetics provide longitudinal biomarker data; mpMRI captures spatial tumor characteristics; prostate biopsy enables tissue-level molecular profiling; and genomic classifiers quantify biological aggressiveness. The routine and standardized availability of these complementary data layers is uncommon in other specialties. To fully leverage this infrastructure, the establishment of inter-institutional data standards and the development of federated learning frameworks are essential prerequisites.

7.3.3. Patient and Clinician Trust: An Empirical Framework for Design

The integration of AI into clinical practice is not solely a technical challenge but also a human-centered one. In a prospective study of 300 urology patients, participants demonstrated a preference for AI in tasks related to consultation time allocation, while expressing greater trust in physicians for critical clinical functions such as treatment recommendation and emotional support (75). Similarly, a global survey of 464 urology healthcare professionals from 47 countries showed that although 83.4% believed AI would enhance productivity, only 18.8% reported sufficient familiarity with AI technologies (76).

Taken together, these findings provide an empirical foundation for the design of future clinical decision support systems: patients tend to favor AI for efficiency and information delivery, whereas clinicians exhibit cautious acceptance constrained by limited operational knowledge. The division of roles between AI and human expertise can thus be defined on an evidence-based basis rather than intuition.

7.3.4 What the ArteraAI Exception Teaches Us

Although large language models demonstrate advanced academic capabilities, the generation of clinically meaningful outcomes from unstructured real-world data remains at an

early stage (60). ArteraAI's inclusion in NCCN guidelines is frequently cited as a landmark success in urological AI; however, its true significance lies in defining a benchmark rather than representing an isolated achievement.

This pathway included multiple Phase III randomized controlled trials, large-scale analysis involving 8,951 patients, independent multicenter validation, and eventual guideline integration. Only a very limited number of models in the current literature meet these criteria.

This observation raises a fundamental question: among the thousands of published models, how many are realistically capable of completing this pathway to clinical implementation? Future research agendas should therefore expand beyond improving model performance to identifying which models possess the necessary evidentiary and structural requirements for clinical translation

7.3.5. Geographic Representation and Local Calibration Requirements

Bibliometric analyses of artificial intelligence applications in urological tumor histopathology indicate that the United States dominates the field in terms of publication output, citation impact, and international collaboration, while structural inequalities persist despite increasing contributions from developing regions (78). This demographic concentration is not merely a methodological concern; it has direct implications for clinical validity.

Prostate cancer incidence, PSA screening practices, and Gleason grade distributions vary systematically across regions such as Turkey, the Middle East, and South Asia compared to North American cohorts. Models calibrated on North American datasets may achieve high discriminatory performance (e.g., AUC), yet fail to account for systematic calibration errors in these populations. As such, apparent predictive accuracy may obscure clinically relevant miscalibration.

Future research should therefore prioritize not only larger datasets, but also those that are geographically and ethnically representative, with explicit attention to local calibration and external validation across diverse populations.

7.3.6. The Role of Prospective Trial Design and Large Language Models

A fundamental methodological bottleneck in the field remains the lack of prospective randomized controlled trials designed to evaluate the real-world clinical impact of AI systems, rather than solely their technical performance (10). Randomized designs comparing AI-guided decision-making with standard care across key oncological outcomes such as recurrence and survival represent the highest level of evidence for establishing clinical utility.

Urology is uniquely positioned to lead in this domain, as exemplified by the ArteraAI pathway. Realizing this potential, however, requires a shift in priorities not only at the level of individual investigators but also among funding bodies and journal policies.

Large language models (LLMs) may serve a complementary role within this ecosystem. While radiomics- and pathology-based models generate predictions, LLMs can facil-

itate the interpretation and communication of these outputs in a manner that is accessible to both clinicians and patients. The future of urological AI is therefore likely to depend on a hybrid architecture in which LLMs function not as replacements for predictive models, but as integrative and communicative interfaces (77).

7.4. Conclusion

This review provides a critical synthesis of the current evidence on artificial intelligence–based predictive modeling and risk stratification in urology. Cumulative evidence from meta-analyses indicates that machine learning models in prostate, bladder, and kidney cancers consistently outperform traditional statistical approaches in terms of discriminatory performance.

However, statistical superiority alone does not equate to clinical utility. Models supported by high-level evidence, particularly those validated through randomized controlled trials and incorporated into clinical guidelines, such as ArteraAI, represent the highest level of methodological maturity and clinical relevance in the field. Future progress will depend not on incremental improvements in model performance, but on rigorous validation, transparency, and demonstrable clinical impact.

8. References

1. Bass, G., Gilani, S. N. S., Walsh, T. N., & Leader, F. (2013). Validating the 5Fs mnemonic for cholelithiasis: Time to include family history. Postgraduate Medical Journal, 89(1057), 638-641. https://doi.org/10.1136/postgradmedj-2012-131346
2. Kattan, M. W., Wheeler, T. M., & Scardino, P. T. (1999). Postoperative nomogram for disease recurrence after radical prostatectomy. Journal of Clinical Oncology, 17(5), 1499-1507. https://doi.org/10.1200/JCO.1999.17.5.1499
3. Cooperberg, M. R., Pasta, D. J., Elkin, E. P., Litwin, M. S., Latini, D. M., DuChane, J., & Carroll, P. R. (2005). The UCSF CAPRA score. Journal of Urology, 173(6), 1938-1942. https://doi.org/10.1097/01.ju.0000158155.33890.e7
4. LeCun, Y., Bengio, Y., & Hinton, G. (2015). Deep learning. Nature, 521(7553), 436-444. https://doi.org/10.1038/nature14539
5. Obermeyer, Z., & Emanuel, E. J. (2016). Predicting the future — big data, machine learning, and clinical medicine. New England Journal of Medicine, 375(13), 1216-1219. https://doi.org/10.1056/NEJMp1606181
6. Alderman, J. E., Palmer, J., Laws, E., et al. (2025). Tackling algorithmic bias and data justice: The STANDING Together consensus recommendations. Lancet Digital Health, 7(1), e64-e88. https://doi.org/10.1016/S2589-7500(24)00224-3
7. Roessler, N., Miszczyk, M., Miyajima, K., et al. (2025). Harnessing artificial intelligence for risk stratification and outcome prediction in urologic cancers: A comprehensive review. European Urology Focus. Advance online publication. https://doi.org/10.1016/j.euf.2025.12.007
8. Bouhadana, D., Lu, X. H., Luo, J. W., et al. (2023). Machine learning for urolithiasis and benign prostatic hyperplasia: A systematic review of the literature using the STREAM-URO framework. Journal of Endourology, 37(4), 474-494. https://doi.org/10.1089/end.2022.0311
9. Steyerberg, E. W. (2019). Clinical prediction models: A practical approach to development, validation, and updating (2nd ed.). Springer. https://doi.org/10.1007/978-3-030-16399-0
10. Collins, G. S., Reitsma, J. B., Altman, D. G., & Moons, K. G. (2015). Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): The TRIPOD statement. BMJ, 350, g7594. https://doi.org/10.1136/bmj.g7594
11. Sylvester, R. J., van der Meijden, A. P., Oosterlinck, W., et al. (2006). Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using EORTC risk tables. European Urology, 49(3), 466-477. https://doi.org/10.1016/j.eururo.2005.11.038
12. Lambin, P., Leijenaar, R. T. H., Deist, T. M., et al. (2012). Radiomics: Extracting more information from medical images using advanced feature analysis. European Journal of Cancer, 48(4), 441-446. https://doi.org/10.1016/j.ejca.2011.11.036
13. Kwong, J. C. C., Khondker, A., Lajkosz, K., et al. (2023). APPRAISE-AI tool for quantitative evaluation of AI studies for clinical decision support. JAMA Network Open, 6(9), e2335377. https://doi.org/10.1001/jamanetworkopen.2023.35377

14. Wolff, R. F., Moons, K. G. M., Riley, R. D., et al. (2019). PROBAST: A tool to assess the risk of bias and applicability of prediction model studies. Annals of Internal Medicine, 170(1), 51-58. https://doi.org/10.7326/M18-1376
15. Vickers, A. J., & Elkin, E. B. (2006). Decision curve analysis: A novel method for evaluating prediction models. Medical Decision Making, 26(6), 565-574. https://doi.org/10.1177/0272989X06295361
16. Lundberg, S. M., & Lee, S. I. (2017). A unified approach to interpreting model predictions. Advances in Neural Information Processing Systems, 30, 4765-4774. https://doi.org/10.48550/arXiv.1705.07874
17. Ribeiro, M. T., Singh, S., & Guestrin, C. (2016). Why should I trust you? Explaining the predictions of any classifier. Proceedings of the 22nd ACM SIGKDD International Conference on Knowledge Discovery and Data Mining, 1135-1144. https://doi.org/10.1145/2939672.2939778
18. Bray, F., Laversanne, M., Sung, H., et al. (2024). Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: A Cancer Journal for Clinicians, 74(3), 229-263. https://doi.org/10.3322/caac.21834
19. Ling, C., Tao, N., Maimaitiyimin, A., et al. (2025). Diagnostic systematic review and meta-analysis of machine learning in predicting biochemical recurrence of prostate cancer. Scientific Reports, 15, 28378. https://doi.org/10.1038/s41598-025-11445-5
20. Liu, J., Zhang, H., Woon, D., Perera, M., & Lawrentschuk, N. (2024). Predicting biochemical recurrence of prostate cancer post-prostatectomy using artificial intelligence: A systematic review. Cancers, 16(21), 3596. https://doi.org/10.3390/cancers16213596
21. Zhang, T., et al. (2025). Predicting biochemical recurrence after robot-assisted radical prostatectomy with interpretable machine learning. Journal of Clinical Medicine, 14(19), 7079. https://doi.org/10.3390/jcm14197079
22. Bergero, A., et al. (2025). Development and validation of an artificial intelligence model for predicting early biochemical recurrence of prostate cancer after robot-assisted radical prostatectomy. Scientific Reports. Advance online publication. https://doi.org/10.1038/s41598-025-16362-1
23. Wu, Y., et al. (2026). AI models integrating preoperative prostate MRI and clinical data for predicting extraprostatic extension: A systematic review and meta-analysis. Journal of Surgical Oncology. Advance online publication. https://doi.org/10.1002/jso.70167
24. Faiella, E., Vaccarino, F., Ragone, R., et al. (2023). Can machine learning models detect and predict lymph node involvement in prostate cancer? A comprehensive systematic review. Journal of Clinical Medicine, 12(22), 7032. https://doi.org/10.3390/jcm12227032
25. Liu, Y., Yang, X., & Guan, Z. (2026). Radiomics-based machine learning models for predicting lymph node metastasis in prostate cancer: A systematic review and meta-analysis. Frontiers in Oncology. Advance online publication. https://doi.org/10.3389/fonc.2026.1710716
26. Denijs, F. B., Nieuweboer, J., Roobol, M. J., et al. (2024). Risk calculators for the detection of prostate cancer: A systematic review. Prostate Cancer and Prostatic Diseases. https://doi.org/10.1038/s41391-024-00852-w
27. Bazarkin, A. K., et al. (2023). Assessment of prostate and bladder cancer genomic biomarkers using artificial intelligence: A systematic review. Current Urology Reports. Advance online publication. https://doi.org/10.1007/s11934-023-01193-2
28. Van Hees, J. E., et al. (2026). AI-based prediction of actionable molecular aberrations in prostate cancer using digital histopathology images: A systematic review. Critical Reviews in Oncology/Hematology. Advance online publication. https://doi.org/10.1016/j.critrevonc.2025.105011
29. Liu, Y., et al. (2024). Artificial intelligence evaluating PSMA PET/CT for intraprostatic tumor detection: A systematic review. BJU International. Advance online publication. https://doi.org/10.1111/bju.16412
30. Piras, A., et al. (2024). AI and statistical models for radiotherapy toxicity prediction in prostate cancer: A systematic review. Applied Sciences, 14(23), 10947. https://doi.org/10.3390/app142310947
31. Naderian, S., et al. (2025). AI-based clinical decision support systems in prostate cancer: A systematic review. Health Technology Letters. Advance online publication. https://doi.org/10.1049/htl2.70026
32. Babjuk, M., Burger, M., Capoun, O., et al. (2022). European Association of Urology guidelines on non-muscle-invasive bladder cancer (TaT1 and carcinoma in situ) 2022 update. European Urology, 81(1), 75-94. https://doi.org/10.1016/j.eururo.2021.08.010
33. Abbas, S., et al. (2025). Artificial intelligence predicting recurrence in non-muscle invasive bladder cancer: A systematic review with study quality appraisal. Frontiers in Oncology, 14, 1509362. https://doi.org/10.3389/fonc.2024.1509362
34. Panebianco, V., Narumi, Y., Altun, E., et al. (2018). Multiparametric magnetic resonance imaging for bladder cancer: Development of VI-RADS (Vesical Imaging-Reporting and Data System). European Urology, 74(3), 294-306. https://doi.org/10.1016/j.eururo.2018.02.027
35. Wang, X., Shi, Y., Wang, H., et al. (2025). AI-driven and traditional radiomic model for predicting muscle invasion in bladder cancer: A systematic review and meta-analysis. Academic Radiology. Advance online publication. https://doi.org/10.1016/j.acra.2025.08.035
36. Kwong, J. C. C., et al. (2024). Predicting non-muscle invasive bladder cancer outcomes using artificial intelligence: A systematic review. npj Digital Medicine, 7, 88. https://doi.org/10.1038/s41746-024-01088-7
37. Liu, Y. S., et al. (2023). Machine learning to predict bladder cancer survival outcomes: A systematic review. Expert Review of Pharmacoeconomics & Outcomes Research, 23(8), 851-859. https://doi.org/10.1080/14737167.2023.2237328

38. Suartz, C. V., Martinez, L. M., Cordeiro, M. D., et al. (2024). Artificial intelligence for predicting neoadjuvant chemotherapy response for muscle-invasive bladder cancer: A systematic review and meta-analysis. Canadian Urological Association Journal, 18(9), E276-E284. https://doi.org/10.5489/cuaj.8681
39. Lotan, Y., Krishna, V., Abuzeid, W. M., et al. (2025). Predicting BCG response in high-risk non-muscle invasive bladder cancer using an AI-powered pathology-based tissue assay. Journal of Urology, 213(2), 192-204. https://doi.org/10.1097/JU.0000000000003785
40. Chang, S. S., Launer, B., Narayan, V., et al. (2025). Computational histology artificial intelligence (CHAI) for risk stratification of high-grade Ta non-muscle-invasive bladder cancer. European Urology, 88(4), 411-413. https://doi.org/10.1016/j.eururo.2025.01.003
41. Bruinsma, A. J., et al. (2026). Diagnostic performance of radiomics for upper tract urothelial carcinoma: A systematic review. World Journal of Urology. Advance online publication. https://doi.org/10.1007/s00345-026-06191-w
42. Ljungberg, B., Albiges, L., Abu-Ghanem, Y., et al. (2022). European Association of Urology guidelines on renal cell carcinoma: The 2022 update. European Urology, 82(4), 399-410. https://doi.org/10.1016/j.eururo.2022.07.007
43. Frank, I., Blute, M. L., Cheville, J. C., et al. (2002). An outcome prediction model for patients with clear cell renal cell carcinoma treated with radical nephrectomy based on tumor stage, size, grade and necrosis: The SSIGN score. Journal of Urology, 168(6), 2395-2400. https://doi.org/10.1016/S0022-5347(02)80057-1
44. Mjaess, G., Diamand, R., Dikete, M., et al. (2026). Radiomics and image-based artificial intelligence for predicting recurrence in patients with localized renal cell carcinoma: A systematic review appraised with APPRAISE-AI. European Urology Focus. Advance online publication. https://doi.org/10.1016/j.euf.2025.12.017
45. Margue, G., Ferrer, L., Etchepare, G., et al. (2024). UroPredict: Machine learning model for prediction of kidney cancer recurrence based on the French national kidney cancer research network (UroCCR-120). npj Precision Oncology, 8, 104. https://doi.org/10.1038/s41698-024-00597-8
46. Li, M. Y., et al. (2025). Digital pathology and artificial intelligence in renal cell carcinoma: A systematic review. Frontiers in Oncology. Advance online publication. https://doi.org/10.3389/fonc.2025.1516264
47. Javid, S., et al. (2025). Artificial intelligence in predicting renal function decline after nephrectomy in renal cell carcinoma: A PROBAST-guided systematic review and meta-analysis. International Urology and Nephrology. Advance online publication. https://doi.org/10.1007/s11255-025-04467-5
48. Scales, C. D., Jr., Smith, A. C., Hanley, J. M., et al. (2012). Prevalence of kidney stones in the United States. European Urology, 62(1), 160-165. https://doi.org/10.1016/j.eururo.2012.01.011
49. Hameed, B. M. Z., Shah, M., Naik, N., et al. (2021). The ascent of artificial intelligence in endourology: A systematic review over the last 2 decades. Current Urology Reports, 22(10), 53. https://doi.org/10.1007/s11934-021-01033-3
50. Panthier, F., Melchionna, A., Crawford-Smith, H., et al. (2024). Can artificial intelligence accurately detect urinary stones on CT and KUB? A systematic review and meta-analysis. Journal of Endourology, 38(8), 725-740. https://doi.org/10.1089/end.2023.0407
51. Talyshinskii, A.E., Juliebo-Jones, PTzelves,L, et al. (2025). Current state of artificial intelligence application for shockwave lithotripsy: A systematic review from YAU and EAU endourology. World Journal of Urology. https://doi.org/10.1007/s00345-025-05830-y
52. Morozov, A., et al. (2025). Intraoperative use of artificial intelligence during endoscopic lithotripsy: A systematic review of current evidence. World Journal of Urology. Advance online publication. https://doi.org/10.1007/s00345-025-06031-3
53. Alves, B. M., Belkovsky, M., Passerotti, C. C., et al. (2023). Artificial intelligence for sepsis risk prediction after flexible ureteroscopy: A systematic review. Revista do Colegio Brasileiro de Cirurgioes, 50, e20233561. https://doi.org/10.1590/0100-6991e-20233561
54. Irwin, D. E., Milsom, I., Hunskaar, S., et al. (2006). Population-based survey of urinary incontinence, overactive bladder, and other lower urinary tract symptoms in five countries: Results of the EPIC study. European Urology, 50(6), 1306-1315. https://doi.org/10.1016/j.eururo.2006.02.006
55. Salem, H. A., et al. (2021). A systematic review of the applications of Expert Expert systems and machine learning in clinical urology. BMC Medical Informatics and Decision Making, 2021; 21(1), 223. https://doi.org/10.1186/s12911-021-01585-9
56. Werneburg, G. T., Werneburg, E. A., Goldman, H. B., Mullhaupt, A. P., & Vasavada, S. P. (2022). Machine learning provides an accurate prognostication model for refractory overactive bladder treatment response and is noninferior to human experts. Neurourology and Urodynamics, 41(3), 813-819. https://doi.org/10.1002/nau.24860
57. Fan, B., Zhang, L., Cui, H., et al. (2025). Development and validation of a machine learning-based model to predict urethral recurrence following radical cystectomy: A multicentre retrospective study and updated meta-analysis. Scientific Reports, 15(1), 19573. https://doi.org/10.1038/s41598-025-04893-6
58. Frewing, I. M., Gibson, A. B., Robertson, R., Urie, P. M., & Della Corte, D. (2024). Don't fear the artificial intelligence: A systematic review of machine learning for prostate cancer detection in pathology. Archives of Pathology & Laboratory Medicine, 148(5), 603-612. https://doi.org/10.5858/arpa.2022-0427-RA
59. John, A., et al. (2025). A systematic review of AI as a digital twin for prostate cancer care Computer Methods and Programs in Biomedicine. https://doi.org/10.1016/j.cmpb.2025.108804
60. Yudovich, M. S., Makarova, E., Hague, C. M., & Raman, J. D. (2024). Performance of GPT-3.5 and GPT-4 on urology in-service knowledge assessment. Journal of Educational Evaluation for Health Professions, 21, 17. https://doi.org/10.3352/jeehp.2024.21.17

61. Zamboglou, C., et al. (2025). oDigital pathology biomarkers for guiding radiotherapy-based treatment concepts in prostate cancer - A systematic review and expert concensus. Radiotherapy and Oncology: journal of the European Society for Therapeutic Radiology and Oncology,210,111039. https://doi.org/10.1016/j.radonc.2025.111039
62. Khene, Z. E., et al. (2024). Clinical application of digital and computational pathology in renal cell carcinoma: A systematic review. European Urology Oncology, 7(3), 401-411. https://doi.org/10.1016/j.euo.2023.10.018
63. Yang, C., Kors, J. A., Ioannou, S., et al. (2022). Trends in the conduct and reporting of clinical prediction model development and validation: A systematic review. Journal of the American Medical Informatics Association, 29(5), 983-989. https://doi.org/10.1093/jamia/ocac002
64. Dhiman, P., Ma, J., Andaur Navarro, C. L., et al. (2022). Methodological conduct of prognostic prediction models developed using machine learning in oncology: A systematic review. BMC Medical Research Methodology, 22(1), 101. https://doi.org/10.1186/s12874-022-01577-x
65. Ghassemi, M., Oakden-Rayner, L., & Beam, A. L. (2021). The false hope of current approaches to explainable artificial intelligence in health care. Lancet Digital Health, 3(11), e745-e750. https://doi.org/10.1016/S2589-7500(21)00208-9
66. Tilki, D., Cornford, P., van den Bergh, R. C. N., et al. (2024). EAU-EANM-ESTRO-ESUR-ISUP-SIOG guidelines on prostate cancer. Part II — 2024 update: Treatment of relapsing and metastatic prostate cancer. European Urology, 86(2), 164-182. https://doi.org/10.1016/j.eururo.2024.04.010
67. Cornford, P., van den Bergh, R. C. N., Briers, E., et al. (2024). EAU-EANM-ESTRO-ESUR-ISUP-SIOG guidelines on prostate cancer — 2024 update. Part I: Screening, diagnosis, and local treatment with curative intent. European Urology, 86(2), 148-163. https://doi.org/10.1016/j.eururo.2024.03.027
68. Nagpal, K., et al. (2019). Development and validation of a deep learning algorithm for improving Gleason scoring of prostate cancer. npj Digital Medicine, 2(1), 48. https://doi.org/10.1038/s41746-019-0112-2
69. Altunhan, A., et al. (2024). Artificial intelligence in urolithiasis: A systematic review of utilization and effectiveness. World Journal of Urology, 42(1), 579. https://doi.org/10.1007/s00345-024-05268-8
70. Bang, S., et al. (2022). Feasibility of a deep learning-based diagnostic platform to evaluate lower urinary tract disorders in men using simple uroflowmetry. Investigative and Clinical Urology, 63(3), 301-308. https://doi.org/10.4111/icu.20210434
71. Werneburg, G. T., et al. (2023). Neural networks outperform expert humans in predicting patient impressions of symptomatic improvement following overactive bladder treatment. International Urogynecology Journal, 34, 1009-1016. https://doi.org/10.1007/s00192-022-05376-4
72. Gallo, M. L., Moriconi, M., & Phé, V. (2025). Current applications and future perspectives of artificial intelligence in functional urology and neurourology. Minerva Urology and Nephrology, 77(1), 33-42. https://doi.org/10.23736/S2724-6051.25.06195-6
73. Ippolito, G. M., Krumm, A., & Singh, K. (2024, January). Artificial intelligence-based decision support: What's possible in urology now? AUA News.
74. Görtz, M., Brandl, C., Nitschke, A., Riediger, A., Stromer, D., Byczkowski, M., . . . Weidemüller, M. (2026). Digital twins for personalized treatment in uro-oncology in the era of artificial intelligence. Nature Reviews Urology, 23(1), 29–39. https://doi.org/10.1038/s41585-025-01096-6
75. Carl, N., Nguyen, L., Haggenmüller, S., Hetz, M. J., Winterstein, J. T., Hartung, F. O., . . . Brinker, T. J. (2024). Comparing patient's confidence in clinical capabilities in urology: Large language models versus urologists. European Urology Open Science, 70, 91-98. https://doi.org/10.1016/j.euros.2024.10.009
76. Ho, Y. T., Dhalas, R. R., Zohair, M., Deb, S., Shoaib, M., Elmer, S., . . . Teoh, J. Y. C. (2025). Artificial intelligence in urology — a survey of urology healthcare providers. Société Internationale d'Urologie Journal, 6(4), 53. https://doi.org/10.3390/siuj6040053
77. Solano, C., Tarazona, N., Gauhar, V., Pauchard, F., Corrales, M., Sierra Del Rio, A., . . . Traxer, O. (2025). Integration of generative artificial intelligence into urological practice: A cross-sectional survey analysis from the EAU endourology. Journal of Endourology, 39(10), 1085–1091. https://doi.org/10.1177/08927790251379460
78. Dai, F., He, Y., Duan, J., Lin, K., Lv, Q., Zhao, Z., . . . Qiu, X. (2025). Global trends in the use of artificial intelligence for urological tumor histopathology: A 20-year bibliometric analysis. Digital Health, 11, 20552076251348834. https://doi.org/10.1177/20552076251348834

CHAPTER 19

Artificial Intelligence–Based Decision Support Systems and Automated Image Analysis in Endovascular Surgery

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1. Introduction

Over the past three decades, endovascular surgery has undergone a profound transformation, evolving from a limited set of catheter-based interventions into a central component of contemporary vascular medicine. Initially confined to relatively simple procedures such as balloon angioplasty, the field now encompasses complex aortic repair, peripheral revascularization, and cerebrovascular interventions. This evolution reflects rapid technological advancements and, importantly, parallels a broader shift toward minimally invasive, patient-centered therapeutic strategies (1). With an aging population and the increasing prevalence of atherosclerotic disease, endovascular techniques have become integral to modern practice, as they are generally associated with reduced perioperative morbidity, shorter hospital stays, and improved recovery compared with open surgical approaches (2).

Despite these advantages, the expanding scope of endovascular interventions has introduced substantial procedural complexity. Contemporary practice relies heavily on advanced imaging modalities, including computed tomography angiography (CTA), digital subtraction angiography (DSA), and intravascular imaging techniques such as intravascular ultrasound (IVUS) and optical coherence tomography (OCT) (3). These modalities provide critical anatomical and morphological information essential for procedural planning and execution. However, their interpretation often requires the integration of large volumes of multidimensional data, frequently in real time and under significant time constraints. Moreover, even subtle variations in vessel geometry, plaque composition, and lesion characteristics may have a considerable impact on procedural strategy and clinical outcomes (4).

Endovascular interventions are also associated with a non-negligible risk of complications, particularly in anatomically complex scenarios. These include vessel dissection, perforation, distal embolization, and access-related injuries, which remain clinically relevant even in experienced hands (5). The likelihood of such complications may increase in the presence of severe calcification, long-segment occlusions, and marked vascular tortuosity (6). Importantly, many of these adverse events are closely linked to intra-procedural decision-making and the accurate interpretation of imaging data (7). Consequently, variability in operator experience and judgment may contribute to heterogeneous outcomes, underscoring the inherent limitations of experience-based decision-making in complex interventions (7).

In this context, the emergence of artificial intelligence (AI) in healthcare appears both timely and potentially transformative. Over the past decade, AI, particularly through machine learning and deep learning approaches has demonstrated the capacity to process large-scale medical datasets, identify complex patterns, and generate predictive insights (8). In imaging-intensive fields such as radiology and cardiology, AI systems have demonstrated performance comparable to expert-level interpretation in selected tasks (9). Given the imaging-dependent nature of endovascular surgery, these advances are highly relevant to vascular practice (10).

Deep learning algorithms have shown considerable promise in tasks such as vessel segmentation, stenosis quantification, and plaque characterization, enabling rapid and reproducible anatomical assessment (9). These approaches may reduce interobserver variability and facilitate standardization in pre-procedural planning, particularly in anatomically complex cases. Furthermore, AI-based platforms are increasingly capable of generating three-dimensional reconstructions and patient-specific models, which may support procedural simulation and device selection (11).

AI-based decision support systems (DSS) are also being developed to augment clinical decision-making in endovascular surgery. By integrating imaging data with clinical and procedural variables, these systems may provide individualized risk assessments, suggest optimal strategies, and anticipate potential complications. Importantly, such systems are intended to complement rather than replace clinician judgment by offering objective, data-driven insights (12). Their potential value is particularly evident in high-stakes clinical environments, where timely and accurate decision-making is critical for optimal patient outcomes (10).

Nevertheless, AI remains in a relatively early phase of adoption within endovascular surgery and is associated with several important challenges. Issues related to data quality, model generalizability, and algorithmic bias continue to limit widespread clinical implementation (13). In addition, the limited interpretability of many deep learning models, the so-called "black box" problem raises concerns regarding transparency, accountability, and clinical trust (13). Legal and regulatory uncertainties surrounding responsibility in AI-assisted decision-making further complicate integration into routine practice (14).

Given these considerations, a comprehensive and practically oriented understanding of AI in endovascular surgery is essential. This chapter provides a structured overview of AI–based decision support systems and automated image analysis within endovascular care. It addresses foundational concepts, current applications in planning and imag-

ing, and practical aspects of clinical integration, while also highlighting key limitations, validation requirements, and future directions, with the aim of presenting a balanced and clinically relevant perspective.

2. Fundamentals of AI in Medicine

2.1. Key Concepts

AI in medicine refers to a broad set of computational approaches designed to extract meaningful patterns from complex, often high-dimensional clinical data. Within this framework, machine learning (ML) represents a core methodological paradigm, enabling algorithms to learn from data without explicit rule-based programming. Unlike traditional deterministic systems, ML models iteratively improve their performance as they are exposed to increasingly diverse and representative datasets, making them particularly well-suited to data-rich environments such as contemporary healthcare (15).

Deep learning (DL), a more advanced subset of ML, is based on multilayered neural network architectures capable of modeling highly nonlinear relationships within data. These architectures, loosely inspired by the structure of the human brain, consist of interconnected layers of artificial neurons that progressively transform input data into more abstract and informative representations. In the context of medical imaging, deep learning has demonstrated the ability to detect subtle features that may not be readily apparent to human observers, thereby enabling high-performance image interpretation in selected applications (16).

Among these architectures, convolutional neural networks (CNNs) form the backbone of most contemporary image analysis systems. CNNs are specifically designed to process grid-like data structures, such as medical images, and have demonstrated strong performance in tasks including feature extraction, segmentation, and classification. In endovascular surgery, these capabilities are directly applicable to clinically relevant tasks such as vessel segmentation, lesion detection, and three-dimensional anatomical reconstruction (17).

Computer vision, a subfield of AI, focuses on enabling machines to interpret and analyze visual information. Its relevance is particularly pronounced in imaging-driven specialties. By integrating deep learning algorithms with large, annotated datasets, computer vision systems are increasingly capable of analyzing both radiological and intraprocedural imaging data with a level of accuracy that may approach expert interpretation in specific contexts. This capability is especially valuable in endovascular interventions, where precise visualization of vascular anatomy and pathology is critical for procedural planning and execution (18).

2.2. Learning Paradigms

Machine learning approaches are commonly categorized based on how algorithms learn from data. The most widely used paradigm in medical applications is supervised learn-

ing, in which models are trained on labeled datasets. In this setting, input data, such as imaging studies, are paired with known outputs, including diagnostic labels or procedural outcomes. Supervised learning is particularly well-suited for tasks such as lesion classification, stenosis grading, and outcome prediction, especially when high-quality annotated datasets are available (15).

In contrast, unsupervised learning operates on unlabeled data and aims to identify underlying structures or patterns without predefined outputs. Techniques such as clustering and dimensionality reduction may reveal previously unrecognized phenotypes or anatomical patterns, which could have implications for risk stratification and personalized treatment planning. Although less frequently implemented in routine clinical workflows, these approaches may provide novel insights when applied to complex vascular datasets (18).

Reinforcement learning represents a distinct and more specialized paradigm, in which algorithms learn optimal decision-making strategies through iterative interaction with an environment. In this framework, the model receives feedback in the form of rewards or penalties and progressively refines its actions to maximize long-term outcomes. While still largely experimental in clinical medicine, reinforcement learning holds potential for procedural planning and real-time decision support, particularly in dynamic, high-stakes environments such as endovascular interventions (19).

2.3. Data Types in Endovascular Surgery

Endovascular surgery is inherently imaging-driven, and the diversity of data modalities presents both significant opportunities and challenges for AI integration. Pre-procedural imaging, most commonly derived from computed tomography angiography (CTA) and magnetic resonance angiography (MRA) provides high-resolution, three-dimensional representations of vascular anatomy. These modalities are essential for evaluating lesion morphology, vessel diameter, and overall anatomical suitability for intervention (3).

Intra-procedural imaging, particularly digital subtraction angiography (DSA), plays a central role in real-time procedural guidance. DSA enables dynamic visualization of blood flow and device deployment, facilitating continuous assessment of procedural progress. However, it also generates substantial volumes of data that must be interpreted rapidly under time-constrained conditions (20). In addition, intravascular imaging modalities such as intravascular ultrasound (IVUS) and optical coherence tomography (OCT) provide high-resolution cross-sectional visualization of the vessel wall and plaque morphology. These techniques can reveal features not readily apparent on angiography, including calcium distribution, plaque burden, and vessel architecture (21).

The integration of these heterogeneous data sources, ranging from macroscopic anatomical imaging to high-resolution intravascular detail creates a complex and multidimensional data environment. This environment appears particularly well-suited for AI-based analysis. By synthesizing information across modalities, AI systems may provide a more comprehensive and quantitative characterization of vascular pathology, thereby supporting more precise and individualized endovascular interventions (10).

3. AI-Based Decision Support Systems (DSS) in Endovascular Surgery

Endovascular interventions increasingly rely on complex, multilevel decision-making processes that integrate anatomical, clinical, and procedural variables. In this context, AI–based decision support systems (DSS) have emerged as advanced analytical tools designed to augment rather than replace clinician judgment (22). These systems are capable of transforming large volumes of heterogeneous data into clinically actionable insights, thereby supporting treatment selection, outcome prediction, and the reduction of unwarranted variability in clinical practice (23).

Conceptually, a DSS in endovascular surgery functions as an integrative analytical framework that combines imaging-derived parameters with patient-specific clinical data. In contrast to traditional rule-based approaches, contemporary AI-based DSS leverage machine learning algorithms to identify complex, and often non-linear, relationships that may not be readily apparent through conventional analysis (22). This capability is particularly relevant in endovascular interventions, where even subtle variations in lesion morphology, vessel geometry, and patient comorbidities may substantially influence procedural strategy, technical success, and long-term outcomes (24).

From a clinical perspective, the value of DSS becomes most evident in scenarios characterized by high anatomical complexity or decision uncertainty. For example, in patients with heavily calcified lesions, long-segment occlusions, or hostile vascular anatomy, the integration of imaging-derived features with clinical risk profiles may help refine strategy selection, guide device choice, and anticipate procedural challenges. In this regard, DSS can be viewed not merely as predictive tools, but as systems that support structured, data-informed clinical reasoning. This integrative role across the endovascular workflow is illustrated in Figure 1.

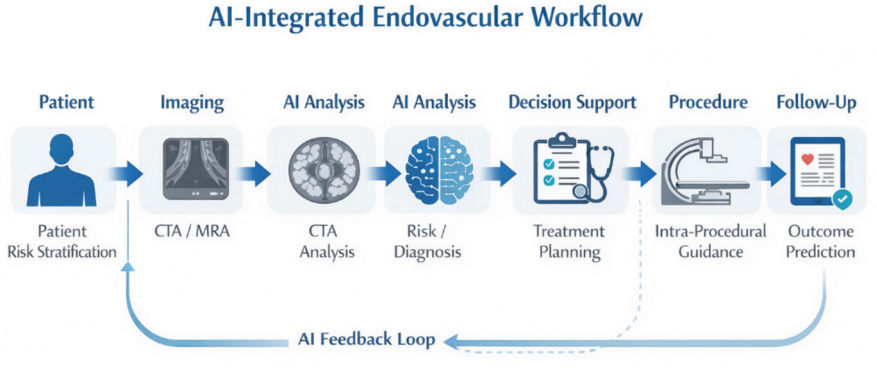


Figure 1. AI-Integrated Endovascular Workflow

Schematic representation of the integration of artificial intelligence (AI) across the endovascular workflow, including patient selection, imaging acquisition, AI-based analysis, decision support, intra-procedural guidance, and post-procedural follow-up. The figure illustrates how AI systems integrate imaging and clinical data to support risk stratification, treatment planning, and outcome prediction. A continuous feedback loop highlights the role of longitudinal data integration and iterative model refinement, reflecting the concept of a learning health system. (AI, artificial intelligence; CTA, computed tomography angiography; MRA, magnetic resonance angiography.)

3.1. Definition and Clinical Role

A decision support system (DSS) may be defined as a computational framework designed to assist clinicians in complex decision-making processes through the integration of data, evidence, and predictive modeling. In endovascular practice, DSS platforms are increasingly applied across multiple stages of care, including pre-procedural planning, intra-procedural guidance, and post-procedural evaluation. Their primary function is to enhance consistency, reduce cognitive burden, and support evidence-informed decision-making in complex, time-sensitive clinical environments (22).

From a clinical standpoint, DSS platforms appear particularly valuable in scenarios characterized by uncertainty or high variability. For instance, determining the optimal revascularization strategy in peripheral arterial disease or selecting an appropriate endovascular approach for complex aortic pathology often requires the integration of multiple interacting variables. In such contexts, DSS may provide quantitative risk estimates and structured recommendations, thereby supporting more consistent and reproducible decision-making while preserving clinician autonomy (13).

Conceptually, AI-based DSS extend beyond traditional rule-based systems by leveraging large-scale datasets to identify complex and often non-linear relationships between variables. This capability enables the transformation of heterogeneous clinical and imaging data into clinically actionable insights that may inform therapeutic strategy and procedural planning (24).

3.2. Pre-procedural Planning

Pre-procedural planning represents one of the most established and clinically relevant applications of AI-based DSS in endovascular surgery. During this phase, DSS platforms integrate imaging-derived parameters such as lesion length, degree of stenosis, vessel diameter, and anatomical complexity with patient-specific clinical variables, including age, comorbidities, and prior interventions. This multidimensional integration facilitates a more comprehensive assessment of procedural feasibility and may support the selection of the most appropriate endovascular strategy (23).

A key contribution of DSS in this setting is risk stratification. Machine learning models have demonstrated the potential to predict procedural success, peri-procedural complications, and early restenosis by leveraging large-scale clinical and imaging datasets.

These predictive outputs may provide quantitative risk estimates that assist clinicians in balancing procedural risks and expected benefits, particularly in high-risk or anatomically complex patients (25).

Beyond risk prediction, AI-based DSS are increasingly being explored for patient-specific procedural planning. By incorporating anatomical and, in some cases, hemodynamic data, these systems may support device selection and strategy optimization. This approach may be particularly relevant in complex scenarios such as endovascular aneurysm repair or multilevel peripheral arterial disease, where precise anatomical matching and strategic planning are critical for procedural success and long-term durability (26).

3.3. Intra-procedural Guidance

Intra-procedural guidance represents a more advanced and evolving application of AI-based DSS in endovascular surgery. Unlike pre-procedural planning, which occurs in a relatively controlled environment, intra-procedural decision-making takes place under dynamic conditions characterized by time constraints, incomplete information, and evolving anatomical and technical factors (24). In this setting, DSS platforms may provide real-time or near-real-time analytical support that complements intra-procedural imaging and operator expertise (27).

During interventions, AI-based DSS may assist with device selection, positioning, and deployment strategies by integrating pre-procedural imaging with intra-procedural findings. This capability is particularly relevant when discrepancies arise between pre-operative planning and intraoperative anatomy. For example, due to vessel deformation, unexpected tortuosity, or suboptimal landing zones necessitating rapid adjustments in procedural strategy (28,29). In addition, AI-based systems are being investigated for the early detection of intra-procedural complications. By continuously analyzing imaging and procedural data streams, these systems may identify patterns suggestive of adverse events such as vessel dissection, perforation, or distal embolization. Although largely investigational at present, such applications highlight the potential role of DSS in enhancing procedural safety by providing an additional layer of real-time situational awareness (29).

Another emerging application involves the integration of DSS with advanced imaging guidance techniques, including image fusion and augmented visualization. These approaches enable the alignment of pre-procedural three-dimensional datasets with live fluoroscopic imaging, thereby improving navigation and spatial orientation during complex interventions. When combined with AI-based analysis, such systems may reduce operator dependency and improve procedural efficiency (30).

3.4. Post-procedural Evaluation

Post-procedural evaluation constitutes a critical phase in endovascular care, during which clinical outcomes are assessed and future management strategies are determined. In this context, AI-based DSS are primarily focused on outcome prediction and longitudinal risk assessment (13). By integrating procedural data, imaging findings, and clinical variables,

these systems may generate individualized risk profiles that help predict adverse events such as restenosis, thrombosis, or the need for reintervention (31).

A notable advantage of AI-based DSS in this phase lies in their ability to capture complex, non-linear relationships between variables that may not be adequately addressed by conventional statistical methods (24). This capability may translate into more accurate predictions of medium- and long-term outcomes, particularly in heterogeneous patient populations with diverse anatomical and clinical characteristics (25).

Beyond risk prediction, DSS platforms may also contribute to the optimization of follow-up strategies. Rather than applying uniform surveillance protocols, AI-based approaches may enable risk-adapted follow-up, ensuring that high-risk patients receive closer monitoring and earlier intervention when necessary (22). In addition, post-procedural DSS applications may support quality improvement initiatives by analyzing large-scale, multicenter datasets to identify patterns associated with suboptimal outcomes. These insights, related to device performance, procedural techniques, or patient selection, may inform evidence-based refinements in clinical practice and contribute to continuous improvement in endovascular care (13).

4. AI-Based Image Analysis in Endovascular Surgery

Endovascular surgery is inherently imaging-driven, positioning it as a particularly relevant domain for the clinical application of AI-based image analysis (24). Traditionally, the evaluation of vascular anatomy, lesion characterization, and procedural planning have relied heavily on operator expertise and subjective interpretation of imaging data. However, the increasing adoption of high-resolution and intravascular imaging modalities has markedly expanded both the volume and complexity of available data. In this context, deep learning–based approaches have demonstrated the potential to enable more objective, reproducible, and quantitatively driven image analysis. Consequently, automated analytical tools may play an increasingly important role in efficiently processing multidimensional imaging data and supporting clinical decision-making (16).

4.1. Automated Vessel Segmentation

Accurate vessel segmentation is fundamental to both diagnosis and procedural planning in endovascular practice. Manual segmentation is time-consuming and subject to inter-observer variability, limiting its scalability in routine clinical workflows. Convolutional neural networks (CNNs), particularly U-Net–based architectures, have emerged as the dominant approach for automated vessel segmentation (17,32).

These models have demonstrated high performance in delineating vascular lumens across multiple imaging modalities, including CTA and MRA, even in anatomically complex regions (33). A key clinical application of automated segmentation is the rapid generation of three-dimensional vascular reconstructions. These reconstructions enable detailed anatomical assessment, including aneurysm morphology, neck configuration,

and landing zone evaluation, all of which are critical for device selection and procedural planning.

From a practical standpoint, segmentation performance may be reduced in challenging scenarios such as heavy calcification, motion artifacts, or suboptimal contrast opacification (34). These limitations are particularly relevant in endovascular cases involving heavily diseased vessels, where accurate lumen delineation directly impacts procedural strategy.

4.2. Lesion Detection and Characterization

Automated lesion detection and characterization represent core applications of AI in endovascular imaging. Deep learning models have demonstrated increasing capability in identifying stenotic segments, quantifying lesion severity, and analyzing plaque composition (35). These functions are clinically significant, as accurate lesion assessment directly informs decisions regarding intervention strategy, device selection, and procedural risk (18).

Intravascular imaging modalities such as IVUS and OCT provide high-resolution characterization of vessel wall architecture and plaque morphology. AI-based systems may enable detailed analysis of these datasets, allowing differentiation between calcified, fibrotic, and lipid-rich plaques at near-microscopic resolution (36). This level of characterization may be particularly valuable in complex or borderline lesions, where plaque composition can influence decisions such as the need for lesion preparation (e.g., atherectomy or lithotripsy) and stent selection.

4.3. 3D Reconstruction and Procedural Planning

AI-based three-dimensional reconstruction is increasingly shaping pre-procedural planning in endovascular interventions. Deep learning–based methods can generate accurate 3D vascular models significantly faster than traditional manual or semi-automated techniques. These models provide a comprehensive representation of vascular anatomy, including tortuosity, branch involvement, and anatomical variants (37).

Recent developments have extended these capabilities beyond static reconstruction toward patient-specific simulation environments. By integrating anatomical imaging with computational modeling, AI-based systems may predict device behavior within individualized vascular geometries (38). This approach is particularly relevant in complex interventions, such as aortic aneurysm repair or multilevel peripheral arterial disease, where precise anatomical matching and procedural planning are critical determinants of technical success and long-term durability.

4.4. Real-Time Image Guidance and Intra-procedural Support

Real-time image analysis represents one of the most promising, yet technically demanding, applications of AI in endovascular surgery. The ability to process angiographic data

during procedures and provide immediate feedback may enhance both procedural safety and efficiency. Emerging systems are capable of tracking device position, automatically identifying vascular structures, and detecting early signs of complications such as vessel dissection or perforation (37). These capabilities may support intra-procedural decision-making by improving situational awareness and reducing reliance on subjective interpretation alone.

The integration of pre-procedural three-dimensional imaging with live fluoroscopy, commonly referred to as image fusion represents a significant advancement in procedural guidance (39). This approach may improve navigation, enhance spatial orientation, and potentially reduce contrast usage, radiation exposure, and overall procedure time. However, real-time AI applications require robust performance under variable imaging conditions, and challenges related to latency, accuracy, and generalizability remain important barriers to routine clinical implementation.

4.5. Limitations and Current Challenges

Despite substantial technological progress, AI-based image analysis has not yet been fully integrated into routine endovascular practice. One of the principal challenges is data heterogeneity, as variations in imaging protocols, acquisition techniques, and patient populations may adversely affect model performance and generalizability (13). In addition, the development of high-quality annotated datasets remains a significant barrier, particularly in specialized domains such as intravascular imaging.

Another critical limitation is the limited interpretability of many deep learning models. The so-called "black box" nature of these systems raises concerns regarding transparency, clinical trust, and regulatory acceptance. Furthermore, although numerous studies have demonstrated strong technical performance and diagnostic accuracy, relatively few prospective studies have established a clear impact on patient outcomes. As such, while the feasibility of AI-based image analysis is well supported, its definitive clinical value in endovascular surgery remains to be fully established (13).

5. Evaluation, Validation, and Clinical Integration of AI-Based Decision Support Systems

The clinical adoption of AI-based decision support systems (DSS) in endovascular surgery requires not only technological advancement but also rigorous evaluation, robust validation, and seamless integration into clinical workflows. Importantly, successful implementation depends not solely on predictive performance, but also on clinical validity, interpretability, and real-world usability (20). Although early studies have demonstrated promising results, the translation of these systems into routine practice remains contingent upon comprehensive, multidimensional evaluation frameworks (27).

5.1. Model Performance and Clinical Validity

The evaluation of AI-based DSS should extend beyond conventional performance metrics such as accuracy or area under the receiver operating characteristic curve (AUROC). While high-performing models have been reported across vascular and surgical domains, such metrics alone are insufficient to establish clinical utility (26). True clinical validity requires that model outputs are not only statistically robust, but also clinically meaningful and generalizable across diverse patient populations and practice settings (20).

A major limitation of current models lies in their reliance on retrospective datasets, which may introduce selection bias and limit external applicability (34). Evidence from surgical outcome prediction studies suggests that model performance may vary substantially across institutions and patient cohorts (31). Consequently, external validation using independent, preferably multicenter datasets is essential prior to widespread adoption. Furthermore, prospective validation studies are required to determine whether DSS-assisted decision-making translates into measurable improvements in patient outcomes, rather than merely enhanced predictive accuracy (13).

5.2. Interpretability and Trustworthiness

A key barrier to the clinical adoption of AI-based DSS is the limited interpretability of many machine learning models, often described as the "black box" problem (27). In high-stakes clinical environments such as endovascular interventions, clinicians may be reluctant to rely on systems that do not provide transparent or explainable reasoning for their outputs. Accordingly, interpretability represents a critical prerequisite for clinical integration (20).

Models that provide explainable outputs—such as feature attribution, risk contribution, or visual overlays on imaging—may facilitate clinician understanding and trust. In imaging-based applications, the incorporation of anatomical priors and structured representations has been shown to enhance both model performance and interpretability (28). Beyond explainability, trustworthiness also encompasses robustness, reproducibility, and resilience to variability in input data (20). These attributes are particularly important in endovascular practice, where decision-making occurs under time pressure and with potentially high clinical consequences (27).

5.3. Workflow Integration and Human–AI Interaction

For AI-based DSS to achieve meaningful clinical impact, they must integrate seamlessly into existing workflows without increasing cognitive burden or disrupting procedural efficiency (27,39). Systems that require extensive manual input or operate outside standard clinical interfaces are unlikely to be adopted in routine practice.

Human–AI interaction represents a central component of successful implementation. Rather than replacing clinician judgment, DSS are best conceptualized as cognitive support tools that enhance decision-making while preserving clinician oversight (20). This

paradigm aligns with the broader perspective in medicine that prioritizes augmentation over automation (24,27).

In endovascular settings, effective integration is particularly critical during intra-procedural decision-making, where real-time, intuitive, and actionable feedback is required. Delays in output, lack of interpretability, or poorly designed interfaces may negate the potential benefits of AI assistance and, in some cases, even introduce additional risk (30).

5.4. Data Quality, Standardization, and Bias

The performance and reliability of AI-based DSS are fundamentally dependent on the quality and representativeness of the underlying data. Variability in imaging protocols, data acquisition methods, and clinical documentation may adversely affect model performance and limit generalizability (2,33).

In addition, biases within training datasets—such as the underrepresentation of specific patient populations—may lead to inequitable predictions and reduced applicability across diverse clinical settings (20). Addressing these challenges requires the development of standardized data collection frameworks, rigorous annotation protocols, and robust data governance strategies (13).

From a broader perspective, advances in surgical data science emphasize the importance of structured, high-quality datasets and interoperable data systems to support the scalable development and deployment of AI tools (34). Without such infrastructure, the clinical translation of DSS in endovascular surgery is likely to remain constrained.

5.5. Regulatory, Ethical, and Implementation Challenges

The deployment of AI-based DSS in clinical practice introduces a range of regulatory and ethical challenges. Unlike traditional medical devices, AI systems may evolve over time through continuous learning processes, thereby complicating regulatory approval and post-market surveillance (20).

Key ethical considerations include data privacy, informed consent, and accountability for adverse outcomes. The question of liability in AI-assisted decision-making whether it resides with the clinician, institution, or system developer remains unresolved and necessitates the establishment of clear legal frameworks (20). In addition, practical implementation barriers including cost, infrastructure requirements, and the need for clinician training may limit equitable access to these technologies. Without careful and deliberate integration strategies, AI-based DSS may inadvertently exacerbate existing disparities in healthcare delivery (13,34).

5.6. Future Directions: Toward Learning Health Systems

The integration of AI-based DSS in endovascular practice is likely to evolve toward interconnected, continuously learning systems (24,34). These platforms are expected to aggregate data across the entire continuum of care, enabling real-time feedback, adaptive

decision-making, and iterative model refinement. Such an approach aligns with the concept of a learning health system, in which clinical practice and data analytics are tightly integrated to drive continuous improvement in patient outcomes. Achieving this vision will require close collaboration among clinicians, data scientists, engineers, and regulatory bodies (26).

Ultimately, the long-term success of AI in endovascular surgery will depend not only on technical performance, but also on the ability to demonstrate measurable improvements in clinical decision-making, workflow efficiency, and, most importantly, patient outcomes in real-world settings (22).

6. Clinical Applications and Use Cases in Endovascular Surgery

The integration of AI into endovascular surgery has progressed beyond early conceptual models, with a growing body of evidence supporting its application across multiple stages of clinical decision-making (20,27). AI-based systems are increasingly incorporated throughout the endovascular workflow, including patient selection, procedural planning, intra-procedural guidance, and post-procedural outcome prediction (31,34), as summarized in Table 1. Collectively, these applications suggest that AI may enhance technical precision and contribute to improved clinical outcomes through data-driven decision support (24,26).

Table 1. AI Applications Across the Endovascular Workflow

Workflow Stage	AI Application	Clinical Benefit	Example
Patient selection	Risk prediction	Better selection	MALE prediction
Pre-procedural	CTA analysis	Planning accuracy	EVAR sizing
Intra-procedural	Real-time guidance	Precision ↑	Image fusion
Post-procedural	Outcome prediction	Follow-up optimization	Endoleak risk

6.1. Patient Selection and Risk Stratification

One of the most clinically impactful applications of AI in endovascular surgery is patient selection and risk stratification. Treatment decisions in vascular disease are inherently complex, requiring a careful balance between procedural risk and expected clinical benefit. Machine learning models have demonstrated the potential to outperform traditional statistical approaches in predicting outcomes such as mortality, major adverse limb events (MALE), and reintervention rates in selected populations (26,31).

By integrating demographic, clinical, and imaging-derived variables, AI-based models may support individualized risk prediction and facilitate more precise patient selection (34). This capability is particularly valuable in borderline scenarios, where the choice between conservative management, endovascular intervention, and open surgical repair is not straightforward. In such cases, DSS-supported risk estimation may provide an addi-

tional layer of objectivity, helping to reduce variability in decision-making while preserving clinician judgment (27).

6.2. Pre-procedural Planning and Imaging Analysis

Pre-procedural planning represents another key domain in which AI demonstrates substantial clinical utility. Advanced image analysis algorithms are capable of automatically extracting relevant anatomical features from computed tomography angiography (CTA), including vessel diameter, lesion length, calcification burden, and vascular tortuosity (14). These capabilities may facilitate automated lesion characterization, optimization of device sizing, and refinement of procedural strategy. In complex interventions such as endovascular aneurysm repair (EVAR), AI-assisted planning tools may support graft selection and enable the prediction of complications such as endoleak or device migration (25). Furthermore, deep learning–based segmentation techniques allow rapid and reproducible vascular reconstruction, thereby reducing operator dependency and improving planning efficiency (12,13).

From a practical standpoint, such tools may be particularly valuable in anatomically challenging cases for example, in patients with hostile neck anatomy or extensive calcific disease where small inaccuracies in measurement or interpretation may significantly influence procedural outcomes.

6.3. Intra-procedural Guidance and Real-Time Decision Support

The application of AI during endovascular procedures represents an emerging and rapidly evolving field. Real-time decision support systems have the potential to assist operators by providing intra-procedural feedback derived from imaging data and procedural parameters (30,40). These systems may support image fusion–based navigation, automated identification of anatomical landmarks, and guidance for optimal device positioning and deployment. By enhancing spatial orientation and procedural precision, such technologies may contribute to reductions in contrast usage, radiation exposure, and overall procedure time (30).

From a clinical perspective, the value of these systems becomes particularly evident in complex interventions, where anatomical ambiguity or unexpected intra-procedural findings necessitate rapid decision-making. However, the implementation of real-time AI remains technically challenging, with issues related to latency, data integration, and reliability representing important barriers to widespread adoption (34,40).

6.4. Prediction and Prevention of Complications

AI-based predictive modeling is increasingly being applied to the identification and prevention of peri-procedural and long-term complications. In endovascular surgery, complications such as restenosis, thrombosis, stent fracture, and endoleak have a substantial impact on long-term outcomes and resource utilization.

Machine learning approaches enable the analysis of large-scale datasets to identify complex, non-linear relationships between risk factors and adverse events (31,34). This may facilitate early identification of high-risk patients, support tailored surveillance strategies, and enable proactive intervention planning. For instance, predictive models in EVAR populations have been developed to stratify the risk of aortic complications, potentially allowing more efficient allocation of follow-up resources and earlier detection of clinically significant events (25).

6.5. Post-procedural Monitoring and Outcome Prediction

Beyond the procedural phase, AI is increasingly applied to post-procedural monitoring and long-term outcome prediction. By integrating longitudinal data from imaging, clinical records, and follow-up assessments, AI-based systems may detect early indicators of complications and predict long-term outcomes (31,34). This capability supports the development of personalized follow-up strategies, facilitates earlier detection of device-related complications, and may inform the optimization of secondary interventions. In addition, AI-driven analytics may contribute to quality improvement by identifying patterns associated with procedural success or failure across institutions, thereby informing evidence-based refinements in clinical practice (2,34).

6.6. Toward Personalized and Data-Driven Endovascular Care

Taken together, these applications are contributing to a gradual shift toward personalized, data-driven endovascular care. AI enables a transition from population-based decision-making toward individualized treatment strategies that incorporate patient-specific anatomical, physiological, and clinical characteristics (20).

While these developments are promising, their successful integration into routine clinical practice will depend on continued validation, the generation of high-quality clinical evidence, and seamless incorporation into existing workflows (13,34). Ultimately, the clinical value of AI in endovascular surgery will be determined not only by its technical capabilities, but by its ability to meaningfully enhance decision-making and improve patient outcomes in real-world settings (27).

7. Advanced Technologies and Emerging Concepts

AI in endovascular surgery is progressively evolving toward integrative, real-time systems that extend beyond conventional decision support (20). Contemporary developments increasingly combine patient-specific data, intra-procedural inputs, and predictive modeling to enable more adaptive and personalized interventions. These advances may contribute to a transition from reactive, experience-based decision-making toward more proactive, data-driven clinical strategies (34).

7.1. Digital Twins and Patient-Specific Modeling

One of the most promising emerging concepts is the development of digital twins, computational representations that replicate the anatomical and physiological characteristics of individual patients. By integrating imaging data with computational fluid dynamics and biomechanical modeling, these systems may simulate blood flow, wall shear stress, and device–vessel interactions within patient-specific vascular geometries (38).

Such models may enable virtual procedural planning, prediction of hemodynamic changes, and pre-procedural assessment of intervention outcomes. From a clinical perspective, this approach may be particularly relevant in complex scenarios such as aortic aneurysm repair or multilevel peripheral arterial disease where individualized anatomical and hemodynamic factors play a critical role in procedural success. By facilitating simulation-based planning, digital twins have the potential to refine strategy selection and reduce procedural uncertainty (34,38).

7.2. Real-Time AI and Intraoperative Intelligence

The evolution of AI toward real-time intraoperative applications represents a significant technological milestone. Unlike traditional offline models, real-time AI systems dynamically process imaging and procedural data, providing immediate feedback to the operator (41). Potential applications include real-time anatomical recognition, adaptive navigation support, and automated intra-procedural risk assessment. These systems may function as "intraoperative copilots," enhancing procedural precision and situational awareness. Their clinical value is likely to be most evident in complex interventions, where rapid interpretation of evolving anatomical conditions is required (27). However, achieving reliable real-time performance remains challenging. Issues related to computational latency, data integration, and system robustness must be addressed before widespread clinical adoption can be realized (27, 30).

7.3. Autonomous and Semi-Autonomous Systems

Advances in machine learning and robotics are facilitating the development of autonomous and semi-autonomous endovascular systems. While fully autonomous interventions remain largely experimental, semi-autonomous systems capable of assisting with navigation, device positioning, and procedural optimization are becoming increasingly feasible (42). These systems typically integrate reinforcement learning, computer vision, and real-time feedback mechanisms to support procedural execution. Importantly, their intended role is not to replace the operator, but to enhance procedural consistency and reduce variability associated with operator experience (20).

Nevertheless, substantial challenges remain, including the need for rigorous safety validation, regulatory approval, and careful consideration of ethical implications. In high-risk procedural environments such as endovascular interventions, maintaining meaningful human oversight will remain essential (27).

7.4. Multimodal AI and Data Integration

Future AI systems are expected to increasingly incorporate multimodal data, including imaging, electronic health records, hemodynamic parameters, and intra-procedural data streams. This integrative approach may provide a more comprehensive representation of patient status and disease progression (43).

By combining heterogeneous data sources, multimodal AI may improve predictive accuracy, enhance decision support, and enable dynamic risk assessment. In the context of endovascular surgery, such integration may facilitate more precise patient selection, refined procedural planning, and adaptive intra-procedural decision-making. This paradigm aligns with the broader concept of data-driven medicine, in which continuous data integration supports iterative clinical decision-making across the care continuum (26,34).

7.5. Edge AI and Cath-Lab Integration

The deployment of AI directly within the catheterization laboratory represents a critical step toward real-world clinical implementation. Edge AI refers to the execution of algorithms locally on medical devices or imaging platforms, enabling real-time processing without reliance on external computing infrastructure (44).

In endovascular settings, this approach may facilitate low-latency decision support, seamless integration with imaging systems, and improved procedural efficiency. From a practical standpoint, edge AI may be particularly valuable in time-sensitive intra-procedural scenarios, where delays in data processing could adversely affect clinical decision-making (30). However, successful integration into cath-lab environments requires robust hardware and software interoperability, regulatory compliance, and user-centered interface design. Without these elements, even technically advanced systems are unlikely to achieve widespread clinical adoption (34).

8. Limitations and Challenges of AI in Endovascular Practice

Although AI demonstrates considerable potential in endovascular surgery, several critical limitations must be addressed before meaningful clinical adoption can be achieved. These challenges span technical, clinical, ethical, and regulatory domains, and collectively highlight the persistent gap between promising experimental performance and real-world clinical impact (20,34). As summarized in Table 2, these limitations should not be viewed as isolated issues, but rather as interrelated factors that influence the reliability, safety, and scalability of AI-based systems in endovascular practice.

Table 2. Limitations and Challenges of AI in Endovascular Surgery

Domain	Limitation	Clinical Impact	Possible Solution
Data	Bias	Wrong predictions	Multicenter data
Model	Black-box	Trust ↓	Explainable AI
Clinical	Workflow	Adoption ↓	Integration
Legal	Liability	Risk	Regulation

8.1. Data Quality, Heterogeneity, and Bias

The performance of AI models is fundamentally dependent on the quality, consistency, and representativeness of the underlying data. In endovascular practice, data heterogeneity arises from variability in imaging protocols, institutional workflows, and operator-dependent practices. Such variability may adversely affect model robustness and limit generalizability across different clinical settings (34).

In addition, biases in training datasets particularly the underrepresentation of specific patient populations may lead to inequitable predictions and reduced applicability in diverse populations (20). From a clinical perspective, this raises concerns regarding the reliability of AI-assisted decision-making in underrepresented or complex patient groups. Addressing these limitations will require standardized data acquisition protocols, rigorous annotation processes, and the development of large-scale, multicenter datasets.

8.2. Lack of External Validation and Generalizability

A substantial proportion of AI models in endovascular and vascular surgery are developed using retrospective, single-center datasets. Although such models may demonstrate strong performance during internal validation, their effectiveness frequently diminishes when applied to external populations (31). This lack of generalizability represents a major barrier to clinical adoption. Reliable implementation requires external validation across independent, multicenter, and ideally international cohorts. Furthermore, prospective validation studies are essential to determine whether AI-assisted decision-making leads to meaningful improvements in clinical outcomes, rather than improvements in predictive metrics alone (13).

8.3. Interpretability and the "Black Box" Problem

Limited interpretability remains one of the most persistent challenges in the clinical deployment of AI systems. Many high-performing models particularly deep learning architectures operate as "black boxes," providing outputs without transparent explanations of the underlying decision process (45).

In high-risk environments such as endovascular interventions, this lack of transparency may undermine clinician trust and limit adoption. While explainable AI techniques have been proposed, their clinical utility remains variable. Bridging the gap between pre-

dictive performance and interpretability is therefore critical for safe and acceptable integration into clinical workflows (20).

8.4. Integration into Clinical Workflow

Even highly accurate AI models may fail to achieve clinical impact if they are not effectively integrated into existing workflows. Systems that require additional manual input, disrupt procedural flow, or increase cognitive burden are unlikely to be adopted in real-world endovascular settings (27,30).

Successful implementation depends on seamless interoperability with imaging platforms, electronic health records, and procedural systems, as well as intuitive user interfaces that support rapid and informed decision-making (30). From a practical standpoint, integration challenges may represent a more significant barrier than algorithmic performance itself.

8.5. Regulatory and Legal Challenges

The regulatory framework for AI-based medical technologies remains in evolution. Unlike conventional medical devices, AI systems may undergo continuous modification through adaptive learning processes, complicating both initial approval and post-market surveillance (20).

Legal considerations, particularly regarding liability in the context of AI-assisted decisions, remain unresolved. Determining whether responsibility lies with the clinician, healthcare institution, or system developer requires the establishment of clear and robust regulatory frameworks (46). Until such frameworks are defined, uncertainty in accountability may limit clinician acceptance and institutional adoption.

8.6. Ethical Considerations

The integration of AI into clinical decision-making raises important ethical concerns, including data privacy, informed consent, algorithmic fairness, and transparency (20). Ensuring that AI-generated recommendations are interpretable and justifiable is essential for maintaining patient trust. Moreover, the presence of algorithmic bias underscores the need for continuous monitoring and ethical oversight. Without appropriate safeguards, AI systems may inadvertently perpetuate or exacerbate existing disparities in healthcare delivery (34).

8.7. Implementation Barriers and Resource Constraints

Practical barriers including cost, infrastructure requirements, and the need for specialized technical expertise may limit the widespread adoption of AI technologies, particularly in resource-constrained settings. In addition, clinician training and acceptance represent critical determinants of successful implementation. Without adequate education and con-

fidence in AI systems, even technically robust tools are unlikely to be integrated into routine practice. As such, implementation challenges should be viewed not only as technical issues, but also as organizational and cultural barriers that must be addressed to achieve sustainable adoption (27).

9. Future Perspectives and Research Directions

The future of AI in endovascular surgery is likely to be shaped by the convergence of advanced computational technologies, large-scale clinical data integration, and increasingly close collaboration between clinicians and data scientists. While current applications remain largely focused on decision support and image analysis, emerging developments suggest a gradual transition toward fully integrated, adaptive, and continuously learning systems capable of supporting the entire continuum of vascular care (20,34).

Importantly, the evolution of AI in this field is unlikely to be defined solely by incremental improvements in algorithmic performance, but rather by its ability to meaningfully integrate into clinical workflows and influence real-world decision-making.

9.1. Toward Personalized and Predictive Endovascular Medicine

A central direction for future research is the advancement of personalized and predictive endovascular medicine. AI has the potential to move clinical decision-making beyond population-based guidelines toward individualized treatment strategies that incorporate patient-specific anatomical, physiological, and clinical variables (26).

Such an approach may enable more accurate risk stratification, refined procedural planning, and tailored follow-up strategies. From a clinical perspective, this paradigm shift may be particularly relevant in anatomically complex or borderline cases, where standard guideline-based approaches may be insufficient to capture individual variability. By aligning treatment strategies with patient-specific characteristics, AI-based approaches may contribute to improved procedural outcomes and long-term disease management (31).

9.2. Continuous Learning Systems and Real-World Data Integration

Future AI systems are expected to evolve into continuous learning frameworks capable of integrating real-world clinical data, including registries, imaging repositories, and electronic health records. These systems may enable dynamic model updating and iterative performance improvement as new data become available (47).

This paradigm is closely aligned with the concept of a learning health system, in which clinical practice and data analytics are continuously interconnected to drive ongoing improvements in care delivery (34). However, the successful implementation of such systems will depend critically on data quality, standardization, interoperability, and governance frameworks (13). Without these foundational elements, continuous learning models may introduce instability rather than improvement.

9.3. Integration with Robotics and Image-Guided Interventions

The integration of AI with robotic and image-guided endovascular systems represents a promising and rapidly evolving frontier. AI-assisted guidance systems may enhance procedural precision, support navigation, and reduce variability related to operator experience (48).

In the longer term, this convergence may enable semi-autonomous procedural components, particularly in standardized or repetitive tasks. However, in complex and high-risk endovascular interventions, maintaining meaningful human oversight will remain essential to ensure safety, adaptability, and appropriate clinical judgment (27,30).

9.4. Multidisciplinary Collaboration and Translational Research

The continued advancement of AI in endovascular surgery will depend on effective collaboration between clinicians, engineers, data scientists, and regulatory authorities. Translational research frameworks that bridge the gap between algorithm development and clinical implementation will be critical to ensure that technological innovations result in tangible clinical benefit (13).

Prospective clinical trials, standardized evaluation methodologies, and multicenter validation studies will be required to establish both the safety and the clinical utility of AI-based systems. Without such evidence, the widespread adoption of these technologies is likely to remain limited (31).

9.5. Education and Training in AI-Enabled Endovascular Practice

As AI becomes increasingly integrated into clinical workflows, education and training will play a pivotal role in its adoption. Future endovascular specialists will require a foundational understanding of AI methodologies, their limitations, and their appropriate clinical applications.

In parallel, AI-based technologies may also transform training paradigms by enabling simulation-based learning environments, objective performance assessment, and real-time feedback. Such tools may contribute to more standardized training processes and potentially reduce variability in operator performance (49). However, the effective integration of AI into training programs will require careful curriculum design and validation to ensure that technological augmentation translates into meaningful improvements in clinical competence.

10. Conclusion

Artificial intelligence (AI) is emerging as a transformative component of endovascular surgery, with applications spanning decision support, image analysis, procedural guidance, and outcome prediction (50). As outlined throughout this chapter, AI has demon-

strated the potential to enhance technical precision and support more consistent, data-informed clinical decision-making across the endovascular workflow.

However, the clinical value of AI should not be defined by algorithmic performance alone. Its true impact will depend on safe, interpretable, and clinically meaningful integration into real-world practice. This requires rigorous validation, high-quality and representative data, transparent model design, and seamless incorporation into existing clinical workflows. In the absence of these elements, even technically advanced systems are unlikely to translate into measurable improvements in patient care.

Looking forward, the convergence of AI with patient-specific modeling, real-time intra-procedural systems, and continuously learning health frameworks may enable a shift toward more personalized and adaptive endovascular care. Nevertheless, AI should be regarded as an adjunctive tool that augments rather than replaces clinical expertise, particularly in complex and high-stakes procedural environments.

Ultimately, the successful adoption of AI in endovascular surgery will depend not only on technological innovation, but on its ability to demonstrate tangible improvements in patient outcomes, earn clinician trust, and integrate effectively within the realities of clinical practice.

11. References

1. Goodney, P. P., Beck, A. W., Nagle, J., Welch, H. G., & Zwolak, R. M. (2009). National trends in lower extremity bypass surgery, endovascular interventions, and major amputations. Journal of vascular surgery, 50(1), 54-60.
2. Greenhalgh, R. M. (2004). Comparison of endovascular aneurysm repair with open repair in patients with abdominal aortic aneurysm (EVAR trial 1), 30-day operative mortality results: randomised controlled trial. The Lancet, 364(9437), 843-848.
3. Napoli, A., Anzidei, M., Zaccagna, F., Cavallo Marincola, B., Zini, C., Brachetti, G., ... & Passariello, R. (2011). Peripheral arterial occlusive disease: diagnostic performance and effect on therapeutic management of 64-section CT angiography. Radiology, 261(3), 976-986.
4. Koizumi, A., Kumakura, H., Kanai, H., Araki, Y., Kasama, S., Sumino, H., ... & Kurabayashi, M. (2009). Ten-year patency and factors causing restenosis after endovascular treatment of iliac artery lesions. Circulation Journal, 73(5), 860-866.
5. Daye, D., & Walker, T. G. (2018). Complications of endovascular aneurysm repair of the thoracic and abdominal aorta: evaluation and management. Cardiovascular diagnosis and therapy, 8(Suppl 1), S138.
6. Scheinert, D., Scheinert, S., Sax, J., Piorkowski, C., Bräunlich, S., Ulrich, M., ... & Schmidt, A. (2005). Prevalence and clinical impact of stent fractures after femoropopliteal stenting. Journal of the American College of Cardiology, 45(2), 312-315.
7. AbuRahma, A. F., Campbell, J. E., Hariri, N., AbuRahma, J., Dean, L. S., Bates, M. C., ... & O'vil, A. (2017). Clinical outcome of carotid artery stenting according to provider specialty and volume. Annals of vascular surgery, 44, 361-367.
8. Ahmed, Z., Mohamed, K., Zeeshan, S., & Dong, X. (2020). Artificial intelligence with multi-functional machine learning platform development for better healthcare and precision medicine. Database, 2020, baaa010.
9. Esteva, A., Kuprel, B., Novoa, R. A., Ko, J., Swetter, S. M., Blau, H. M., & Thrun, S. (2017). Dermatologist-level classification of skin cancer with deep neural networks. nature, 542(7639), 115-118.
10. Lareyre, F., Yeung, K. K., Guzzi, L., Di Lorenzo, G., Chaudhuri, A., Behrendt, C. A., ... & Raffort, J. (2023, September). Artificial intelligence in vascular surgical decision making. In Seminars in Vascular Surgery (Vol. 36, No. 3, pp. 448-453). WB Saunders.
11. Zou, H., Zheng, X., Wu, L., Zhang, S., Chang, P., & Chen, Y. (2025). Digital twins in cardiovascular disease: a scoping review. International Journal of Medical Informatics, 106138.
12. Krittanawong, C., Zhang, H., Wang, Z., Aydar, M., & Kitai, T. (2017). Artificial intelligence in precision cardiovascular medicine. Journal of the American College of Cardiology, 69(21), 2657-2664.
13. Kelly, C. J., Karthikesalingam, A., Suleyman, M., Corrado, G., & King, D. (2019). Key challenges for delivering clinical impact with artificial intelligence. BMC medicine, 17(1), 195.
14. Gerke, S., Minssen, T., & Cohen, G. (2020). Ethical and legal challenges of artificial intelligence-driven healthcare. In Artificial intelligence in healthcare (pp. 295-336). Academic Press.

15. Rajkomar, A., Dean, J., & Kohane, I. (2019). Machine learning in medicine. New England Journal of Medicine, 380(14), 1347-1358.
16. LeCun, Y., Bengio, Y., & Hinton, G. (2015). Deep learning. nature, 521(7553), 436-444.
17. Litjens, G., Kooi, T., Bejnordi, B. E., Setio, A. A. A., Ciompi, F., Ghafoorian, M., ... & Sánchez, C. I. (2017). A survey on deep learning in medical image analysis. Medical image analysis, 42, 60-88.
18. Shen, D., Wu, G., & Suk, H. I. (2017). Deep learning in medical image analysis. Annual review of biomedical engineering, 19, 221-248.
19. Liu, A. (2025). Models of Cognition in Deep Reinforcement Learning Agents (Doctoral dissertation, The University of Utah).
20. Zeng, Q., Huang, C., & Zhu, J. (2025). AI-driven transformation of precision medicine: a comprehensive narrative review of key application areas, emerging paradigms, and future directions. Frontiers in Public Health, 13, 1656603.
21. Tearney, G. J., Regar, E., Akasaka, T., Adriaenssens, T., Barlis, P., Bezerra, H. G., ... & Weisz, G. (2012). Consensus standards for acquisition, measurement, and reporting of intravascular optical coherence tomography studies: a report from the International Working Group for Intravascular Optical Coherence Tomography Standardization and Validation. Journal of the American College of Cardiology, 59(12), 1058-1072.
22. de Mik, S. M., Stubenrouch, F. E., Balm, R., & Ubbink, D. T. (2021). Development of three different decision support tools to support shared decision-making in vascular surgery. Patient Education and Counseling, 104(2), 282-289.
23. Roux, M., Spear, R., Haigron, P., Demeure, A., & Fouard, C. (2024, July). Toward Decision Support System for Lower Limb Endovascular Revascularization. In 2024 46th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC) (pp. 1-4). IEEE.
24. Topol, E. J. (2019). High-performance medicine: the convergence of human and artificial intelligence. Nature medicine, 25(1), 44-56.
25. Karthikesalingam, A., Holt, P. J., Vidal-Diez, A., Choke, E. C., Patterson, B. O., Thompson, L. J., ... & Thompson, M. M. (2013). Predicting aortic complications after endovascular aneurysm repair. Journal of British Surgery, 100(10), 1302-1311.
26. Li, B., Warren, B. E., Eisenberg, N., Beaton, D., Lee, D. S., Aljabri, B., ... & Al-Omran, M. (2024). Machine learning to predict outcomes of endovascular intervention for patients with PAD. JAMA Network Open, 7(3), e242350.
27. Hashimoto, D. A., Rosman, G., Rus, D., & Meireles, O. R. (2018). Artificial intelligence in surgery: promises and perils. Annals of surgery, 268(1), 70-76.
28. Oktay, O., Ferrante, E., Kamnitsas, K., Heinrich, M., Bai, W., Caballero, J., ... & Rueckert, D. (2017). Anatomically constrained neural networks (ACNNs): application to cardiac image enhancement and segmentation. IEEE transactions on medical imaging, 37(2), 384-395.
29. Maier-Hein, L., Vedula, S. S., Speidel, S., Navab, N., Kikinis, R., Park, A., ... & Jannin, P. (2017). Surgical data science for next-generation interventions. Nature Biomedical Engineering, 1(9), 691-696.
30. Tacher, V., Lin, M., Desgranges, P., Deux, J. F., Grünhagen, T., Becquemin, J. P., ... & Kobeiter, H. (2013). Image guidance for endovascular repair of complex aortic aneurysms: comparison of two-dimensional and three-dimensional angiography and image fusion. Journal of Vascular and Interventional Radiology, 24(11), 1698-1706.
31. Senders, J. T., Staples, P. C., Karhade, A. V., Zaki, M. M., Gormley, W. B., Broekman, M. L., ... & Arnaout, O. (2018). Machine learning and neurosurgical outcome prediction: a systematic review. World neurosurgery, 109, 476-486.
32. Ronneberger, O., Fischer, P., & Brox, T. (2015, October). U-net: Convolutional networks for biomedical image segmentation. In International Conference on Medical image computing and computer-assisted intervention (pp. 234-241). Cham: Springer international publishing.
33. Livne, M., Rieger, J., Aydin, O. U., Taha, A. A., Akay, E. M., Kossen, T., ... & Madai, V. I. (2019). A U-Net deep learning framework for high performance vessel segmentation in patients with cerebrovascular disease. Frontiers in neuroscience, 13, 97.
34. Shahzad, R., Kirişli, H., Metz, C., Tang, H., Schaap, M., van Vliet, L., ... & van Walsum, T. (2013). Automatic segmentation, detection and quantification of coronary artery stenoses on CTA. The international journal of cardiovascular imaging, 29(8), 1847-1859.
35. Siegersma, K. R., Leiner, T., Chew, D. P., Appelman, Y., Hofstra, L., & Verjans, J. W. (2019). Artificial intelligence in cardiovascular imaging: state of the art and implications for the imaging cardiologist. Netherlands Heart Journal, 27(9), 403-413.
36. Mintz, G. S., & Guagliumi, G. (2017). Intravascular imaging in coronary artery disease. The Lancet, 390(10096), 793-809.
37. Swerdlow, N. J., Jones, D. W., Pothof, A. B., O'Donnell, T. F., Liang, P., Li, C., ... & Schermerhorn, M. L. (2019). Three-dimensional image fusion is associated with lower radiation exposure and shorter time to carotid cannulation during carotid artery stenting. Journal of Vascular Surgery, 69(4), 1111-1120.
38. Morris, P. D., Narracott, A., von Tengg-Kobligk, H., Soto, D. A. S., Hsiao, S., Lungu, A., ... & Gunn, J. P. (2016). Computational fluid dynamics modelling in cardiovascular medicine. Heart, 102(1), 18-28.
39. Robertshaw, H., Karstensen, L., Jackson, B., Sadati, H., Rhode, K., Ourselin, S., ... & Booth, T. C. (2023). Artificial intelligence in the autonomous navigation of endovascular interventions: a systematic review. Frontiers in Human Neuroscience, 17, 1239374.
40. Madani, A., Arnaout, R., Mofrad, M., & Arnaout, R. (2018). Fast and accurate view classification of echocardiograms using deep learning. NPJ digital medicine, 1(1), 6.

41. Magouliotis, D. E., Sicouri, N., Ramlawi, L., Baudo, M., Androutsopoulou, V., & Sicouri, S. (2026). Artificial Intelligence in Adult Cardiovascular Medicine and Surgery: Real-World Deployments and Outcomes. Journal of Personalized Medicine, 16(2), 69.
42. Moustris, G. P., Hiridis, S. C., Deliparaschos, K. M., & Konstantinidis, K. M. (2011). Evolution of autonomous and semi-autonomous robotic surgical systems: a review of the literature. The international journal of medical robotics and computer assisted surgery, 7(4), 375-392.
43. Jaltotage, B., Lu, J., & Dwivedi, G. (2024). Use of artificial intelligence including multimodal systems to improve the management of cardiovascular disease. Canadian Journal of Cardiology, 40(10), 1804-1812.
44. Beyar, R., Davies, J., Cook, C., Dudek, D., Cummins, P., & Bruining, N. (2021). Robotics, imaging, and artificial intelligence in the catheterisation laboratory: cath lab robotics, imaging, and AI. EuroIntervention, 17(7), 537.
45. Tran, Z., Byun, J., Lee, H. Y., Boggs, H., Tomihama, E. Y., & Kiang, S. C. (2023, September). Bias in artificial intelligence in vascular surgery. In Seminars in Vascular Surgery (Vol. 36, No. 3, pp. 430-434). WB Saunders.
46. O'Sullivan, S., Nevejans, N., Allen, C., Blyth, A., Leonard, S., Pagallo, U., ... & Ashrafian, H. (2019). Legal, regulatory, and ethical frameworks for development of standards in artificial intelligence (AI) and autonomous robotic surgery. The international journal of medical robotics and computer assisted surgery, 15(1), e1968.
47. Dossabhoy, S. S., Ho, V. T., Ross, E. G., Rodriguez, F., & Arya, S. (2023, September). Artificial intelligence in clinical workflow processes in vascular surgery and beyond. In Seminars in vascular surgery (Vol. 36, No. 3, pp. 401-412). WB Saunders.
48. Boeken, T., Lim, H. P. D., & Cohen, E. I. (2024). The role and future of artificial intelligence in robotic image-guided interventions. Techniques in Vascular and Interventional Radiology, 27(4), 101001.
49. Ismail, M., & Rahimi, M. (2025). Evolution of Vascular Surgery Training: Simulation, AI, and Competency-Based Models. JVS-Vascular Insights, 100294.
50. Dinc, R., & Ardic, N. (2026). Artificial Intelligence for Computer-Aided Detection in Endovascular Interventions: Clinical Applications, Validation, and Translational Perspectives. Bioengineering, 13(4), 399.

CHAPTER 20

The Future of Surgery: Integration of AI into Minimally Invasive Procedures

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1. Introduction

Surgical skills have traditionally been assessed based on the manual dexterity and experience of the surgeon. However, with the advancements in technology, especially in relation to the recording of surgical procedures and the use of learning robots in surgery, the issue of whether artificial intelligence can replace the surgeon has come into sharper focus (1, 2).

In our review article, we will discuss, among other things, whether artificial intelligence can be used as a guide to reduce the cognitive load on the surgical team or replace the surgeon, especially in complex procedures in gastrointestinal and oncologic surgery, such as gastrectomy, pancreaticoduodenectomy (Whipple procedure), and mesorectal excision. In addition, we will discuss whether artificial intelligence can be used in the preservation of structures, including the common bile duct, ureters, and mesenteric vessels (3, 4).

2. Methods

This systematic review was conducted according to the guidelines for transparency and reproducibility proposed by the PRISMA group. An extensive literature search was conducted on different academic and technical sources such as PubMed, arXiv, Google Scholar, SciSpace, and IEEE EMBC Archives. The search was restricted to articles published in the time period from January 2021 to March 2026 to gather information on the latest technological and clinical advancements.

The systematic reviews, meta-analyses, randomized controlled trials, and articles on the technical parameters (FPS, mIoU) and clinical parameters (R0 margins, LOS) of the application of artificial intelligence in surgery, robot-assisted minimally invasive surgery (MIS), and endoscopic procedures were considered. Articles published before 2021, case reports on fewer than 10 patients, articles on preoperative diagnostic imaging, and non-English articles were excluded.

3. Technological Evolution: Artificial Intelligence Models

The architecture of artificial intelligence in surgery has evolved through three distinct phases: the era of local feature extraction (convolutional neural networks [CNNs]), the introduction of temporal context (Transformers), and the current era of task-agnostic Surgical Foundation Models.

3.1. Convolutional Neural Networks (CNNs) Recurrent Neural Networks (RNNs)

Convolutional Neural Networks (CNNs) have been the basis for surgeries that involve imaging and provide an advanced approach to image processing. They are used in applications such as detecting polyps or tumors, but they cannot capture the dynamics associated with the changing environment as they cannot make decisions regarding new scenarios (5, 6).

On the other hand, Recurrent Neural Networks (RNNs) are those whose memory holds information about past observations, which is then used by the system for further analysis. The system tries to predict the future step through previous visual input (7, 8).

3.2. Vision Transformers (ViT) and Temporal Context

The introduction of Vision Transformers (ViT) marked a significant paradigm shift. Unlike CNNs, Transformers employ self-attention mechanisms that enable long-range temporal modeling. Models such as GSViT and ARST have achieved high accuracy in intraoperative phase recognition while reaching real-time inference speeds of up to 66 frames per second (fps) (9).

3.3. Surgical Foundation Models (2024–2026)

Currently, models are pre-trained on large datasets and can be fine-tuned for a variety of tasks with little additional training data.

SurgSAM2: Offers a solution to reduce computation by threefold without compromising segmentation accuracy (10).

EndoMamba: Offers a solution to efficiently deal with long-form endoscopic videos (7, 6).

LemonFM (Surg-3M): Trained on 85 million frames, showing high generalization capabilities in instrument detection and segmentation (12).

3.4. Future Trends and Predictions for Artificial Intelligence Models

Robotics and AI Synergy: Autonomously operated endoscope guidance systems can be developed to shorten the duration of the procedure and provide a better patient experience.(13)

Multi-Data Analysis: Future artificial intelligence models will go beyond visual data processing by considering patients' genetic information and their medical records for tailored risk prediction.

Affordability: Endoscopic procedures with AI support will become more accurate in areas where there are fewer expert physicians, ensuring better health care equality.

4. Real-time Decision Support and Navigation

The main goal is to have real-time decision support that is capable of recognizing anatomy and predicting risk faster than the human brain.

There have been various models developed to do this. Models include TernausNet and OP-U-Net, which are used to define anatomical boundaries. In radical gastrectomy, the accurate definition of perigastric vasculature is important to ensure clear resection margins and reduce intraoperative blood loss (4, 7).

Real-time image-guided navigation is a game-changer in complex oncologic resections with narrow boundaries. The Spatial Surgical Transformer (SST) is a model that uses 3D spatial priors to aid with complex robotic procedures, including knot tying and organ dissection.

5. Clinical Outcomes

According to the results obtained from clinical studies, the use of Computer-Aided Detection (CADe) systems increases the detection rate of polyps and adenomas. The software uses algorithms for analyzing video images of the gastrointestinal tract during colonoscopy and highlights suspicious lesions, such as small flat polyps (6, 14).

The Computer-Aided Diagnosis (CADx) system will enable real-time prediction of the histopathology of discovered pathologies and, thus, avoid the need to conduct biopsy procedures and resort to the strategy of characterization and preservation. Several studies proved that deep learning-based techniques demonstrated a high diagnostic accuracy (90%) in recognizing Barrett's disease and early stages of gastric cancer (15).

According to the literature review, the use of AI-assisted surgical robotic systems improves intraoperative patient safety. Compared to conventional surgeries, there is a 30% decline in the occurrence of complications during the procedure performed by using robot systems with AI (2). Additionally, robotic surgery minimizes intraoperative bleeding in patients.

Using 3D visualization technology in treating rectal cancer cases results in better specimen quality and lower incidences of recurrence. In terms of lymph node dissection, some studies suggest that the utilization of AI could result in better surgical outcomes and higher patient survival rates (16). AI-assisted surgeries also tend to increase the speed of recovery for patients since the procedures become more efficient. Patients recover around 15% quicker compared to normal surgeries. Some research has even reported a 25% reduction in operating time due to efficiency gains (2). Several systematic reviews suggest that AI-assisted colonoscopy procedures could greatly boost adenoma detection rates (ADR) (6, 15).

6. Economic Impact and Healthcare Value

The AI-assisted colonoscopy is considered a "dominant" approach due to the importance of cancer prevention and detection. In the case of robotic surgery, a reduction of 10% is estimated in terms of healthcare costs due to reduced complication rates. A reduction of 15% in recovery time means an enormous potential to increase the capacity utilization rate of hospital beds (2, 16).

The high initial investment and maintenance costs are major impediments to the adoption of AI-assisted colonoscopies.

7. Regional Trends and Ethical Barriers

China, Japan, and India are the leaders in the development of real-time navigation tools, while the US and European countries have been more focused on systematic validation and health economic modeling (3, 17).

The uncertainty in the liability in case of a mistake in the system, owing to the 'black box' nature of the system, remains a concern in the division of liability between the surgeon and the manufacturer (14).

Moreover, the requirement for millions of frames to develop foundation models also creates challenges in the sharing of data and the concern for data privacy.

8. Conclusion: The Human-in-the-Loop Model

The role of artificial intelligence in minimally invasive surgery is progressing from a technical curiosity to a clinical necessity. Although artificial intelligence systems have been seen to decrease complications by 30% and recovery periods by 15%, there is also a decrease in cognitive and mechanical burdens on the surgical staff.

The data-driven approach of artificial intelligence systems, based on past surgeries, and the lack of clear accountability for artificial intelligence-induced complications have led many to believe that artificial intelligence will not replace human surgeons completely.

The dominant view is not one in which artificial intelligence replaces the human surgeon but one in which artificial intelligence works as a "human-in-the-loop" or "digital co-pilot" concept. This means artificial intelligence will deal with data-intensive and perceptual tasks such as segmentation and phase recognition, while humans will deal with high-level case management and judgment, which are still core aspects of surgery.

9. References

1. Schmidgall, S., Kim, J. W., Jopling, J. ve Krieger, A. (2024). General surgery vision transformer: A video pre-trained foundation model for general surgery. arXiv.org. https://doi.org/10.48550/arxiv.2403.05949
2. AI-driven robotic surgery outcomes: A 2024–2025 synthesis. (2025).
3. Li, S., Xu, M., Meng, Y., Sun, H., Zhang, T., Yang, H., . . . Ma, X. (2024). The application of the combination of artificial intelligence and endoscopy in gastrointestinal tumors. MedComm - Oncology, 3(1). https://doi.org/10.1002/mog2.91
4. Miao, Y., Jiang, H., Zhang, S. ve Chen, L. (2025). Challenges in clinical translation of artificial intelligence and real-time imaging navigation in radical gastrectomy. World Journal of Gastroenterology, 31(40). https://doi.org/10.3748/wjg.v31.i40.111389
5. Comparison of CNNs and Transformer model families in surgery. (2024).
6. CDA-AMC. (2024). Artificial Intelligence–Assisted Colonoscopy for Detecting Polyps, Adenomas, Precancerous Lesions, and Colorectal Cancer. Canadian Journal of Health Technologies. https://doi.org/10.51731/cjht.2024.1036
7. EndoMamba: Endoscopic video foundation model optimized for inference. (2024).
8. Park, J., Kim, S., Lee, H., Choi, Y. ve Kang, D. (2024). PECI-Net: Bolus segmentation from video fluoroscopic swallowing study images. Computers in Biology and Medicine. https://doi.org/10.1016/j.compbiomed.2024.108241
9. Transformer-based vision systems in surgical video tasks. (2024).
10. Liu, H., Zhang, E., Wu, J., Hong, M. ve Jin, Y. (2024). Surgical SAM 2: Real-time Segment Anything in Surgical Video by Efficient Frame Pruning. arXiv.org.
11. Zhang, X., Chen, J., Zhang, Q., Zhou, C., Zhang, Z., Li, X. ve Qian, D. (2024). SPRMamba: Surgical Phase Recognition for Endoscopic
12. LemonFM (Surg-3M): Foundation model pretrained on large surgical video corpus. (2024).
13. Ness, S., Shepherd, N. J., Xuan, T. R. (2023). Synergy Between AI and Robotics: A Comprehensive Integration. Asian Journal of Research in Computer Science
14. Wei, M., Lee, C., Tan, J., Lim, H. ve Ng, K. (2023). Artificial Intelligence–Assisted Colonoscopy in Real-World Clinical Practice: A Systematic Review and Meta-Analysis. Clinical and Translational Gastroenterology. https://doi.org/10.14309/ctg.0000000000000671
15. Comparison of robotic platform and evidence in rectal cancer. (2025). MDPI Cancers Summary.
16. Sheng, Y., Wang, L., Chu, X., Deng, J., Cheng, M., Zhang, Y., . . . Ji, J. (2026). Learning Surgical Robotic Manipulation with 3D Spatial Priors.

CHAPTER 21

Various Approaches with Artificial Intelligence Paradigms in Radiology

Prof. Dr. Volkan Kizilgoz

1. Introduction

In the year 2014, Budovec et al. emphasized that a formal knowledge model of differential diagnoses in radiology, named as the Radiology Gamuts Ontology, comprised 1,674 differential diagnoses, 19,017 terms, and 52,976 interconnections among those terms. (1). This complex actuality brings a huge workload, necessity of sophisticated analysis complex, and burnout. Additionally human error factor is also another issue to be discussed within this subject. From that time, the increasing number of illnesses and developing imaging technologies provided a broader data list and made it even more complex.

Considering this huge workload and the inevitable mistakes made while trying to handle it, this situation renders the AI to become an attractive partner that may have a complementary and a critical role for case interpretations. However, AI is not expected to replace radiologists ultimately, many researchers in radiology presage that radiologists who integrate AI into their practice will overtake those who do not (2-4). According to a report in 2022, among 690 radiologists who were European Society of Radiology members, participated in a survey of which 40% had prior experience using AI in clinical practice. Of the 185 radiologists who employed AI-based algorithms for diagnostic purposes, 140 (75.7%) considered the algorithm outputs to be generally reliable (5).

New imaging technologies may be a part of new imaging approach, clinical guidelines may be updated, disease incidence may change over time and humans may adapt to these situations easily. The performance of AI models may decrease over time since they may not keep up with new imaging protocols, changes in patient demographics or software updates (6). On the other hand, the AI models cannot be upgraded or significantly adjusted easily to avoid losing the certifications such as US Food and Drug Administration (FDA)

- approved AI systems (7). In addition, FDA approval is not a warrant for an AI system to be generalized. Most of the AI models revealed a reduced performance when applied to external datasets (8,9).

To understand the association between clinicians' diagnostic performance and the utility of machine learning-based clinical decision support systems (CDSSs) a meta-analysis reported the results of six investigations assessing the CDSSs in a representative clinical environment regarding the same evaluation parameters and they indicated 20 results that were reported with statistical significance. Among these investigations, 16 (80%) of them indicated no difference in clinician's performance, and 4 (20%) of them showed an increase in sensitivity, positive predictive value, area under the receiver operating curves, or interobserver agreement (10). The studies focused on performance comparison between AI and radiologists may be significant in terms of determination of the level of AI algorithms as an interpreter of the radiologic images.

Given the rapid expansion of the AI market, understanding how these technologies are utilized is essential for their effective integration into future clinical practice. Between 2008 and 2022, the FDA approved 201 AI systems, and this number is projected to increase tenfold over the following decade. An online resource (www.healthairegister.com) provides an overview of FDA-approved as well as Conformité Européenne (CE)-marked AI algorithms based on vendor-reported data. This platform allows users to easily identify the imaging modality, clinical specialty (e.g., breast, thoracic), and regulatory status (FDA approval or CE marking) of each system. According to these reports, the majority of AI applications focus on neuroradiology, chest imaging, musculoskeletal radiology, abdominal imaging, cardiac imaging, and breast imaging. However, many FDA-approved AI systems have been evaluated in a limited number of centers with non-diverse study populations, which has substantially limited the generalizability of their findings (11).

2. Technical Considerations

2.1. Generative AI and Large Language Models

Generative AI represents a subset of artificial intelligence that encompasses various models, including variational autoencoders, generative adversarial networks (GANs), and diffusion models, which are designed to learn data distributions and generate new synthetic data. This capability supports advanced applications in medical imaging, such as image synthesis, data augmentation, and image-to-image translation. A large language model (LLM) on the other hand, is a kind of AI algorithm which utilizes deep learning techniques and massive data to understand, summarize, generate, and predict new content. Based on transformer architecture, these models process text in parallel to recognize patterns and relationships between words or powering applications. Although LLMs are not strictly classified as a subset of generative AI, their generative capabilities have demonstrated substantial potential in the medical field. Their strengths in language comprehension, along with multimodal learning abilities, allow them to process both textual and multimodal

data, thereby facilitating the interpretation of relationships between radiologic images and clinical reports. These models can support automated report generation, assist in validating differential diagnoses, and contribute to patient risk stratification (12).

2.2. Technical Difficulties Encountered in Development and Training of Artificial Intelligence Models

Researchers and developers produce interpretative AI algorithms using training sets of radiological images which have been focused on a particular pathology of interest. However, the datasets used in the training process consisting of limited sample sizes and limited distribution of radiological findings impact their generalizability. The data used for training may represent specific patient populations; the data may exclude certain pathological conditions or artefacts. This may cause overfitting and the model "memorizes" the training data, learning noise and unnecessary details, but performs poorly on new, unfamiliar data. To overcome this handicap, training sets should be sufficiently comprehensive and should encompass a various range of samples across many anatomic locations, imaging modalities, and diverse patient populations (13).

Through the learning process AI algorithms may generate shortcuts or false correlations, particularly in the context of deep learning models (14). This error is observed when an AI system tends to make decisions while it encounters some imaging features that are irrelevant to the actual diagnostic criteria, caused by imaging artifacts or incidental findings (15). To illustrate, an AI algorithm may mistakenly learn to evaluate radiographs for the presence or absence of a disease by focusing on the density of text markers that indicate X-ray projection or the patient's position, rather than focusing on the targeted anatomical region. To overcome this problem, curation of diverse and representative training datasets is required to prevent the AI-system from focusing too heavily on irrelevant or specific features. Data augmentation, regularization or other specific techniques may be helpful to increase the variability of the training data and aid the AI system in focusing on relevant features (13).

In some cases, AI models may not efficiently localize the presence of a particular radiopathology because of co-existing pathological conditions or other signals on the image that have distinct relevance to the finding that the AI algorithm seeks to detect. For instance, an AI model may not detect pulmonary embolism while that patient has a co-existing lung consolidation due to obscuring of vascular borders of the pulmonary artery by adjacent lung space opacities (16). Developers may adjust system parameters to empower the algorithm and provide high accuracy in specific regions or conditions of images in which AI shows inadmissible or weak performance. The training datasets should be tailored to these kinds of specific challenges, ensuring adequate representation of the disease to effectively demonstrate and identify such conditions (17).

Continually monitorization of an AI system by expert human interpretations and repetitive improvements seems to be a significant part of this AI development process. The continuous corrections and refinement process has significant value in optimizing the

model by evaluating the disadvantages, modifying parameters and retraining to prevent the deflections and factors causing ongoing errors (13). Many inaccuracies in AI algorithms can largely be tailored to limited training processes and biases which are related to the diversity, quantity, and quality of the dataset that AI has been trained (17,18).

3. AI for Interpretative Uses in Radiology

There are many different uses of AI in radiology in different imaging concepts such as prostate, spine, thyroid or vascular imaging, and interventional radiology. The AI products developed mostly on neuroradiology, chest radiology, musculoskeletal radiology, abdominal radiology, cardiac imaging and breast imaging according to the www.healthairegister.com. In this chapter, these major imaging concepts that AI used for interpretative tasks are going to be discussed. Many subsets of AI are going to be mentioned related to different regions of interest in imaging under this subheading. The classical AI scheme is shown just to keep in mind and comprehend each subset of AI better (Figure 1).

3.1. Neuroradiology

The integration of deep learning neural network (DLNN) models with brain magnetic resonance imaging (MRI) holds substantial promise for transforming neuroradiological diagnostics. Such combined approaches may play a pivotal role in enhancing both the detection and morphological characterization of intracranial aneurysms. Recent studies have also demonstrated the application of generative adversarial networks (GANs) for brain tumor classification by generating synthetic MRI datasets, thereby addressing data scarcity while maintaining high diagnostic performance (19,20). Furthermore, DLNN-based quantitative volumetric analyses, along with preliminary qualitative assessments derived from MRI, may contribute to the standardization of intracranial lesion reporting and help reduce reporting turnaround times (21). In an evaluation of Nicolab's StrokeViewer, the performance of the AI system was compared with that of 4 neuroradiologists, 15 general radiologists, and 10 senior residents who reviewed CT angiography scans from 474 patients. The sensitivity of StrokeViewer (77.3%) was comparable to that of the radiologists (78.7%), with no statistically significant difference. However, the specificity of the AI system (88.5%) was significantly lower than that achieved by the radiologists (100%) ($p<0.001$) (22). In a review by Daga et al., machine learning models were assessed for their ability to predict rupture risk in intracranial aneurysms. The analysis included 20 eligible studies encompassing a total of 20,286 aneurysm cases. Imaging modalities varied across studies: 6 used digital subtraction angiography (DSA), 6 employed 3D-DSA, 6 utilized computed tomography angiography (CTA), 3 applied a combination of CTA, DSA, and magnetic resonance angiography (MRA), while 5 studies did not specify the imaging modality. Reported model performance ranged from 0.66 to 0.90 in accuracy. In a systematic review and meta-analysis by Din et al., 43 studies evaluating AI performance in detecting cerebral aneurysms were analyzed. The majority of these studies were retrospective

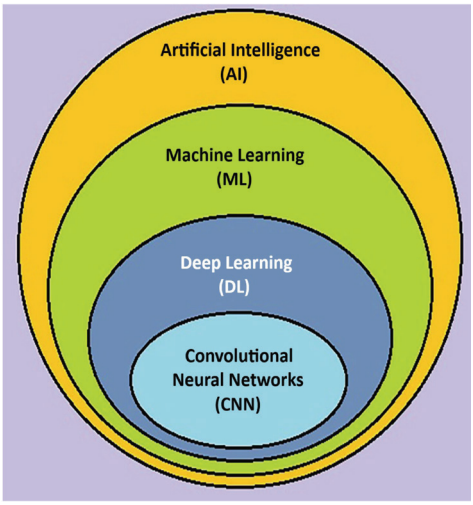


Figure 1. The classical scheme for AI and its subsets.

(41/43, 95%). AI was used as a standalone tool in 34 studies (79%), while 9 studies (21%) implemented AI as a decision-support system for readers. Deep learning approaches were applied in 23 studies (53%). Overall, the review identified a high risk of bias and concerns regarding applicability across many studies. In the standalone AI meta-analysis, six studies demonstrated a pooled sensitivity of 91.2%, a false-positive rate of 16.5%, and a receiver operating characteristic area under the curve (ROC-AUC) of 0.936. In contrast, five reader-assistive AI studies showed a pooled sensitivity of 90.3%, a false-positive rate of 7.9%, and a ROC-AUC of 0.910.

3.2. Chest Radiology

Concerning the chest X-rays (CXRs), conventional computer-aided detection (CAD) was used for decades before the AI era. Recent advancements in deep learning (DL) have influenced this area and markedly improved the performance of AI-driven tools. Nam et al. created a DL algorithm using training data from 146717 CXRs, which can detect 10 frequent abnormalities on radiographic images with an area under the receiver operating characteristic curve (AUROC) value ranging from 0.895 to 1.00 (24). To detect malignant pulmonary nodules on CXRs performance of a deep learning-based automatic detection algorithm (DLAD) has been compared with physicians in a study. The results of the investigation of radiograph classification accuracy and nodule detection capability performances of the algorithm were in an AUROC range of 0.92-0.99 and jackknife alternative free-response receiver-operating characteristic figure of merit (JAFROC FOM) were 0.831-0.924. DLAD indicated a higher AUROC values (higher from 17 of 18 physicians) and a higher JAFROC FOM values (higher from 15 of 18 physicians) at the observer performance test ($p< 0.05$). Additionally, it is revealed that all physicians' performance in-

creased with this algorithm (25). AI has not only tried for lesion detection, it has also been an assistant to enhance the interpreter's confidence and reduce reviewing time. In Ahn et al.'s study, a total of six radiologists, consisting of 2 attending radiologists, 2 fellows in thoracic radiology, and 2 residents were reviewed regarding 4 target findings (nodule, pneumothorax, pneumonia and pleural effusion) among 497 frontal chest radiographs with AI. In this research, AI's sensitivity was higher (for nodules 0.816 vs 0.567; for pneumothorax, 0.988 vs 0.792; for pneumonia, 0.887 vs 0.673; for pleural effusion, 0.872 vs 0.889) compared with the other reviewers. Additionally, reporting time was reduced by 10% for chest radiographs when utilizing AI compared to interpretations without using AI (36.9 vs 40.8 seconds) (26). Moreover, a stimulation study showed that by using commercial AI-based triaging that excludes normal CXRs from review, 42.9% of normal radiographs were removed from the worklist, although 3.5% of CXRs with detectable abnormalities and 1.8% with obvious abnormalities were mistakenly removed. The study indicated the possibilities offered by AI to reduce the workload of physicians, especially radiologists (27).

Computed Tomography (CT) on the other hand is a very useful and robust tool in detecting a broad spectrum of diseases. In the year 2019, Pehrson et al. reported that deep learning (DL) algorithms achieved high accuracy values ranging from 82.2% to 97.6% for the identification of the lung nodules (28). The DL system used by Ciompi et al. showed an accuracy (69.6%) comparable to that of six physicians (72.9%), and the lung nodules were classified into four different types in their study (29). In Ardila et al's study, the researchers utilized a DL to estimate lung cancer risk using both current and prior CT volumes, achieving an AUC of 0.944 (30). Huang et al developed a DL model called "PENet" for the automatic identification of pulmonary embolism (PE) on volumetric computed tomography pulmonary angiography (CTPA) images. This model indicated an AUROC of 0.85 on external dataset (31). A DL algorithm for the automated classification of fibrotic lung disease on high resolution CT images using existing diagnostic guidelines. The model reached accuracies of 76.4% and 73.3% across different test datasets and the results of the model outperformed 66% of 91 thoracic radiologists (32).

3.3. Musculoskeletal Radiology

Musculoskeletal injuries place a substantial financial burden on healthcare systems; moreover, failure to diagnose them promptly or accurately can result in higher rates of mortality and morbidity (33). So, advanced AI with high capacity dedicated to diagnosing the radiologic results of trauma would not only prevent short and long term undesirable medical outcomes but also avoid potential expenses. Gale et al. proposed a DenseNet-based model to be used for indicating hip fractures using frontal pelvic radiographies, achieving a performance level similar to a human radiologist (34). Chen et al. designed a ResNeXt-based model and applied transfer learning to abdominal radiographs for the identification of vertebral fractures. The model demonstrated performance only slightly lower than that of clinicians-including radiologists and orthopedic surgeons-with an accuracy of 73%, compared to the physicians' average accuracy of 76.8% (35). In the field of

fracture classification, Chung et al. proposed a model for categorizing proximal humerus fractures according to the Neer classification, utilizing anteroposterior radiographs (36). Likewise, Tanzi et al. and Lind et al. introduced deep learning approaches for the classification of proximal femoral fractures and peri-knee fractures, respectively, grounded in the Arbeitsgemeinschaft für Osteosynthesefragen (AO) Foundation–Orthopaedic Trauma Association (AO-OTA) classification framework (37). Li et al. designed a deep learning model to grade vertebral fractures based on the Genant classification, using lateral plain radiographs from 941 individuals and achieving an AUC between 0.919 and 0.99 (38). Moreover, Olczak et al. developed and trained a deep learning algorithm on a cohort of 4,941 patients to identify and classify ankle fractures, reporting a mean AUC of 0.90 (39). Zhou et al. created a convolutional neural network that integrated clinical data with CT images to both detect rib fractures and categorize them as acute, healing, or chronic (40). Bien et al. demonstrated a deep learning model capable of performing multiple tasks, including the detection of anterior cruciate ligament (ACL) and meniscal tears. However, when compared with radiologists, the model exhibited lower sensitivity for ACL tear detection and lower specificity for identifying meniscal tears (41). In addition, Liu et al. developed a deep learning approach aimed at increasing the sensitivity of ACL tear detection, achieving performance comparable to that of radiologists, with no statistically significant difference (42).

Bone age estimation is also another region of interest for the machine learning community, and this mission is a matter of typical object identification and classification of deep learning, with promising outcomes. AI has also been used for classification and prediction for osteoarthritis. Additionally artificial intelligence–assisted postoperative image evaluation may help alleviate clinician workload, decrease errors associated with fatigue, accelerate interpretation time, and enhance overall efficiency (43). On the other hand, the use of computer-assisted systems for the diagnosis of bone tumors has attracted attention for over five decades. The use of AI in musculoskeletal oncology revealed a rapid increase in machine learning studies over time. In a systematic review, conventional machine learning comprised 77%, while deep learning represented 23% among the included studies (44). Most conventional machine learning research focused on radiomics applied to CT and MRI. Currently, the emphasis is on AI and radiomics as emerging noninvasive tools for providing diagnostic and prognostic information. (43).

3.4. Abdominal Radiology

Various aspects of abdominal imaging have been included in the studies with AI perspective. Ultrasound was the specific modality focused on Cai et al.'s review, which included 57 manuscripts in the final review. The primary region-based applications consisted of multiorgan evaluation (28%), gynecology (26%), hepatobiliary applications (23%), and musculoskeletal applications (14%). When based on the main methodological approach, the applications were classified as deep learning (65%), machine learning (23%), natural language processing (9%), and robots (4%) in their study (45). In an MRI study by Dai et al. the

researchers compared the diagnostic success of radiologists, AI and their combination to determine the sensitivity of AI and the radiologists in the identification of focal liver lesions and compared the pathological sizes of 122 lesions which were surgically removed. The radiologist–AI collaboration outperformed the radiologist working independently, regarding detection rate (0.894 vs. 0.825) and sensitivity (0.883 vs. 0.806). The AI revealed significantly higher sensitivity than radiologists in identifying all lesions smaller than 20 mm (0.848 vs. 0.788) (46). In a review comprising 44 studies about Hepatocellular Carcinoma and Cholangiocarcinoma identification through the use of abdominal CT imaging, they revealed that convolutional neural networks (CNNs) were the most frequently applied model architectures, though several studies also employed more sophisticated deep learning approaches and hybrid models combining radiomic and clinical data. The reported diagnostic capability was generally high, with sensitivity and specificity ranging between 75% and 100%, overall accuracy between 73% and 96%, and AUC values spanning from 0.74 to 0.99 for the included studies. Studies that integrated multi-modal imaging data (CT and MRI) or combined radiomic features with genomic information demonstrated the best diagnostic performance, with both accuracy and specificity surpassing the 90–95% range (47). Convolutional neural networks (CNNs) developed for pancreas segmentation form the basis of many pancreatic ductal adenocarcinoma (PDA) detection models. In one study, an AI model trained on 696 portal-phase diagnostic CT scans containing PDA and 1,080 control images achieved 92% accuracy on an internal test dataset (1,238 cases: 409 PDA and 829 controls) and 86% accuracy on an external dataset (194 PDA and 80 controls) (48). Another system, PANDA (Pancreatic Cancer Detection with Artificial Intelligence), also demonstrated strong performance in detecting PDA despite being trained on non-contrast CT scans, which were previously regarded as less suitable for identifying pancreatic cancer. Using a dataset of 3,208 patients, PANDA reached an AUC of 0.986–0.996 across several validation cohorts and significantly outperformed radiologists, improving sensitivity by 34.1% and specificity by 6.3% (49). Earlier systematic reviews evaluated the methodological quality of 30 studies investigating the application of AI in renal mass identification and underscored the significant role of artificial intelligence in facilitating clinical integration (50). There are many more aspects related to the integration of AI in abdominal imaging. To illustrate, abdominal trauma is one of these issues; however, AI applications in trauma radiology are still at an early stage of development, and only a limited number of tools have received FDA approval so far as Dreizin et al. concluded in their review article (51).

3.5. Cardiac Imaging

MRI has progressively become a key tool in the diagnosis and management of cardiovascular diseases. Over recent decades, extensive research has demonstrated its strong diagnostic capability across numerous clinical indications, often complementing other imaging modalities such as nuclear imaging, echocardiography, and computed tomography (CT). Owing to its ability to comprehensively assess the entire heart, MRI has a pivotal role in evaluating myocardial viability in patients with ischemic cardiomyopathy, noninvasively differentiating among various causes of nonischemic cardiomyopathy, and

informing surgical planning for structural and congenital heart diseases. These advantages arise from the diverse imaging techniques used in cardiac MRI. Cine steady-state free-precession (SSFP) imaging provides detailed morphological and functional information, while T1 and T2 mapping together with delayed enhancement imaging allow evaluation of myocardial tissue characteristics. In addition, 4D flow phase-contrast imaging offers hemodynamic insights, enabling investigation of valvular function and quantification of intracardiac shunts. Comprehensive information obtained through cardiac MRI makes it possible to diagnose and predict the course of various cardiac diseases that cannot otherwise be evaluated noninvasively. Accordingly, it has been established as a routine diagnostic method in many advanced cardiac care facilities (52).

Masutani et al. developed a modified 3D U-Net model designed to estimate myocardial velocities from cine SSFP MRI images, using co-registered myocardial velocity information derived from 4D Flow MRI as training data. Their results demonstrated that a CNN could successfully detect areas of abnormal myocardial wall motion in a test cohort of 53 patients with ischemic heart disease. The model achieved 86% sensitivity, 85% specificity, and an overall accuracy of 86%, performance levels that were comparable to those of four expert cardiac radiologists (53). To segment the left ventricular myocardial scar Zabihollahy et al. developed a 3D CNN model (54). Fahmy and colleagues later developed a three-dimensional CNN that was trained using a large dataset consisting of manually segmented images collected from multiple centers and different imaging vendors. The results of this study demonstrated that LGE scars in patients with hypertrophic cardiomyopathy could be quantified automatically, with an accuracy level comparable to the manual assessments performed by expert readers (55).

3.6. Breast Imaging

According to the Global Cancer Observatory (GCO) data belongs to the year 2022, breast cancer is the most frequent cancer type in females and in the second place including for both sexes (56). Breast cancer screening lowers cancer-related mortality and enables less invasive treatment. The primary imaging method used for screening is digital mammography, which demanstrates limited sensitivity (especially in women with dense breast tissue) and generates a relatively high rate of false-positive results. These limitations have historically led to substantial interest in the development of computer-assisted tools to aid radiologists in more effective early cancer detection (11).

In mammography research, numerous publicly accessible datasets play a key role in supporting the development of machine learning methods. By providing annotated data and a variety of images, these resources allow researchers to effectively train, test, and validate their algorithms. Applicating AI to be used for mammography can be mainly discussed according to detection and classification of the masses, segmentation of the lesions, improving image quality, and breast cancer risk assessment. Additionally, AI can be practiced using datasets which have been particularly based on breast ultrasound images (57). In a study comprising 22,621 mammograms, AI software reached an AUC of 89.6% in breast cancer detection (58). MRI additionally plays a critical role in detection of breast masses by detailed anatomical images and delineation of soft tissues of the breast with

high precision. A systematic review and meta-analysis encompassing 40 investigations revealed that convolutional neural networks (CNNs) were utilized in 62.5% (25 of 40) of the models, whereas the remaining 37.5% (15 of 40) employed hybrid composite models (HCMs). The pooled results indicated a high diagnostic capacity, with an area under the curve (AUC) of 0.90, sensitivity of 88%, and specificity of 90% (59).

4. AI for Non-Interpretative Uses in Radiology

This illustration presents main diagnostic tasks where radiological diagnostic process is involved. After data acquisition to construct the image, preprocessing is involved which represents computerized operations performed on the raw data after image capturing to correct errors and standardize the image before it is displayed for a radiologist or AI. Image-based clinical tasks [which consists of lesion detection, segmentation and characterization of the lesion to constitute the diagnosis and staging or/and comparison of the lesion with previous imaging(s)], reporting radiological results and lastly collecting and analyzing patient's other medical results and integration of these results together to indicate the final diagnosis (Figure 2). AI is not only an option for image interpretations, but also useful and provides time-saving solutions for the workflow. AI also assists in patient triage and enables refinement of image, increase image quality and reduce radiation doses in imaging protocols.

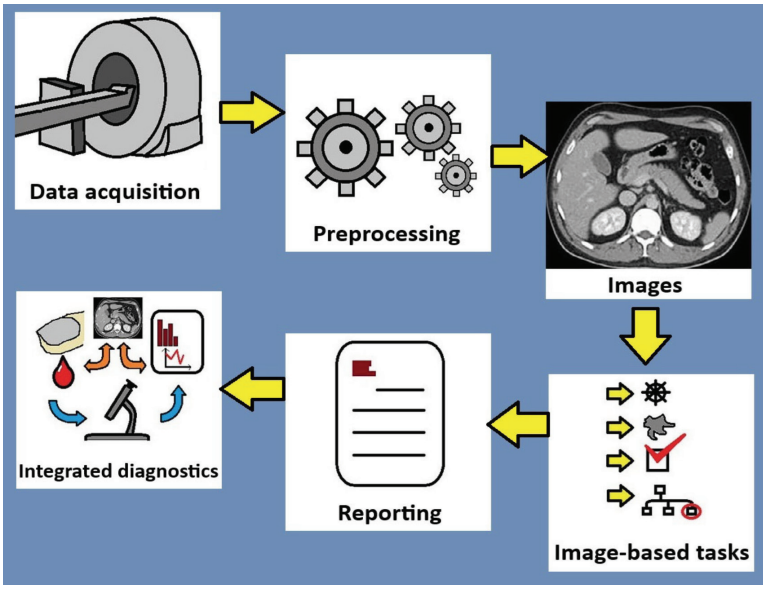


Figure 2. The diagnostic workflow of radiology and final decision making together with patient's other medical results. Data acquisition enables raw data, and the images are created after preprocessing. Through a further analyzation using image -based tasks such as detecting lesions, segmentation (for AI), lesion characterization, classification, staging, comparison of the lesion or anomaly with previous images, the data is documented by a structured and standardized radiology report. A final diagnosis can be made by integrating the radiological findings along with other medical results of the patient. AI may contribute to any step in this process to reach the final diagnosis.

4.1. AI for Scheduling Scans

AI can be helpful to triage patients and determine patient priority. When patients who have more critical conditions are detected by radiological images and higher medical priority than other patients, an AI system may arrange this radiologist's review list and put these patients in front lines or at the top of the list when medically required. In the research by Arbabshirani et al. they suggested a machine learning (ML) model to analyze head CT images, prioritize radiologist's worklist and time-saving diagnosis of intracranial hemorrhage. This ML indicated 94 of 347 routine radiological studies as being an emergent case and the results indicated 60 true positives and 34 false positives with additional determination of 5 new hemorrhages. The reduction time of the reporting process was 8.5 h to 19 min in their study (60). Moreover, AI-based applications are being developed to improve the efficiency of scanner utilization and to minimize the waiting times of the patients. Using data obtained from the Radiology Information System (RIS), delays can be predicted, with ultrasound examinations typically showing the highest likelihood of delay, followed by radiography, CT, and MRI (61).

4.2. Refinement of Image Quality, Image Processing and Radiation Dose Reduction

Refinements of the processed images and directly transforming the raw images are the two main approaches that have been used to upgrade image quality (62). Noise reduction is one of the important topics in this regard. Algorithms based on artificial intelligence, such as AUTOMAP, have been designed to operate directly on sensor data in order to enhance imaging performance. By utilizing deep learning techniques, AUTOMAP can generate MR images with higher quality by greater resistance to noise and fewer reconstruction artifacts than traditional reconstruction approaches, all without requiring the acquisition of additional data (63). Abdominal MR examinations such as liver MRI or MR choangiopancreatography (MRCP) require sequence repetitions due to patient's motion during the scan, to optimize the anatomic coverage, extra scans added by the radiologist or technologist, and some other reasons (64). A CNN trained to indicate non-diagnostic image quality of T2-weighted liver images in comparison with two radiologists yielded sensitivity and specificity values of 67% and 81% while reviewer 1 indicated 47% and 80% and reviewer 2 indicated 94% and 86% in a study (65). The relatively long acquisition period required for MRI often forces a compromise in image quality in order to fit within limited scanning durations. In addition, MR sequences that rely on incomplete sampling of k-space (a method used to shorten acquisition time) can lead to prolonged image reconstruction processes. Deep learning approaches have been applied to reconstruct MR images from undersampled k-space data by training convolutional neural networks (CNNs) to learn the relationship between zero-filled images and fully sampled MR images. Similarly, deep learning has been utilized for reconstructing MR images from clinical multicoil datasets, which helps shorten scan times through parallel imaging techniques. Overall, these methods can significantly reduce the time required to obtain diagnostically useful MR images. For instance, diffusion MRI acquisition can be accelerated up to twelvefold when deep learning is used to optimize the processing of q-space data (62).

Dose reduction in CT images results in relatively lower quality images. CT images obtained by lower radiation dosage but optimized by AI would make an excellent contribution to radiology practice. This can be achieved with training AI by making the system learn what normal morphology and pathological conditions look like in images obtained by both reduced and standardized radiation doses. AI models can increase the quality of radiological images acquired by low-dose raw sensor data (66,67). In a multicenter study, the diagnostic quality of low-dose scans produced using this approach was compared with standard-dose CT scans from the same patients. The results showed that 28% of reviews of standard reconstruction images and 91% of artificial neural network (ANN) images were rated as diagnostic. If an image was considered non-diagnostic with the standard reconstruction technique 89% of reviewers considered the images diagnostic when reconstructed with ANN (68).

4.3. Effect of AI on Workflow

In radiology practice, a hanging protocol refers to a collection of automated rules within a Picture Archiving and Communication System (PACS) system that determines how medical images (such as X-rays, CT, and MRI scans) are displayed on the screen, including their arrangement, size, and orientation. By automatically organizing imaging studies for review, it removes the need for manual adjustments like resizing, rotating, or rearranging images, thereby enhancing workflow efficiency and ensuring more consistent image interpretation. Developing optimal hanging protocols can be difficult due to variations in individual user preferences, inconsistencies within (Digital Imaging and Communications in Medicine) DICOM metadata, and differences among imaging equipment vendors. For instance, a brain MRI obtained from one vendor's scanner may use sequence names that differ from those used by another vendor, making it difficult for simple rule-based machine learning methods to determine the appropriate hanging protocol. One potential solution is the use of AI systems that generate hanging protocols dynamically by analyzing the image content itself rather than relying solely on metadata (62). On the other hand, constitution of study protocols is a significant part of the radiology practice. For the optimal study protocol, adequate information about patient's medical condition such as clinical information, results of the laboratory tests, or reports of the previous radiological examinations should be considered carefully. AI may also be helpful for this time-consuming process and may prevent human error factors.

5. Problems and Ethical Facts for AI

5.1. Challenges of AI in Medical Imaging

Machine learning can be achieved by supervised training, or the system may learn itself without guiding supervision. The dataset should contain adequate information and comprise enough information about a broad spectrum of diseases. The labelled data is crucial for the model with a supervisor and data labelling is a very time-consuming process

and requires a dedicated, meticulous labor effort. Several techniques have been developed to reduce the heavy burden of supervised learning (69). These include approaches such as transfer learning, in which knowledge gained from one domain is applied to another domain; active learning, where the algorithm selectively requests input or annotations from a human user for certain data samples; and weakly supervised learning, in which the available labels are considered incomplete, imprecise, or noisy. The widespread publicity surrounding AI has begun to discourage some medical students from choosing radiology as a career. Some surveys conducted in the United Kingdom, Canada, Germany, and the United States indicate that many students are concerned that AI could eventually replace diagnostic radiologists, leading them to avoid specializing in this field. Conversely, a considerable number of practicing radiologists report that they are reluctant to adopt AI technologies because they do not fully understand how these systems function (11). Additionally, the need for regulations (such as FDA or CE) and their necessities for the clearance of the new AI algorithms is another aspect to discuss.

5.2. Medicolegal Issues and Ethics

In the year 2013 Lee et al. reported that Approximately 75% of malpractice claims involving radiologists stem from diagnostic errors. Radiologists are therefore highly concerned about overlooking abnormalities or producing false-positive interpretations. Studies indicate that retrospective reviews of radiologic examinations reveal error rates of about 30%, whereas real-time error rates in routine clinical practice average around 3–5% (70). Radiological errors are generally divided into two main types: perceptual errors (where the radiologist fails to see the finding) and cognitive (interpretive) errors (where the finding is observed but misinterpreted). Among these, perceptual errors are much more frequent, representing about 60–80% of all radiologists' mistakes (71). A well-trained AI system is expected to reduce perceptual errors and indicate accurate diagnosis.

Medicolegal problems related to utilizing AI in radiology practice are another point of view to discuss. With the utilization of AI systems some questions will rise inevitably such as: Who will be responsible for malpractice? Which part of the decision-making is in the responsibility of radiologists if some (with variable percentages) of the work is proceeded by AI? If radiologists just take part in the diagnostic process, will they remain as the primary responsible for the incorrect diagnosis? Will the developers of the AI system be responsible for incorrect decisions? If the AI is still in the learning process will the manufacturer still be responsible for malpractice and how? Legal responsibility for medical malpractice arising from the use of AI in clinical practice remains unresolved, and regulatory frameworks are still evolving (72).

In the condensed summary of an international multi society statement on ethics of artificial intelligence (AI) in radiology produced by the European Society of Radiology, American College of Radiology, Society for Imaging Informatics in Medicine, Radiological Society of North America, Canadian Association of Radiologists, European Society of Medical Imaging Informatics, and American Association of Physicists in Medicine some important key points were declared. Those were: "The ethical application of AI in radiol-

ogy should aim to enhance patient well-being, reduce potential harm, and ensure that both the benefits and risks are fairly distributed among all stakeholders. AI systems used in radiology must be transparent, reliable, and designed to minimize bias in decision-making processes, while maintaining clear human responsibility and accountability for their design and operation. The radiology community should begin developing ethical guidelines and professional standards for the use of AI. Radiologists will continue to be responsible for patient care and will need to develop new competencies to effectively practice within an evolving AI-driven healthcare environment." They also concluded that new ethical challenges are likely to arise quickly and on a regular basis, and our understanding and evaluation of these issues will evolve over time. Therefore, while it is important to examine the ethical aspects of AI in radiology today, it will also be necessary to revisit and reassess this topic periodically as our knowledge of its impact and potential expands. In addition, the AI algorithms or tools used in radiology should be regularly reviewed to ensure that they continue to comply with updated regulations and standards (73).

6. Conclusion

There are many aspects of using AI in radiology practice. Not only does the interpretative use of the AI systems regarding different modalities and region based radiological approaches but also other benefits of AI, which may provide significant assistance to workflow in a radiology department, are discussed along with difficulties of the AI training and the possible medicolegal problems of AI in radiology within this chapter. In this era of AI in many sectors worldwide, medicine and particularly the radiology departments are expected to change swiftly and adapt to this course of action. AI is becoming a smart partner to radiologists and the medical service in radiology which seems to have a huge capacity to alter today's radiology perspective. It seems that today's radiologists and all other physicians should adapt to this process and work with AI in harmony to consummate medical practice.

7. References

1. Budovec JJ, Lam CA, Kahn CE Jr. (2014). Informatics in radiology: radiology gamuts ontology: differential diagnosis for the Semantic Web. Radiographics, 34(1): 254-264. https://doi.org/10.1148/rg.341135036.
2. Miles RC, Lehman CD. (2021). Artificial Intelligence for Image Interpretation: Point-The Radiologist's Potential Friend. AJR Am J Roentgenol, 217(3): 556-557. https://doi.org/10.2214/AJR.21.25564.
3. Lexa FJ, Jha S. (2021). Artificial Intelligence for Image Interpretation: Counterpoint-The Radiologist's Incremental Foe. AJR Am J Roentgenol, 217(3): 558-559. https://doi: 10.2214/AJR.21.25484.
4. Langlotz CP. (2019). Will Artificial Intelligence Replace Radiologists? Radiol Artif Intell, 1(3): e190058. https://doi.org/10.1148/ryai.2019190058.
5. European Society of Radiology (ESR). (2022). Current practical experience with artificial intelligence in clinical radiology: a survey of the European Society of Radiology. Insights Imaging, 13(1): 107. https://doi.org/10.1186/s13244-022-01247-y.
6. Pianykh OS, Langs G, Dewey M, Enzmann DR, Herold CJ, Schoenberg SO, Brink JA. (2020). Continuous Learning AI in Radiology: Implementation Principles and Early Applications. Radiology, 297(1): 6-14. https://doi.org/10.1148/radiol.2020200038.
7. Tariq A, Purkayastha S, Padmanaban GP, Krupinski E, Trivedi H, Banerjee I, Gichoya JW. (2020). Current Clinical Applications of Artificial Intelligence in Radiology and Their Best Supporting Evidence. J Am Coll Radiol, 17(11): 1371-1381. https://doi.org/10.1016/j.jacr.2020.08.018.

8. Yu AC, Mohajer B, Eng J. (2022). External Validation of Deep Learning Algorithms for Radiologic Diagnosis: A Systematic Review. Radiol Artif Intell, 4(3): e210064. https://doi.org/10.1148/ryai.210064.
9. Allen B, Dreyer K, Stibolt R Jr, Agarwal S, Coombs L, Treml C, Elkholy M, Brink L, Wald C. (2021). Evaluation and Real-World Performance Monitoring of Artificial Intelligence Models in Clinical Practice: Try It, Buy It, Check It. J Am Coll Radiol, 18(11): 1489-1496. https://doi.org/10.1016/j.jacr.2021.08.022.
10. Vasey B, Ursprung S, Beddoe B, Taylor EH, Marlow N, Bilbro N, Watkinson P, McCulloch P. (2021). Association of Clinician Diagnostic Performance With Machine Learning-Based Decision Support Systems: A Systematic Review. JAMA Netw Open, 4(3): e211276. https://doi.org/10.1001/jamanetworkopen.2021.1276.
11. Mello-Thoms C, Mello CAB. (2023). Clinical applications of artificial intelligence in radiology. Br J Radiol, 96(1150): 20221031. https://doi.org/10.1259/bjr.20221031.
12. Koohi-Moghadam M, Bae KT. (2023). Generative AI in Medical Imaging: Applications, Challenges, and Ethics. J Med Syst, 47(1): 94. https://doi.org/10.1007/s10916-023-01987-4.
13. Behzad S, Tabatabaei SMH, Lu MY, Eibschutz LS, Gholamrezanezhad A. (2024). Pitfalls in Interpretive Applications of Artificial Intelligence in Radiology. AJR Am J Roentgenol, 223(4): e2431493. https://doi.org/10.2214/AJR.24.31493.
14. Yang Y, Mei G, Piccialli F. (2024). A Deep Learning Approach Considering Image Background for Pneumonia Identification Using Explainable AI (XAI). IEEE/ACM Trans Comput Biol Bioinform, 21(4): 857-868. https://doi.org/10.1109/TCBB.2022.3190265.
15. Banerjee I, Bhattacharjee K, Burns JL, Trivedi H, Purkayastha S, Seyyed-Kalantari L, Patel BN, Shiradkar R, Gichoya J. (2023). "Shortcuts" Causing Bias in Radiology Artificial Intelligence: Causes, Evaluation, and Mitigation. J Am Coll Radiol, 20(9): 842-851. https://doi.org/10.1016/j.jacr.2023.06.025.
16. Chambon P, Cook TS, Langlotz CP. (2023). Improved Fine-Tuning of In-Domain Transformer Model for Inferring COVID-19 Presence in Multi-Institutional Radiology Reports. J Digit Imaging, 36(1):164-177. https://doi.org/10.1007/s10278-022-00714-8.
17. Rubin DL. (2019). Artificial Intelligence in Imaging: The Radiologist's Role. J Am Coll Radiol, 16(9 Pt B): 1309-1317. https://doi.org/10.1016/j.jacr.2019.05.036.
18. Eche T, Schwartz LH, Mokrane FZ, Dercle L. (2021). Toward Generalizability in the Deployment of Artificial Intelligence in Radiology: Role of Computation Stress Testing to Overcome Underspecification. Radiol Artif Intell, 3(6): e210097. https://doi.org/10.1148/ryai.2021210097.
19. Onakpojeruo EP, Mustapha MT, Ozsahin DU, Ozsahin I. (2024). A Comparative Analysis of the Novel Conditional Deep Convolutional Neural Network Model, Using Conditional Deep Convolutional Generative Adversarial Network-Generated Synthetic and Augmented Brain Tumor Datasets for Image Classification. Brain Sci, 14(6): 559. https://doi.org/10.3390/brainsci14060559.
20. Onakpojeruo EP, Mustapha MT, Ozsahin DU, Ozsahin I. (2024). Enhanced MRI-based brain tumour classification with a novel Pix2pix generative adversarial network augmentation framework. Brain Commun, 6(6): fcae372. https://doi.org/10.1093/braincomms/fcae372.
21. Szmyd B, Podstawka M, Wiśniewski K, Zaczkowski K, Puzio T, Tomczyk A, Wojciechowski A, Jaskólski DJ, Bobeff EJ. (2025). AI-Driven Innovations in Neuroradiology and Neurosurgery: Scoping Review of Current Evidence and Future Directions. Cancers (Basel), 17(16): 2625. https://doi.org/10.3390/cancers17162625.
22. Fasen BACM, Berendsen RCM, Kwee RM. (2022). Artificial intelligence software for diagnosing intracranial arterial occlusion in patients with acute ischemic stroke. Neuroradiology, 64(8): 1579-1583. https://doi.org/10.1007/s00234-022-02912-1.
23. Daga K, Agarwal S, Moti Z, Lee MBK, Din M, Wood D, Modat M, Booth TC. (2025). Machine Learning Algorithms to Predict the Risk of Rupture of Intracranial Aneurysms: a Systematic Review. Clin Neuroradiol, 35(1): 3-16. https://doi.org/10.1007/s00062-024-01474-4.
24. Nam JG, Kim M, Park J, Hwang EJ, Lee JH, Hong JH, Goo JM, Park CM. (2021). Development and validation of a deep learning algorithm detecting 10 common abnormalities on chest radiographs. Eur Respir J, 57(5): 2003061. https://doi.org/10.1183/13993003.03061-2020.
25. Nam JG, Park S, Hwang EJ, Lee JH, Jin KN, Lim KY, Vu TH, Sohn JH, Hwang S, Goo JM, Park CM. (2019). Development and Validation of Deep Learning-based Automatic Detection Algorithm for Malignant Pulmonary Nodules on Chest Radiographs. Radiology, 290(1): 218-228. https://doi.org/10.1148/radiol.2018180237.
26. Ahn JS, Ebrahimian S, McDermott S, Lee S, Naccarato L, Di Capua JF, Wu MY, Zhang EW, Muse V, Miller B, Sabzalipour F, Bizzo BC, Dreyer KJ, Kaviani P, Digumarthy SR, Kalra MK. (2022). Association of Artificial Intelligence-Aided Chest Radiograph Interpretation With Reader Performance and Efficiency. JAMA Netw Open, 5(8): e2229289. https://doi.org/10.1001/jamanetworkopen.2022.29289.
27. Yoo H, Kim EY, Kim H, Choi YR, Kim MY, Hwang SH, Kim YJ, Cho YJ, Jin KN. (2022). Artificial Intelligence-Based Identification of Normal Chest Radiographs: A Simulation Study in a Multicenter Health Screening Cohort. Korean J Radiol, 23(10): 1009-1018. https://doi.org/10.3348/kjr.2022.0189.
28. Pehrson LM, Nielsen MB, Ammitzbøl Lauridsen C. (2019). Automatic Pulmonary Nodule Detection Applying Deep Learning or Machine Learning Algorithms to the LIDC-IDRI Database: A Systematic Review. Diagnostics (Basel), 9(1): 29. https://doi.org/10.3390/diagnostics9010029.
29. Ciompi, F., Chung, K., van Riel, S. J., Setio, A. A. A., Gerke, P. K., Jacobs, C., Scholten, E. T., Schaefer-Prokop, C., Wille, M. M. W., Marchianò, A., Pastorino, U., Prokop, M., & van Ginneken, B. (2017). Towards automatic pulmonary nodule management in lung cancer screening with deep learning. Scientific Reports, *7*, 46479. https://doi.org/10.1038/srep46479. Erratum: Ciompi, F., et al. (2017). Erratum to: Towards automatic pulmonary nodule management in lung cancer screening with deep learning. Scientific Reports, *7*, 46878. https://doi.org/10.1038/srep46878

30. Ardila, D., Kiraly, A. P., Bharadwaj, S., Choi, B., Reicher, J. J., Peng, L., Tse, D., Etemadi, M., Ye, W., Corrado, G., Naidich, D. P., & Shetty, S. (2019). End-to-end lung cancer screening with three-dimensional deep learning on low-dose chest computed tomography. Nature Medicine, *25*(6), 954–961. https://doi.org/10.1038/s41591-019-0447-x. Erratum*:* Ardila, D., et al. (2019). Erratum to: End-to-end lung cancer screening with three-dimensional deep learning on low-dose chest computed tomography. Nature Medicine, *25*(8), 1319. https://doi.org/10.1038/s41591-019-0536-x
31. Huang, S. C., Kothari, T., Banerjee, I., Chute, C., Ball, R. L., Borus, N., Huang, A., Patel, B. N., Rajpurkar, P., Irvin, J., Dunnmon, J., Bledsoe, J., Shpanskaya, K., Dhaliwal, A., Zamanian, R., Ng, A. Y., & Lungren, M. P. (2020). PENet: A scalable deep-learning model for automated diagnosis of pulmonary embolism using volumetric CT imaging. NPJ Digital Medicine, 3, 61. https://doi.org/10.1038/s41746-020-0266-y Erratum: Huang, S. C., et al. (2020). Erratum to: PENet: A scalable deep-learning model for automated diagnosis of pulmonary embolism using volumetric CT imaging. NPJ Digital Medicine, 3, 102. https://doi.org/10.1038/s41746-020-00310-6
32. Walsh SLF, Calandriello L, Silva M, Sverzellati N. (2018). Deep learning for classifying fibrotic lung disease on high-resolution computed tomography: a case-cohort study. Lancet Respir Med, 6(11): 837-845. https://doi.org/10.1016/S2213-2600(18)30286-8.
33. Laur O, Wang B. (2022). Musculoskeletal trauma and artificial intelligence: current trends and projections. Skeletal Radiol, 51(2): 257-269. https://doi.org/10.1007/s00256-021-03824-6.
34. Gale W, Oakden-Rayner L, Carneiro G, Bradley AP, Palmer LJ. (2017). Detecting hip fractures with radiologist-level performance using deep neural networks. https://doi.org/10.48550/arXiv.1711.06504
35. Chen HY, Hsu BW, Yin YK, Lin FH, Yang TH, Yang RS, Lee CK, Tseng VS. (2021). Application of deep learning algorithm to detect and visualize vertebral fractures on plain frontal radiographs. PLoS One, 16(1): e0245992. https://doi.org/10.1371/journal.pone.0245992.
36. Chung SW, Han SS, Lee JW, Oh KS, Kim NR, Yoon JP, Kim JY, Moon SH, Kwon J, Lee HJ, Noh YM, Kim Y. (2018). Automated detection and classification of the proximal humerus fracture by using deep learning algorithm. Acta Orthop, 89(4): 468-473. https://doi.org/10.1080/17453674.2018.1453714.
37. Tanzi L, Vezzetti E, Moreno R, Aprato A, Audisio A, Massè A. (2020). Hierarchical fracture classification of proximal femur X-Ray images using a multistage Deep Learning approach. Eur J Radiol, 133: 109373. https://doi.org/10.1016/j.ejrad.2020.109373.
38. Li YC, Chen HH, Horng-Shing Lu H, Hondar Wu HT, Chang MC, Chou PH. (2021). Can a Deep-learning Model for the Automated Detection of Vertebral Fractures Approach the Performance Level of Human Subspecialists? Clin Orthop Relat Res, 479(7): 1598-1612. https://doi.org/10.1097/CORR.0000000000001685.
39. Olczak J, Emilson F, Razavian A, Antonsson T, Stark A, Gordon M. (2021). Ankle fracture classification using deep learning: automating detailed AO Foundation/Orthopedic Trauma Association (AO/OTA) 2018 malleolar fracture identification reaches a high degree of correct classification. Acta Orthop, 92(1): 102-108. https://doi.org/ 10.1080/17453674.2020.1837420.
40. Zhou QQ, Tang W, Wang J, Hu ZC, Xia ZY, Zhang R, Fan X, Yong W, Yin X, Zhang B, Zhang H. (2021). Automatic detection and classification of rib fractures based on patients' CT images and clinical information via convolutional neural network. Eur Radiol, 31(6): 3815-3825. https://doi.org/10.1007/s00330-020-07418-z.
41. Bien N, Rajpurkar P, Ball RL, Irvin J, Park A, Jones E, Bereket M, Patel BN, Yeom KW, Shpanskaya K, Halabi S, Zucker E, Fanton G, Amanatullah DF, Beaulieu CF, Riley GM, Stewart RJ, Blankenberg FG, Larson DB, Jones RH, Langlotz CP, Ng AY, Lungren MP. (2018). Deep-learning-assisted diagnosis for knee magnetic resonance imaging: Development and retrospective validation of MRNet. PLoS Med, 15(11): e1002699. https://doi.org/10.1371/journal.pmed.1002699.
42. Liu F, Guan B, Zhou Z, Samsonov A, Rosas H, Lian K, Sharma R, Kanarek A, Kim J, Guermazi A, Kijowski R. (2019). Fully Automated Diagnosis of Anterior Cruciate Ligament Tears on Knee MR Images by Using Deep Learning. Radiol Artif Intell, 1(3): 180091. https://doi.org/10.1148/ryai.2019180091.
43. Gitto S, Serpi F, Albano D, Risoleo G, Fusco S, Messina C, Sconfienza LM. (2024). AI applications in musculoskeletal imaging: a narrative review. Eur Radiol Exp, 8(1): 22. https://doi.org/10.1186/s41747-024-00422-8.
44. Li MD, Ahmed SR, Choy E, Lozano-Calderon SA, Kalpathy-Cramer J, Chang CY. (2022). Artificial intelligence applied to musculoskeletal oncology: a systematic review. Skeletal Radiol, 51(2): 245-256. https://doi.org/10.1007/s00256-021-03820-w.
45. Cai L, Pfob A. (2025). Artificial intelligence in abdominal and pelvic ultrasound imaging: current applications. Abdom Radiol (NY), 50(4): 1775-1789. https://doi.org/10.1007/s00261-024-04640-x.
46. Dai H, Xiao Y, Fu C, Grimm R, von Busch H, Stieltjes B, Choi MH, Xu Z, Chabin G, Yang C, Zeng M. (2025). Deep Learning-Based Approach for Identifying and Measuring Focal Liver Lesions on Contrast-Enhanced MRI. J Magn Reson Imaging, 61(1): 111-120. https://doi.org/10.1002/jmri.29404.
47. Rattanapitoon SK, Arunsarn P, Meererksom T, Thanchonnang C, Boonsuya A, Phinsiri S, Nomsungnoen P, Pongseeda P, Keeratibharat N, Chansangrat J, Pechdee P, Rattanapitoon NK. (2026). Advancing Diagnostic Accuracy in Liver Cancer: A Systematic Review of Artificial Intelligence Applications in Hepatocellular Carcinoma and Cholangiocarcinoma Detection Using Abdominal CT Imaging. Asian Pac J Cancer Prev, 27(1): 5-18. https://doi.org/10.31557/APJCP.2026.27.1.5.
48. Korfiatis P, Suman G, Patnam NG, Trivedi KH, Karbhari A, Mukherjee S, Cook C, Klug JR, Patra A, Khasawneh H, Rajamohan N, Fletcher JG, Truty MJ, Majumder S, Bolan CW, Sandrasegaran K, Chari ST, Goenka AH. (2023). Automated Artificial Intelligence Model Trained on a Large Data Set Can Detect Pancreas Cancer on Diagnostic Computed Tomography Scans As Well As Visually Occult Preinvasive Cancer on Prediagnostic Computed Tomography Scans. Gastroenterology, 165(6): 1533-1546.e4. https://doi.org/ 10.1053/j.gastro.2023.08.034.
49. Cao K, Xia Y, Yao J, Han X, Lambert L, Zhang T, Tang W, Jin G, Jiang H, Fang X, Nogues I, Li X, Guo W, Wang Y, Fang W, Qiu M, Hou Y, Kovarnik T, Vocka M, Lu Y, Chen Y, Chen X, Liu Z, Zhou J, Xie C, Zhang R, Lu H, Hager GD, Yuille AL, Lu

L, Shao C, Shi Y, Zhang Q, Liang T, Zhang L, Lu J. (2023). Large-scale pancreatic cancer detection via non-contrast CT and deep learning. Nat Med, 29(12): 3033-3043. https://doi.org/ 10.1038/s41591-023-02640-w.
50. Sheikhy A, Dehghani Firouzabadi F, Lay N, Jarrah N, Yazdian Anari P, Malayeri A. (2025). State of the art review of AI in renal imaging. Abdom Radiol (NY), 50(11): 5305-5323. https://doi.org/10.1007/s00261-025-04963-3.
51. Dreizin D, Cheng CT, Liao CH, Jindal A, Colak E. (2025). Artificial intelligence for abdominopelvic trauma imaging: trends, gaps, and future directions. Abdom Radiol (NY), 50(10): 5028-5043. https://doi.org/10.1007/s00261-025-04816-z
52. Mahmoodi A, Yeluru A, Aguirre-Chavez J, Lamar-Bruno K, Punjabi K, Malkasian S, Song A, Masutani E, Hsiao A. (2026). Artificial Intelligence in Cardiovascular MRI: From Imaging to Biomechanics and Diagnosis. J Thorac Imaging, 41(2): 10.1097/RTI.0000000000000864. https://doi.org/10.1097/RTI.0000000000000864.
53. Masutani EM, Chandrupatla RS, Wang S, Zocchi C, Hahn LD, Horowitz M, Jacobs K, Kligerman S, Raimondi F, Patel A, Hsiao A. (2023). Deep Learning Synthetic Strain: Quantitative Assessment of Regional Myocardial Wall Motion at MRI. Radiol Cardiothorac Imaging, 5(3): e220202. https://doi.org/10.1148/ryct.220202.
54. Zabihollahy F, White JA, Ukwatta E. (2019). Convolutional neural network-based approach for segmentation of left ventricle myocardial scar from 3D late gadolinium enhancement MR images. Med Phys, 46(4): 1740-1751. https://doi.org/10.1002/mp.13436.
55. Fahmy AS, Neisius U, Chan RH, Rowin EJ, Manning WJ, Maron MS, Nezafat R. (2020). Three-dimensional Deep Convolutional Neural Networks for Automated Myocardial Scar Quantification in Hypertrophic Cardiomyopathy: A Multicenter Multivendor Study. Radiology, 294(1): 52-60. https://doi.org/10.1148/radiol.2019190737.
56. https://gco.iarc.who.int/media/globocan/factsheets/populations/900-world-fact-sheet.pdf
57. Al-Karawi D, Al-Zaidi S, Helael KA, Obeidat N, Mouhsen AM, Ajam T, Alshalabi BA, Salman M, Ahmed MH. (2024). A Review of Artificial Intelligence in Breast Imaging. Tomography, 10(5): 705-726. https://doi.org/10.3390/tomography10050055.
58. Seker ME, Koyluoglu YO, Ozaydin AN, Gurdal SO, Ozcinar B, Cabioglu N, Ozmen V, Aribal E. (2024). Diagnostic capabilities of artificial intelligence as an additional reader in a breast cancer screening program. Eur Radiol, 34(9): 6145-6157. https://doi.org/10.1007/s00330-024-10661-3.
59. Abdullah KA, Marziali S, Nanaa M, Escudero Sánchez L, Payne NR, Gilbert FJ. (2025). Deep learning-based breast cancer diagnosis in breast MRI: systematic review and meta-analysis. Eur Radiol, 35(8): 4474-4489. https://doi.org/10.1007/s00330-025-11406-6.
60. Arbabshirani MR, Fornwalt BK, Mongelluzzo GJ, Suever JD, Geise BD, Patel AA, Moore GJ. (2018). Advanced machine learning in action: identification of intracranial hemorrhage on computed tomography scans of the head with clinical workflow integration. NPJ Digit Med, 1: 9. https://doi.org/10.1038/s41746-017-0015-z.
61. Curtis C, Liu C, Bollerman TJ, Pianykh OS. (2018). Machine Learning for Predicting Patient Wait Times and Appointment Delays. J Am Coll Radiol, 15(9): 1310-1316. https://doi.org/10.1016/j.jacr.2017.08.021.
62. Richardson ML, Garwood ER, Lee Y, Li MD, Lo HS, Nagaraju A, Nguyen XV, Probyn L, Rajiah P, Sin J, Wasnik AP, Xu K. (2021). Noninterpretive Uses of Artificial Intelligence in Radiology. Acad Radiol, 28(9): 1225-1235. https://doi.org/10.1016/j.acra.2020.01.012.
63. Zhu B, Liu JZ, Cauley SF, Rosen BR, Rosen MS. (2018). Image reconstruction by domain-transform manifold learning. Nature, 555(7697): 487-492. https://doi.org/10.1038/nature25988.
64. Schreiber-Zinaman J, Rosenkrantz AB. (2017). Frequency and reasons for extra sequences in clinical abdominal MRI examinations. Abdom Radiol (NY), 42(1): 306-311. https://doi.org/10.1007/s00261-016-0877-6.
65. Esses SJ, Lu X, Zhao T, Shanbhogue K, Dane B, Bruno M, Chandarana H. (2018). Automated image quality evaluation of T_2 -weighted liver MRI utilizing deep learning architecture. J Magn Reson Imaging, 47(3): 723-728. https://doi.org/10.1002/jmri.25779.
66. Chen H, Zhang Y, Zhang W, Liao P, Li K, Zhou J, Wang G. (2017). Low-dose CT via convolutional neural network. Biomed Opt Express, 8(2): 679-694. https://doi.org/10.1364/BOE.8.000679.
67. Chen H, Zhang Y, Kalra MK, Lin F, Chen Y, Liao P, Zhou J, Wang G. (2017). Low-Dose CT With a Residual Encoder-Decoder Convolutional Neural Network. IEEE Trans Med Imaging, 36(12): 2524-2535. https://doi.org/10.1109/TMI.2017.2715284.
68. Cross, N., DeBerry, J., Ortiz, D., Kemp, J., & Morey, J. (2017). Diagnostic quality of machine learning algorithm for optimization of low dose computed tomography data. Society of Imaging Informatics in Medicine.
69. El Naqa I, Haider MA, Giger ML, Ten Haken RK. (2020). Artificial Intelligence: reshaping the practice of radiological sciences in the 21st century. Br J Radiol, 93(1106): 20190855. https://doi.org/10.1259/bjr.20190855.
70. Lee CS, Nagy PG, Weaver SJ, Newman-Toker DE. (2013). Cognitive and system factors contributing to diagnostic errors in radiology. AJR Am J Roentgenol, 201(3):611-617. https://doi.org/10.2214/AJR.12.10375.
71. Bruno MA, Walker EA, Abujudeh HH. (2015). Understanding and Confronting Our Mistakes: The Epidemiology of Error in Radiology and Strategies for Error Reduction. Radiographics, 35(6): 1668-1676. https://doi.org/10.1148/rg.2015150023.
72. Hedderich DM, Weisstanner C, Van Cauter S, Federau C, Edjlali M, Radbruch A, Gerke S, Haller S. (2023). Artificial intelligence tools in clinical neuroradiology: essential medico-legal aspects. Neuroradiology, 65(7): 1091-1099. https://doi.org/10.1007/s00234-023-03152-7.
73. Geis JR, Brady A, Wu CC, Spencer J, Ranschaert E, Jaremko JL, Langer SG, Kitts AB, Birch J, Shields WF, van den Hoven van Genderen R, Kotter E, Gichoya JW, Cook TS, Morgan MB, Tang A, Safdar NM, Kohli M. (2019). Ethics of artificial intelligence in radiology: summary of the joint European and North American multisociety statement. Insights Imaging, 10(1): 101. https://doi.org/10.1186/s13244-019-0785-8.

CHAPTER 22

Artificial Intelligence Applications in Nephrology: Current Status and Future Perspectives

Prof. Dr. Gulperi Celik

1. Introduction

Artificial intelligence (AI) has rapidly evolved into a major transformative force in contemporary medicine, fundamentally influencing diagnostic frameworks, therapeutic approaches, and healthcare delivery systems. The integration of AI and machine learning (ML) into healthcare has facilitated data-driven clinical decision-making, enhanced diagnostic precision, and improved patient management strategies. ML, a core component of AI, refers to the development of computational models capable of learning from data to generate predictions or decisions without explicit programming. Key ML paradigms include supervised learning, which utilizes labeled datasets to predict outcomes; unsupervised learning, which uncovers latent structures within data; and reinforcement learning, which refines decision-making through iterative feedback processes (1).

Compared with other medical disciplines, the adoption of AI in nephrology has historically been slower; however, recent developments underscore its increasing relevance. Nephrology is particularly well-suited for AI implementation due to the abundance of structured clinical data, including laboratory measurements, imaging modalities, and electronic health records (EHRs), alongside the quantitative nature of kidney disease evaluation (1,2). The incorporation of ML, deep learning (DL), and predictive analytics has enabled clinicians to derive meaningful insights from complex, high-dimensional datasets. The growing accessibility of EHRs, imaging technologies, and molecular datasets has further accelerated AI integration into nephrology research and practice. This trend is especially notable in a field characterized by complex pathophysiology, heterogeneous disease progression, and reliance on longitudinal data (2,3).

Kidney diseases constitute a substantial global health burden, affecting over 850 million individuals worldwide and contributing significantly to morbidity and mortality. Chronic kidney disease (CKD) alone impacts approximately 13% of the global population and is frequently diagnosed at advanced stages due to its asymptomatic course (4). Acute kidney injury (AKI) is also a prevalent and serious condition among hospitalized patients, particularly in intensive care units, where it is associated with high mortality rates and increased healthcare costs. These challenges emphasize the need for innovative strategies for early detection, risk assessment, and individualized treatment (5).

AI technologies offer a unique opportunity to address these unmet clinical needs by integrating diverse data sources, including EHRs, laboratory data, imaging, and multi-omics datasets. Their ability to detect subtle patterns and nonlinear relationships enables earlier diagnosis, improved prognostic evaluation, and enhanced clinical decision-making. Additionally, AI-powered clinical decision support systems are increasingly augmenting clinical workflows, improving both efficiency and accuracy (6).

In nephrology, AI applications span the full spectrum of kidney disease management. Predictive models have demonstrated strong performance in forecasting AKI onset using real-time data, while ML approaches in CKD facilitate risk stratification and disease phenotyping to support personalized management (3). In dialysis, AI has been utilized to predict complications such as intradialytic hypotension, optimize treatment settings, and manage anemia, often with high predictive accuracy. Similarly, in kidney transplantation, AI is applied to donor–recipient matching, graft survival prediction, and digital pathology-assisted diagnostics (7).

Beyond conventional clinical datasets, the integration of AI with omics technologies—including genomics, proteomics, and metabolomics is advancing the field toward precision nephrology. These approaches provide deeper insights into disease mechanisms and support the discovery of novel biomarkers for early diagnosis and targeted therapies. Such integrative models are expected to reshape disease classification and treatment paradigms (8).

Despite these advancements, the clinical implementation of AI in nephrology remains constrained by several challenges, including data heterogeneity, model interpretability, lack of external validation, and integration difficulties within clinical workflows. Ethical concerns, such as data privacy, algorithmic bias, and accountability, further complicate adoption. Overcoming these barriers is essential for the safe and equitable deployment of AI technologies (9).

This chapter aims to present a comprehensive and critical overview of AI applications in nephrology, covering major domains such as AKI, CKD, dialysis, transplantation, and renal pathology. It also addresses emerging areas including multi-omics integration, precision medicine, and rare genetic kidney diseases, while discussing ethical, legal, and practical considerations alongside future research directions.

2. Fundamentals of AI in Nephrology: Core Concepts of AI in Nephrology

Artificial intelligence encompasses a wide range of computational methodologies designed to emulate human cognitive functions, including learning, reasoning, and pattern recog-

nition. In medicine, AI has progressed from rule-based expert systems to advanced data-driven models capable of processing large and complex datasets. In nephrology, where clinical decisions often require integration of heterogeneous and longitudinal data, AI offers a robust framework to enhance diagnostic accuracy and therapeutic decision-making (3).

AI includes several subdomains, such as machine learning, deep learning, and natural language processing. ML enables systems to learn from data without explicit programming and includes supervised, unsupervised, and reinforcement learning approaches (2,10). Supervised learning is commonly employed for predictive modeling, whereas unsupervised learning is used to identify hidden structures within datasets. Reinforcement learning facilitates adaptive decision-making through continuous interaction with data. These approaches are particularly relevant in nephrology due to the dynamic nature of disease progression.

The concept of "big data" is central to AI applications. Large volumes of structured and unstructured data, ranging from laboratory values to genomic information, must be converted into analyzable formats. This enables AI algorithms to uncover patterns and generate predictions beyond traditional statistical approaches. Natural language processing (NLP) further enhances this capability by extracting meaningful information from unstructured data such as clinical notes (1).

2.1. Machine Learning in Nephrology

Machine learning, a fundamental branch of AI, focuses on algorithms that learn from data without explicit programming. It is typically categorized into supervised, unsupervised, and reinforcement learning. Supervised learning is the most commonly applied approach in nephrology. Models are trained on labeled datasets, where both input features and outcomes are known. Common algorithms include logistic regression, random forests, support vector machines, and gradient boosting models. These methods are widely used for prediction, classification, and prognostic modeling in kidney diseases (6).

For example, ML models utilizing EHR data have demonstrated strong predictive capability for AKI in hospitalized patients by incorporating temporal changes in serum creatinine, urine output, and hemodynamic parameters, enabling early intervention (5).

Unsupervised learning, in contrast, focuses on identifying patterns in unlabeled data. Techniques such as clustering and dimensionality reduction have been used to identify novel CKD phenotypes based on clinical and molecular characteristics, supporting personalized care approaches (3). Reinforcement learning represents a more advanced paradigm, where models learn optimal strategies through interaction with the environment. Although still emerging in nephrology, it shows promise in optimizing treatment decisions such as fluid management and dialysis settings (5).

2.2. Deep Learning and Neural Networks

Deep learning, a subset of ML, employs multi-layered neural networks to model complex nonlinear relationships. It has demonstrated superior performance in high-dimension-

al tasks such as imaging and NLP (1,2). In nephrology, convolutional neural networks (CNNs) are extensively used in renal imaging and histopathology. These models can automatically extract features from images and accurately classify renal structures such as glomeruli and tubules. Studies indicate that DL-based systems can achieve high diagnostic accuracy in kidney biopsy interpretation, supporting clinical decision-making (11). Similarly, DL has been applied to whole-slide imaging (WSI) in transplant pathology, enabling automated quantification of histological features and improving diagnostic consistency (12). Recurrent neural networks (RNNs), particularly long short-term memory (LSTM) models, are well-suited for time-series data and are increasingly used for predicting disease progression and clinical outcomes in nephrology (11,12).

2.3. Natural Language Processing in Nephrology

Natural language processing focuses on extracting structured information from unstructured clinical text. A significant portion of clinical data exists in free-text formats such as physician notes and discharge summaries.NLP enables automated extraction of clinically relevant information, including symptoms, diagnoses, and treatment responses. In nephrology, it has been applied to detect early disease indicators, identify complications, and enhance clinical documentation (7).The emergence of large language models (LLMs) has further expanded capabilities in clinical decision support, medical summarization, and patient education. However, their application in nephrology is still in early stages and requires rigorous validation (3).

2.4. Data Sources and Multimodal Integration

A key feature of AI in nephrology is the integration of multimodal data, including clinical, imaging, histopathological, and molecular datasets.Combining these diverse data types enables the development of comprehensive predictive models that capture complex biological interactions. For example, integrating EHR data with dialysis machine parameters has improved prediction of complications such as intradialytic hypotension (4,5,7).The incorporation of multi-omics data further enhances precision nephrology by enabling deeper insights into disease mechanisms and biomarker discovery (8).

2.5. Model Validation and Performance Metrics

The clinical applicability of AI models depends on rigorous validation. Common evaluation metrics include accuracy, sensitivity, specificity, AUROC, and calibration. Although many models demonstrate high performance in retrospective studies, for instance, AUROC values up to 0.9.5 in predicting dialysis-related complications, external validation across diverse populations remains essential (7). Prospective studies and real-world implementation are still limited, highlighting a gap between model development and clinical adoption. Addressing this gap requires interdisciplinary collaboration and standardized reporting (5).

3. Data Ecosystem in Nephrology

The effective implementation of artificial intelligence (AI) in nephrology fundamentally relies on the accessibility, quality, and integration of diverse data sources. Kidney diseases are inherently complex and multifactorial, necessitating longitudinal monitoring and multidimensional data interpretation. Consequently, nephrology represents a data-intensive specialty in which AI-driven methodologies can utilize heterogeneous datasets to enhance diagnosis, prediction, and treatment optimization (3).

3.1. Electronic Health Records (EHRs)

Electronic health records constitute the primary data infrastructure for AI applications in nephrology. These systems provide comprehensive longitudinal patient information, including demographics, comorbidities, medication usage, laboratory results, and clinical outcomes. The digitization of healthcare systems has enabled the accumulation of large-scale datasets suitable for predictive modeling and clinical decision support. AI models trained on EHR data have demonstrated substantial effectiveness in predicting AKI, CKD progression, and hospitalization risk. High-resolution data streams, particularly from intensive care settings, enable real-time risk assessment and early intervention. Additionally, temporal modeling of EHR data allows dynamic rather than static risk predictions.However, EHR datasets often contain missing values, inconsistencies, and inter-institutional variability. These limitations require advanced preprocessing techniques such as imputation, normalization, and feature engineering to ensure model robustness (2,5).

3.2. Laboratory and Biomarker Data

Laboratory parameters are central to nephrology and play a critical role in AI-based models. Conventional biomarkers such as serum creatinine and estimated glomerular filtration rate (eGFR) remain essential, yet their limitations-particularly in early detection-have driven the exploration of novel biomarkers. Emerging biomarkers, including NGAL, KIM-1, cystatin C, and suPAR, offer improved sensitivity and specificity for early kidney injury detection. AI models integrating these biomarkers enhance diagnostic precision and facilitate earlier intervention. Furthermore, combining multiple biomarkers into composite panels analyzed through machine learning supports more refined risk stratification and individualized patient care, representing a transition toward multidimensional diagnostic frameworks (4).

3.3. Imaging Data

Imaging modalities such as ultrasound, CT, and MRI provide critical structural and functional insights into renal pathology. AI, particularly deep learning, has significantly advanced imaging analysis.CNN-based models can automatically detect and segment renal structures, identify pathological abnormalities, and assist in diagnostic classification. Applications include detection of renal masses, morphological assessment, and disease progression monitoring (6).Digital pathology has further expanded AI applications. Whole-slide imaging enables

high-resolution analysis of kidney biopsies, allowing automated detection of glomerular lesions, fibrosis quantification, and transplant pathology evaluation with high accuracy (12).

Despite these advances, challenges remain in standardization, data quality, and inter-institutional variability, necessitating large annotated datasets and collaborative efforts.

3.4. Dialysis Machine and Monitoring Data

Dialysis generates high-frequency data, including blood flow rates, ultrafiltration volumes, hemodynamic parameters, and treatment duration. AI models leveraging these datasets have shown strong predictive capabilities for complications such as intradialytic hypotension (IDH), hospitalization, and mortality. Predictive models for IDH have achieved AUROC values approaching 0.9.5, enabling proactive clinical interventions and individualized treatment adjustments. Real-time AI-integrated monitoring systems further enhance decision-making during dialysis sessions (2,7).

3.5. Multi-Omics Data Integration

The integration of genomics, proteomics, transcriptomics, and metabolomics represents a major advancement in nephrology. These datasets provide insights into disease mechanisms and enable precise disease classification. AI plays a crucial role in analyzing high-dimensional omics data, identifying complex biological interactions beyond traditional statistical methods. Integrating omics with clinical and imaging data supports precision nephrology and biomarker discovery (8).

3.6. Wearables and Remote Monitoring

Recent developments in wearable devices and remote monitoring technologies have significantly broadened the range of data accessible for AI applications in nephrology. These systems, capable of continuously tracking physiological indicators such as heart rate, blood pressure, and physical activity, enable uninterrupted patient monitoring beyond conventional clinical environments. Such technologies are particularly valuable for individuals with chronic kidney disease and patients receiving dialysis, as they facilitate earlier identification of complications and more efficient disease management. AI algorithms can process continuous data streams to detect deviations from individual baseline patterns and generate alerts that prompt timely clinical intervention. Moreover, integrating wearable-generated data with electronic health records (EHRs) and other clinical datasets further strengthens the capacity for personalized and proactive care, supporting the broader objectives of digital health transformation (3,8).

3.7. Clinical Applications of AI in Nephrology

Artificial intelligence has demonstrated substantial potential in both the prediction and management of kidney diseases, particularly acute kidney injury (AKI) and chronic kid-

ney disease (CKD). Machine learning techniques enable the analysis of large-scale datasets to identify high-risk individuals, thereby facilitating early intervention and improving patient outcomes (10). The scope of AI applications in nephrology continues to expand rapidly. A major focus lies in risk prediction for AKI and CKD, where ML models can effectively identify vulnerable patients using complex datasets, allowing for earlier and more targeted clinical responses (13). Beyond predictive capabilities, AI plays a central role in advancing personalized medicine. By incorporating patient-specific characteristics, reinforcement learning approaches can optimize treatment strategies, including medication dosing and dialysis parameters. In the context of kidney transplantation, AI models are utilized to estimate graft survival and predict post-transplant complications by integrating clinical and genetic information (10).

In CKD management, AI-based models combine clinical, demographic, and biochemical variables to produce comprehensive risk assessments. These models outperform conventional statistical approaches by capturing intricate nonlinear relationships among variables. Additionally, AI systems applied to EHR data can detect early indicators of disease progression and support timely referral to nephrology specialists (1,14). AI is also contributing to the development of non-invasive diagnostic strategies. Techniques such as retinal imaging and biomarker-based assessments can identify early signs of kidney dysfunction, offering cost-effective alternatives to traditional diagnostic methods, particularly in resource-constrained settings (13).

Furthermore, AI enables the integration of multimodal datasets, including clinical, imaging, and molecular information. This integrative approach enhances the understanding of disease mechanisms and supports more accurate and informed clinical decision-making (2).

4. Artificial Intelligence in Acute Kidney Injury (AKI)

Acute kidney injury is a prevalent and multifactorial clinical syndrome characterized by a sudden deterioration in renal function, typically reflected by elevated serum creatinine levels or reduced urine output. It affects approximately 10% of hospitalized patients and up to half of critically ill individuals in intensive care units, and is associated with considerable morbidity, mortality, and healthcare expenditure. Early detection remains challenging due to delayed biomarker responses and the complex underlying pathophysiology (5).

AI has emerged as a promising approach to address these challenges by enabling earlier detection, improved risk stratification, and more precise clinical decision-making. The application of machine learning to large-scale clinical datasets has significantly enhanced the ability to predict AKI prior to the onset of overt clinical manifestations. In nephrology practice, ML has been extensively employed for AKI prediction. Conventional models, including logistic regression and risk scoring systems, are limited in capturing complex variable interactions. In contrast, advanced ML methods- such as random forests, gradient boosting techniques, and deep learning- have demonstrated superior predictive per-

formance. Notably, deep learning models have been shown to predict AKI up to 48 hours in advance, although challenges such as false-positive rates and limited external validation persist (1,4).

4.1. Early Detection and Prediction Models

One of the most significant contributions of AI in AKI is the development of predictive models capable of identifying at-risk patients before clinical onset. These models typically rely on high-dimensional EHR data, including laboratory measurements, vital signs, medication exposure, and comorbid conditions.Recent evidence indicates that AI models can predict AKI several hours to days in advance with high accuracy. Supervised learning approaches applied to ICU datasets have demonstrated strong predictive performance, enabling earlier interventions and improved patient outcomes. These models often incorporate temporal trends in key parameters such as serum creatinine, urine output, and hemodynamic variables to generate dynamic risk scores (5).

In addition to traditional ML techniques, deep learning models, particularly recurrent neural networks and long short-term memory architectures, are increasingly used for time-series analysis. These models effectively capture temporal dependencies and nonlinear relationships, making them well-suited for predicting AKI in dynamic clinical settings (1,4,5).

4.2. Clinical Decision Support Systems

AI-powered clinical decision support systems are being developed to assist healthcare providers in the prevention, early detection, and management of AKI. By embedding predictive models into clinical workflows, these systems can generate real-time alerts and recommendations based on patient-specific data.For instance, AI-based alert mechanisms can notify clinicians when a patient's predicted risk exceeds a predefined threshold, prompting early interventions such as medication adjustment, fluid optimization, or intensified monitoring. Such approaches support a shift toward proactive care and may reduce both the incidence and severity of AKI. However, the effectiveness of these systems depends on factors such as predictive accuracy, interpretability, and seamless integration into clinical workflows. Poorly designed systems may contribute to alert fatigue, thereby reducing clinician engagement and limiting their practical utility (1,4,5).

4.3. Risk Stratification and Phenotyping

AKI is a heterogeneous condition with diverse causes, clinical presentations, and outcomes. Traditional classification frameworks, such as KDIGO criteria, are primarily based on functional markers and may not adequately reflect underlying biological diversity. AI-driven approaches, particularly unsupervised learning methods, have been employed to identify distinct AKI phenotypes using clinical and molecular data. These phenotypes differ in terms of pathophysiology, prognosis, and treatment response, enabling more

individualized management strategies. For example, clustering analyses applied to ICU datasets have revealed subgroups of AKI patients with varying clinical trajectories and risk profiles, providing insights that can inform targeted therapeutic interventions (3).

4.4. Integration with Biomarkers and Multi-Omics

The combination of AI with emerging biomarkers and multi-omics data represents a major advancement in AKI research. Traditional biomarkers, such as serum creatinine, are limited by delayed responsiveness and insufficient specificity. In contrast, novel biomarkers-including NGAL, KIM-1, and cystatin C offer earlier and more sensitive detection of kidney injury. AI models that integrate these biomarkers with clinical variables can significantly improve predictive accuracy and enable earlier diagnosis. Furthermore, multi-omics approaches- encompassing genomics, proteomics, and metabolomics- provide deeper insights into disease mechanisms and facilitate the identification of new therapeutic targets (8). In complex conditions such as cardiorenal syndrome, AI models can integrate multi-organ data to better characterize disease interactions and optimize patient management (2,3).

4.5. Real-World Implementation and Challenges

Despite the strong performance of AI models in AKI prediction, their adoption in routine clinical practice remains limited. A key challenge is the lack of prospective validation; although many models perform well in retrospective analyses, their effectiveness in real-world settings is not always established. Generalizability is another important concern, as models trained on specific datasets may not perform consistently across different populations or healthcare systems. Variability in data quality, clinical practices, and patient characteristics can significantly influence model performance. Interpretability also remains a critical issue. Clinicians may be hesitant to rely on "black-box" models, particularly in high-risk clinical scenarios. Therefore, explainable AI approaches are essential to enhance transparency and build trust. Finally, ethical and regulatory considerations—including data privacy, algorithmic bias, and accountability—must be carefully addressed to ensure the safe and equitable implementation of AI in AKI management (15).

5. Artificial Intelligence in Chronic Kidney Disease (CKD)

Chronic kidney disease (CKD) is a progressive and irreversible disorder characterized by a gradual decline in renal function over time. It represents a significant global health challenge, affecting approximately 13.4.% of the world's population and contributing substantially to morbidity, mortality, and healthcare costs. A major difficulty in CKD management is its asymptomatic nature in early stages, which frequently results in delayed diagnosis and missed opportunities for timely intervention (4). Conventional clinical indicators, such as estimated glomerular filtration rate (eGFR) and albuminuria, provide valuable

prognostic information; however, they are insufficient to fully capture the complexity and heterogeneity of CKD progression. In this context, artificial intelligence (AI) offers the ability to integrate heterogeneous data sources and generate more accurate and individualized risk assessments (14). AI has increasingly become a transformative approach in both CKD research and clinical practice, enabling improvements in early detection, risk stratification, disease progression modeling, and personalized treatment. By leveraging large-scale datasets and combining multiple data modalities, AI supports a transition from reactive management toward proactive and precision-based nephrology (2,14).

5.1. Early Detection and Risk Prediction

Early identification of CKD remains challenging due to the limitations of traditional biomarkers such as serum creatinine and eGFR, which are influenced by demographic and physiological factors including age, sex, and muscle mass (4). AI-driven models have demonstrated enhanced capability in identifying individuals at risk of developing CKD. By utilizing longitudinal data derived from electronic health records (EHRs)—including laboratory results, comorbid conditions, and medication histories—these models can detect subtle patterns indicative of early renal impairment. Machine learning techniques such as random forests, gradient boosting algorithms, and neural networks are widely employed for this purpose, generating individualized risk scores that facilitate targeted preventive interventions (6).

Risk prediction represents one of the most impactful applications of AI in CKD. Traditional models rely heavily on kidney-specific markers such as eGFR and proteinuria, which, although strongly associated with outcomes like end-stage kidney disease (ESKD) and cardiovascular events, do not fully reflect the multifactorial nature of disease progression. In contrast, AI-based approaches integrate a broad spectrum of variables, including genetic, biochemical, and imaging data, to produce comprehensive risk profiles. These models can capture complex nonlinear interactions, enabling more accurate prediction of both renal and cardiovascular outcomes. Furthermore, the incorporation of longitudinal data allows continuous updating of risk estimates, supporting dynamic and personalized clinical decision-making (14).

5.2. Disease Progression Modeling

Accurately predicting CKD progression is essential for optimizing clinical management and resource allocation. Disease trajectories vary considerably among patients due to differences in etiology, comorbidities, and genetic predisposition (14). AI models have been increasingly utilized to forecast CKD progression, including risks of ESKD, dialysis initiation, and mortality. These models rely on longitudinal datasets to capture temporal changes in renal function and associated clinical parameters (2). Deep learning techniques, particularly recurrent neural networks (RNNs), are especially suited for modeling disease progression due to their ability to process time-series data. By identifying complex temporal patterns, these models often achieve greater predictive accuracy than traditional statistical approaches (1,4,5).

Additionally, AI facilitates the identification of distinct progression trajectories, allowing patients to be stratified into risk categories. This stratification supports individualized treatment planning and more efficient utilization of healthcare resources (16).

5.3. Integration of Biomarkers and Multi-Omics

The integration of novel biomarkers and multi-omics data with AI represents a major advancement in CKD research. Traditional diagnostic approaches are increasingly complemented by biomarkers that provide earlier and more specific indications of kidney injury.Biomarkers such as NGAL, KIM-1, cystatin C, and soluble urokinase plasminogen activator receptor (suPAR) have shown significant promise in improving both diagnosis and prognosis. AI models incorporating these markers enhance predictive performance and enable more refined risk stratification (4).

Multi-omics approaches- including genomics, proteomics, metabolomics, and transcriptomics- offer comprehensive insights into the molecular basis of CKD. AI plays a critical role in analyzing these high-dimensional datasets, identifying complex biological interactions, and uncovering novel disease pathways. By combining omics data with clinical and imaging information, AI enables the development of integrative models that support precision nephrology, allowing for individualized therapeutic strategies and improved patient outcomes (8).

5.4. Phenotyping and Precision Nephrology

CKD is a highly heterogeneous condition encompassing diverse etiologies and clinical manifestations. Traditional classification systems often fail to adequately represent this complexity, limiting their effectiveness in guiding treatment. AI-based methodologies, particularly unsupervised learning techniques, have been applied to identify distinct CKD phenotypes based on clinical, biochemical, and molecular data. These phenotypes differ in progression patterns, treatment responses, and prognostic outcomes. The identification of such subgroups enables more targeted therapeutic approaches and aligns with the principles of precision nephrology, which aims to tailor interventions to individual patient characteristics. Additionally, AI-driven phenotyping contributes to the discovery of novel disease mechanisms and potential therapeutic targets (8).

5.5. Cost-Effectiveness and Healthcare Optimization

Beyond clinical benefits, AI has the potential to improve the economic efficiency of CKD management. Early detection and timely intervention may reduce the need for costly treatments such as dialysis and transplantation, thereby lowering overall healthcare expenditures. AI models can also enhance resource allocation by identifying patients who would benefit most from specific interventions, such as intensive monitoring or early specialist referral. Furthermore, automation of routine processes and improved decision-making can reduce clinician workload and increase healthcare system efficiency. However, the

economic implications of AI implementation require further investigation through prospective studies (16).

5.6. Limitations and Challenges

Despite its promise, several challenges must be addressed for the effective implementation of AI in CKD. Data quality and completeness remain critical concerns, as missing or inconsistent information can adversely affect model performance. Generalizability is another key issue, as models developed in specific populations may not perform consistently across different settings. External validation across diverse cohorts is therefore essential. Integration into clinical workflows also requires careful consideration, particularly regarding usability, interpretability, and clinician acceptance. Explainable AI approaches are crucial for enhancing transparency and fostering trust. Finally, ethical considerations-including data privacy, algorithmic bias, and equitable Access- must be addressed to ensure that AI benefits all patient populations (15).

6. Artificial Intelligence in Dialysis

Dialysis is a life-sustaining therapy for patients with end-stage kidney disease, yet it is associated with high morbidity, mortality, and reduced quality of life. Both hemodialysis (HD) and peritoneal dialysis (PD) involve complex clinical decision-making related to fluid balance, electrolyte management, and cardiovascular stability. The large volume of high-frequency data generated during dialysis sessions makes this domain particularly suitable for AI applications. AI-based approaches aim to enhance treatment personalization, predict complications, and improve clinical outcomes through real-time data analysis and decision support.

6.1. Complexity of Dialysis Care

Patients undergoing dialysis experience significant clinical challenges despite advances in treatment. Effective management requires the integration of multiple variables, including hemodynamic status, fluid balance, electrolyte levels, and vascular access conditions. Modern dialysis systems generate extensive real-time data, including continuous monitoring of blood pressure, heart rate, ultrafiltration rates, and machine parameters. When combined with longitudinal EHR data, these datasets provide a comprehensive representation of patient status. AI and ML techniques are particularly well-suited to analyzing such complex datasets, enabling the identification of patterns and predictive relationships not readily apparent through conventional analysis (7).

6.2. Prediction of Intradialytic Complications

One of the most well-established applications of AI in dialysis is the prediction of intradialytic hypotension (IDH), a common complication associated with adverse outcomes (7).

Machine learning models have demonstrated high predictive accuracy using both real-time and historical data. Deep learning approaches, including RNN-based models, have achieved AUROC values approaching 0.9.4, allowing clinicians to implement preventive measures such as adjusting ultrafiltration rates and optimizing fluid management. These models incorporate demographic, physiological, and treatment-related variables to generate individualized risk predictions. In addition to IDH, AI has been applied to predict complications such as arrhythmias, vascular access failure, and hospitalization risk (17–20).

Advanced architectures, including temporal fusion transformers, further improve predictive performance by integrating multiple data streams and capturing temporal dependencies, supporting a transition toward proactive dialysis care.

6.3. Prognostic Modeling and Risk Stratification

AI has also been widely applied to long-term outcome prediction in dialysis populations. Models have been developed to estimate mortality, hospitalization risk, and disease progression. Machine learning algorithms consistently outperform traditional statistical methods, with mortality prediction models achieving strong discriminatory performance (C-index up to ~0.8.3). These models integrate diverse variables to generate individualized risk profiles (7). Such tools support clinical decision-making, resource allocation, and targeted interventions, particularly in resource-limited settings (21,22).

6.4. Real-Time Monitoring and Clinical Decision Support Systems

The integration of AI into real-time monitoring systems is transforming dialysis care. High-frequency data generated during treatment can be continuously analyzed to detect early signs of instability. AI-driven clinical decision support systems provide real-time alerts and recommendations, enabling timely interventions such as preventing hypotension (23,24). These systems improve patient safety, reduce clinician workload, and enhance consistency in care delivery.

In dialysis care, CDSS have been applied to several domains, including:

- **Anemia management:** AI models can optimize erythropoiesis-stimulating agent (ESA) dosing by predicting hemoglobin response and minimizing adverse effects.
- **Fluid management:** Predictive models can guide ultrafiltration strategies to prevent complications such as IDH.
- **Vascular access monitoring:** AI-driven image analysis can detect early signs of vascular access dysfunction, enabling timely intervention.
- **Hospitalization risk prediction:** Early identification of patients at risk of hospitalization allows for preventive care strategies (25,26, 27).

Applications include anemia management, fluid optimization, vascular access monitoring, and hospitalization risk prediction. Additionally, these systems support continuous learning frameworks that improve performance over time (28).

6.5. Treatment Personalization and Optimization

Dialysis treatment requires individualized parameter adjustment. AI facilitates this by analyzing large datasets to identify optimal treatment strategies.Reinforcement learning models are particularly promising, as they can adapt to patient-specific responses and optimize treatment dynamically. Applications include personalized ultrafiltration strategies and improved anemia management, minimizing both under- and overtreatment (23,24).

6.6. Peritoneal Dialysis and Remote Monitoring

Peritoneal dialysis (PD), particularly home-based therapy, presents unique challenges related to patient adherence, monitoring, and early detection of complications. AI-driven remote monitoring systems have the potential to address these challenges by enabling continuous data collection and analysis the clinical setting.Wearable devices and connected PD systems can transmit data on fluid balance, dwell times, and treatment adherence to centralized platforms. AI models can analyze these data to detect anomalies, predict complications peritonitis, and provide early warnings to clinicians.This approach supports the transition toward home-based, patient-centered care, reducing hospital visits and improving quality of life. Additionally, AI-enabled telemedicine platforms can facilitate remote consultations and personalized care planning (1).

6.7. Challenges and Implementation Barriers

Despite promising advancements, several barriers hinder widespread AI adoption in dialysis. Data heterogeneity and lack of standardization remain major issues.Seamless integration into clinical workflows is essential to avoid increasing clinician burden. Model interpretability is particularly critical due to the high-risk nature of dialysis care.Finally, ethical and regulatory challenges- including data privacy, security, and algorithmic bias-must be addressed to ensure safe and equitable implementation (9,29,30).

7. Artificial Intelligence in Kidney Transplantation: Applications in Kidney Transplantation

Kidney transplantation is considered the optimal treatment modality for patients with end-stage kidney disease (ESKD), providing superior survival outcomes and quality of life compared with dialysis. Nevertheless, it is a highly intricate process that encompasses donor selection, recipient matching, perioperative care, and long-term follow-up. Despite advancements in immunosuppression and surgical techniques, complications such as graft rejection, delayed graft function, and long-term graft failure continue to represent significant clinical challenges (31,32). Accurate prediction of graft outcomes and post-transplant complications remains difficult. In this context, artificial intelligence (AI)-based models have been developed to enhance donor–recipient matching

and to predict transplant outcomes through the integration of clinical, immunological, and genetic data. By utilizing large-scale clinical datasets, imaging, and molecular information, AI supports decision-making throughout the transplantation pathway, improving matching accuracy, outcome prediction, and graft surveillance (10). Machine learning (ML) approaches can estimate the risk of acute rejection and long-term graft loss, enabling early preventive interventions. Additionally, AI contributes to individualized immunosuppressive management, particularly for agents such as tacrolimus, by modeling patient-specific pharmacokinetic responses. Compared to conventional methods, which typically rely on limited variables, AI-based models provide more precise and robust predictions (33). In clinical practice, ML algorithms have also been applied to evaluate genetic polymorphisms, demographic variables, and clinical parameters to predict transplant outcomes, including drug bioavailability and post-transplant complications such as new-onset diabetes. Although these approaches show promising performance, most remain in the experimental phase and have not yet been fully implemented in routine transplantation care (10).

Overall, AI enhances clinical decision-making by enabling real-time analysis of large datasets and supporting early diagnosis, risk stratification, and treatment optimization in transplantation.

7.1. Donor-Recipient Matching

Successful transplantation relies heavily on optimal donor–recipient compatibility. Traditional assessment methods include ABO compatibility, HLA matching, and crossmatch testing; however, these factors alone do not fully capture the complexity of immunological and clinical compatibility. AI-based models can integrate a wider range of variables such as comorbidities, demographic data, immunological profiles, and donor-specific characteristics. Machine learning techniques are capable of identifying complex nonlinear interactions among these variables, thereby improving risk stratification and allocation strategies. Such models can estimate graft survival probabilities for specific donor–recipient pairs, supporting selection strategies that optimize long-term outcomes and improve organ utilization while reducing waitlist mortality (33).

7.2. Prediction of Graft Survival and Outcomes

Accurate prediction of graft survival remains a central goal in transplantation medicine. Conventional risk models are often limited in scope and may fail to reflect the dynamic nature of post-transplant evolution. AI-based models demonstrate improved performance in predicting graft survival, delayed graft function (DGF), and patient mortality by integrating longitudinal clinical data, including laboratory results, immunosuppressive therapy, and clinical events. Deep learning models, particularly those designed for time-series analysis, enable continuous monitoring of patient status and dynamic updating of risk profiles. This facilitates early identification of high-risk patients and timely intervention strategies. Moreover, AI supports personalized immunosuppressive management

by predicting individual drug responses and minimizing risks associated with over- or under-immunosuppression (34,35).

7.3. Detection and Prediction of Rejection

Acute and chronic rejection remain leading causes of graft failure, making early detection essential for preserving graft function.AI methods have been applied to clinical and molecular datasets to improve rejection prediction. Machine learning models can detect early patterns in laboratory trends such as serum creatinine and immunological markers. Furthermore, integration of omics data, including transcriptomic and proteomic signatures, has enabled identification of molecular biomarkers associated with rejection. These high-dimensional datasets can be processed by AI algorithms to improve diagnostic sensitivity and enable earlier, more individualized interventions (8,36,37).

7.4. Digital Pathology and Imaging

Digital pathology plays an increasingly important role in transplantation, particularly in kidney biopsy evaluation. Whole-slide imaging (WSI) enables digitization of histological samples, facilitating AI-based analysis. Deep learning models, especially convolutional neural networks (CNNs), can automatically identify histopathological features such as rejection patterns, fibrosis, and structural alterations. These tools enhance diagnostic accuracy, reduce inter-observer variability, and standardize reporting. AI-based pathology systems can detect subtle histological changes that may not be easily recognized by human observers, thereby improving early diagnosis and clinical decision-making. In addition, imaging modalities such as ultrasound and MRI can be analyzed using AI to evaluate graft perfusion and structural integrity (6,38,39).

7.5. Post-Transplant Monitoring and Personalized Care

Long-term post-transplant management requires continuous monitoring for complications such as rejection, infection, and drug toxicity. AI facilitates this by integrating data from electronic health records, laboratory findings, and wearable devices. Predictive models can identify patients at increased risk of adverse outcomes and support individualized care strategies. AI systems can also optimize immunosuppressive regimens by balancing rejection risk with infection susceptibility. Furthermore, remote monitoring technologies enable continuous patient assessment and early detection of complications (6,40).

7.6. Challenges and Future Directions

Despite its potential, AI application in transplantation faces several challenges. Data heterogeneity and limited availability of large, high-quality datasets remain major limitations, as transplant data are often fragmented across institutions. Ethical concerns are particularly relevant in organ allocation, where transparency, fairness, and bias prevention are critical.

Algorithmic bias may lead to inequities in access to transplantation. Additionally, model interpretability remains essential for clinical trust and safe decision-making in high-stakes contexts. Finally, prospective validation studies and real-world implementation research are required to confirm the clinical utility of AI systems in transplantation (6,15).

8. Artificial Intelligence in Renal Pathology and Imaging

Renal pathology represents one of the most promising fields for AI integration. Kidney biopsy remains the diagnostic gold standard for many renal diseases; however, interpretation is often affected by inter-observer variability and dependency on expert experience. AI, particularly deep learning, offers solutions for standardized and automated histopathological analysis (41). Convolutional neural networks (CNNs) are widely used for segmentation, classification, and feature extraction in digital pathology. These models can accurately identify structures such as glomeruli, tubules, and fibrotic areas, improving diagnostic precision. They also detect subtle morphological alterations that may be overlooked by human observers, enhancing early diagnosis and prognosis. AI-based image analysis reduces variability, improves reproducibility, and allows quantitative assessment of disease severity. However, successful implementation requires large, high-quality annotated datasets and external validation across diverse populations (6,12).

8.1. Deep Learning in Renal Imaging

Imaging modalities such as ultrasound, CT, and MRI provide essential diagnostic information but require expert interpretation.CNN-based deep learning models have demonstrated high accuracy in identifying renal abnormalities, including cysts, tumors, structural anomalies, and changes in kidney morphology (42). AI applications include tumor detection, lesion classification, hydronephrosis assessment, and kidney volume quantification, improving diagnostic consistency and efficiency (6).

8.2. Digital Pathology and Biopsy Analysis

Kidney biopsy is essential for diagnosing glomerular and interstitial diseases as well as transplant rejection. Whole-slide imaging enables digitization of biopsy samples and application of AI.AI systems can detect and quantify glomeruli, fibrosis, tubular injury, inflammatory infiltration, and disease classification patterns. These tools provide reproducible and scalable analysis while reducing observer variability. Importantly, AI can identify subtle histological patterns that support earlier and more accurate diagnosis (6,43,44).

8.3. Image Segmentation and Quantification

Image segmentation enables precise delineation of renal structures for quantitative assessment. Deep learning-based segmentation models, including U-Net architectures and fully

convolutional networks, have demonstrated high performance in segmenting renal histology and imaging data. These models enable precise measurement of structural features. These structural features:

- Glomerular size and density
- Fibrosis extent
- Tubular damage
- Vascular changes

Deep learning models such as U-Net architectures allow accurate segmentation of glomeruli, tubules, and interstitial compartments. Quantitative metrics derived from segmentation include glomerular density, fibrosis extent, tubular damage, and vascular changes. These objective measurements support disease staging, prognosis, and therapeutic monitoring (6,12,45).

8.4. AI in Classification and Prognosis

Beyond feature extraction, AI models can perform complex classification tasks, distinguishing between different renal pathologies based on imaging and histological data. Machine learning algorithms can integrate multiple features to generate diagnostic predictions with high accuracy.For example, AI systems have been used to classify glomerular diseases, differentiate diabetic nephropathy from other causes of CKD, and predict disease progression based on histopathological features.In addition, prognostic models can use imaging and pathology data to predict clinical outcomes, such as progression to end-stage kidney disease (ESKD) or response to therapy. These models support personalized treatment planning and risk stratification (6,12).

8.5. Multimodal Integration

AI systems increasingly integrate imaging, clinical, and molecular data to improve diagnostic and prognostic accuracy. This multimodal approach enables a more comprehensive understanding of kidney disease and aligns with precision nephrology principles (16).

8.6. Challenges

Key challenges include limited annotated datasets, variability in imaging protocols, and lack of standardization across institutions. Model interpretability and regulatory concerns also remain important barriers to clinical adoption (15).

9. Artificial Intelligence in Hypertension and Cardiovascular Risk

Hypertension is a critical risk factor for both cardiovascular disease and kidney disease, making it an important area for AI applications. AI-driven tools can improve blood pres-

sure measurement accuracy and enable more effective diagnosis and management of hypertension. Machine learning models can analyze longitudinal patient data to predict hypertension-related complications and optimize treatment strategies. Furthermore, AI supports population-level health management by identifying high-risk groups and enabling targeted interventions. The successful implementation of these technologies requires collaboration between clinicians, engineers, and data scientists (16,46).

10. Artificial Intelligence in Rare Genetic Kidney Diseases

Rare genetic kidney diseases comprise over 150 heterogeneous conditions involving numerous genetic variants. Although individually uncommon, they collectively contribute significantly to disease burden (47,48).Diagnosis is challenging due to phenotypic overlap, genetic heterogeneity, and limited datasets. AI provides solutions through high-dimensional data analysis and precision medicine approaches (49).

10.1. Challenges

Rare kidney diseases are defined by their low prevalence, typically affecting fewer than 1 in 2,000 individuals. Despite their rarity, they present substantial clinical challenges. One of the primary difficulties lies in the heterogeneity of these conditions. Many rare kidney diseases exhibit overlapping phenotypes, making differential diagnosis complex. For instance, similar clinical presentations may arise from distinct genetic mutations, while identical genetic variants can lead to diverse phenotypic outcomes.This complexity is further compounded by limited data availability. Due to the rarity of these conditions, datasets are often small, fragmented, and collected across multiple institutions. Traditional statistical methods struggle to extract meaningful insights from such datasets, limiting the ability to develop robust diagnostic and prognostic tools. AI, with its capacity to analyze high-dimensional and heterogeneous data, offers a promising solution to these challenges(49).

10.2. Deep Phenotyping

AI enables deep phenotyping using clinical, imaging, and genetic data. Clustering and unsupervised learning methods identify disease subgroups, while NLP extracts relevant information from unstructured clinical records (49).

10.3. Genotype–Phenotype Integration

A central challenge in rare genetic kidney diseases is the establishment of accurate genotype–phenotype correlations. The relationship between genetic variants and clinical manifestations is often complex, with significant variability in disease expression even among individuals with the same mutation. AI provides powerful tools for integrating

multi-omics data, including genomics, transcriptomics, proteomics, and metabolomics. By analyzing these datasets in conjunction with clinical information, AI models can uncover relationships between genetic variants and phenotypic outcomes. This integrative approach facilitates the identification of novel biomarkers, disease pathways, and therapeutic targets. For example, machine learning algorithms can analyze genomic sequencing data to identify pathogenic variants and predict their functional impact. Similarly, AI-driven models can integrate gene expression data with clinical features to identify disease subtypes and predict disease progression. These capabilities are particularly valuable in rare diseases, where traditional approaches are limited by small sample sizes and high variability (4,49).

10.4. Clinical Decision Support

AI has the potential to significantly reduce the "diagnostic odyssey" experienced by patients with rare kidney diseases. Many patients undergo years of testing and consultations before receiving a definitive diagnosis. AI-driven clinical decision support systems can analyze patient data and suggest potential diagnoses, guiding clinicians toward more targeted investigations. For instance, AI models can compare patient profiles with large databases of known cases to identify similar patterns and generate diagnostic hypotheses. These systems can also prioritize genetic testing based on predicted likelihood of specific conditions, thereby improving diagnostic efficiency and reducing healthcare costs (16,49,50). Moreover, AI can assist in prognostic modeling, enabling clinicians to predict disease progression and tailor treatment strategies accordingly. This is particularly important in rare diseases, where early intervention can significantly impact outcomes.

10.5. Federated Learning

Federated learning enables multi-institutional model training without data sharing, improving generalizability while preserving privacy (49).

11. Multi-Omics and Precision Nephrology

Multi-omics integrates genomics, transcriptomics, proteomics, metabolomics, and epigenomics to provide a systems-level understanding of kidney disease. Combined with AI, it enables precision nephrology.

11.1. Rationale

Kidney diseases are inherently heterogeneous, with diverse etiologies, pathophysiological pathways, and clinical trajectories. Traditional diagnostic methods, rely largely on functional biomarkers such as serum creatinine and estimated glomerular filtration

rate (eGFR), which provide limited insight into underlying molecular processes. In CKD, multi-omics studies have identified novel biomarkers and molecular pathways associated with disease progression, inflammation, fibrosis, and cardiovascular complications. These findings highlight the potential of multi-omics to redefine disease classification and improve clinical outcomes (4). Multi-omics approaches address the limitations by capturing molecular alterations at multiple biological levels. For example, genomics identifies genetic variants associated with disease susceptibility, while proteomics and metabolomics reveal downstream functional changes. This layered information enables a more comprehensive understanding of disease mechanisms and progression (16) .

11.2. AI Integration

The integration and analysis of multi-omics data present significant computational challenges due to their high dimensionality, complexity, and heterogeneity. AI, particularly machine learning (ML) and deep learning (DL), plays a critical role in addressing these challenges.

AI algorithms can:

- Identify patterns and correlations across multiple omics layers
- Reduce dimensionality and extract relevant features
- Integrate heterogeneous datasets into unified predictive models

Machine learning techniques such as random forests, support vector machines, and neural networks have been widely used for biomarker discovery and disease classification. More advanced approaches, including deep learning architectures, can capture complex nonlinear relationships and interactions between molecular variables.By integrating multi-omics data with clinical and imaging data, AI enables the development of comprehensive models that provide patient-specific insights, facilitating personalized diagnosis and treatment (16) .

11.3. Biomarker Discovery

One of the most promising applications of AI-driven multi-omics is the identification of novel biomarkers for early detection of kidney disease. Traditional biomarkers often fail to detect disease in its early stages, whereas omics-based markers can reveal molecular changes in the very early stages.Emerging biomarkers such as NGAL, KIM-1, cystatin C, and suPAR have demonstrated improved sensitivity and specificity for detecting kidney injury. AI models that integrate these biomarkers with omics data can further enhance diagnostic accuracy and enable earlier intervention. In addition, multi-biomarker panels analyzed using AI can provide more robust and reliable predictions compared to single biomarkers. These panels capture multiple aspects of disease biology, improving both sensitivity and specificity (4).

11.4. Personalized Medicine

AI enables prediction of drug response, adverse effects, and optimal treatment strategies (4,16).

11.5. Molecular Applications

The integration of AI and multi-omics data enables the development of personalized treatment strategies. By analyzing patient-specific molecular profiles, AI models can predict treatment responses and identify optimal therapeutic approaches (4,16).

For example, AI-driven analyses can:
- Predict responsiveness to specific medications
- Identify patients at risk of adverse drug reactions
- Optimize dosing strategies

Moreover, multi-omics data can reveal novel therapeutic targets by identifying key molecular pathways involved in disease progression. AI facilitates the identification of these targets by complex datasets and uncovering previously unrecognized interactions. This approach has the potential to accelerate drug discovery and improve treatment outcomes in nephrology (2).

12. Ethical, Legal, and Clinical Challenges

AI in nephrology raises important ethical and governance issues, including bias, privacy, and lack of regulatory frameworks (51). Human oversight remains essential to ensure safe and patient-centered care. Challenges include data quality, algorithmic bias, and limited interpretability. Explainable AI (XAI) is proposed to improve transparency (1,14,52).

12.1. Data Privacy

Large-scale clinical and genomic data raise concerns about privacy, requiring secure storage and encryption. AI systems in nephrology rely heavily on large-scale patient data, including electronic health records (EHRs), imaging, and increasingly, genomic and multi-omics data. While these data are essential for training robust models, they also raise significant concerns about patient privacy and data security (15).

12.2. Bias and Fairness

Bias in training data may lead to inequitable outcomes, necessitating diverse datasets and fairness-aware approaches. In nephrology, disparities in healthcare access and outcomes are well-documented across demographic groups, including differences based on race, ethnicity, socioeconomic status, and geographic location. If AI models are

trained on biased datasets, they may perpetuate or even exacerbate these disparities. For example, models developed using data from specific populations may not generalize well to underrepresented groups, resulting in reduced accuracy and potentially harmful clinical decisions. Addressing bias requires careful dataset curation, inclusion of diverse populations, and ongoing evaluation of model performance across subgroups (1,14).

12.3. Explainability

Black-box models limit clinical trust; XAI methods aim to improve interpretability (5).

12.4. Clinical Integration

The successful implementation of AI in nephrology depends not only on model performance but also on its integration into clinical workflows. Poorly integrated systems can disrupt workflows, increase clinician workload, and reduce efficiency.

Clinical decision support systems (CDSS) must be designed with usability in mind, providing actionable insights without overwhelming clinicians. Issues such as alert fatigue, caused by excessive or irrelevant notifications, can reduce the effectiveness of AI systems and hinder adoption. Interoperability is another critical challenge, as AI systems must be compatible with existing healthcare infrastructure, including EHR platforms and medical devices. Standardization of data formats and communication protocols is essential to facilitate seamless integration. Furthermore, training and education of healthcare professionals are necessary to ensure that clinicians can effectively interpret and utilize AI-generated outputs (6,7,12).

12.5. Accountability

Legal responsibility in AI-driven decisions remains unclear and requires regulatory clarification (30).

12.6. Academic Ethics

Beyond clinical applications, AI also raises ethical concerns in academic nephrology, particularly in the context of research and scholarly writing. The increasing use of AI tools for literature review, manuscript preparation, and data analysis has introduced new challenges related to academic integrity. There is growing concern that the misuse of AI-generated content may undermine the authenticity and credibility of scientific publications. Instances of AI-assisted writing without proper disclosure have been reported, highlighting vulnerabilities in the peer-review process. To address these issues, it is essential to establish clear guidelines for the ethical use of AI in research, including transparency in reporting AI involvement, the use of AI-detection tools, and the incorporation of AI-specific review processe (15,30).

12.7. Path Forward

Key priorities include regulation, fairness, transparency, education, and ethical governance (15,30).

13. Future Directions and Emerging Trends

AI in nephrology is evolving toward multimodal integration, combining clinical, imaging, and molecular data (2).Federated learning, wearable technologies, and learning health systems are key emerging directions (51). The future of AI in nephrology will depend on addressing current limitations while leveraging emerging technologies to create more robust, interpretable, and clinically integrated systems. It is closely linked to advancements in data integration, computational methods, and collaborative research. One promising approach is federated learning, which allows multiple institutions to collaboratively train AI models without sharing sensitive patient data. This method addresses privacy concerns while improving model generalizability. Another important trend is the integration of multimodal data, including clinical, imaging, and omics datasets. This approach supports the development of precision medicine, enabling personalized diagnosis and treatment strategies tailored to individual patients. For example, AI models analyzing electrocardiogram (ECG) waveforms have shown potential in identifying cardiovascular risks in patients with kidney disease (2,53,54).

13.1. Explainable AI

Future systems must be interpretable and trustworthy, ensuring clinical adoption (5). Future AI systems must provide transparent and interpretable outputs that allow clinicians to understand the rationale behind predictions. Explainable AI (XAI) techniques, such as feature attribution methods, attention mechanisms, and surrogate models, are expected to play a central role in bridging the gap between performance and usability. Trustworthy AI also requires rigorous validation, reproducibility, and adherence to ethical standards. Models must be evaluated across diverse populations and healthcare settings to ensure fairness and generalizability (5)

13.2. Integration into Clinical Practice

The translation of AI from research to routine clinical practice represents one of the most significant challenges and opportunities. Future efforts will focus on embedding AI systems into clinical workflows in a seamless and user-friendly manner.

This includes:

- Integration with electronic health record (EHR) systems
- Real-time decision support at the bedside
- Automated data processing and reporting

Prospective clinical trials and implementation studies will be essential to evaluate the real-world impact of AI systems on patient outcomes, workflow efficiency, and healthcare costs. Such studies are currently limited but are expected to increase as AI technologies mature (5).

13.3. Precision Nephrology and Personalized Medicine

The convergence of AI with multi-omics technologies, wearable devices, and digital health platforms will drive the transition toward precision nephrology. Future models will integrate diverse data sources to generate comprehensive, patient-specific profiles.

These advancements will enable:

- Early disease detection through AI
- Accurate prediction of disease trajectories
- Personalized treatment strategies
- Optimization of drug dosing and therapy selection

AI-driven precision medicine has the potential to transform nephrology from a reactive specialty into a proactive and preventive discipline (16).

13.4. Real-Time and Adaptive AI Systems

Future AI systems will increasingly operate in real time, continuously analyzing data streams and adapting to changes in patient condition. This is particularly relevant in settings such as intensive care units, dialysis centers, and transplant monitoring.Reinforcement learning (RL) and adaptive algorithms will enable dynamic decision-making, models learn from ongoing patient data and refine their recommendations over time. These systems will support continuous monitoring and proactive intervention, improving patient safety and outcomes (6,8).

13.5. Expansion of Data Sources

The expansion of data sources will further enhance AI capabilities in nephrology. Emerging technologies such as wearable devices, remote monitoring systems, and mobile health applications will generate continuous streams of patient data. In addition, advances in multi-omics and molecular diagnostics will provide deeper insights into disease mechanisms. The integration of these diverse data types into unified AI models will enable more comprehensive and accurate predictions. However, this expansion also necessitates improved data governance, standardization, and interoperability to ensure effective utilization (1,3).

13.6. Collaborative and Multidisciplinary Approaches

The future of AI in nephrology will heavily on collaboration between multiple disciplines, including nephrologists, data scientists, bioinformaticians, engineers, and policymakers. Multicenter collaborations and data-sharing initiatives will be essential for creating large, diverse datasets that improve model robustness and generalizability. Open science approaches and standardized reporting frameworks will further transparency and reproducibility. In addition, partnerships between academia, industry, and healthcare institutions will accelerate innovation and facilitate the translation of research findings into clinical applications (4,6,7).

13.7. Ethical and Regulatory Evolution

As AI technologies continue to evolve, ethical and regulatory frameworks must also adapt. Future efforts will focus on developing comprehensive guidelines that address issues such as data privacy, algorithmic bias, and accountability. Regulatory agencies are expected to play a more active role in evaluating AI systems, about their safety, effectiveness, and fairness. Continuous monitoring and post-deployment evaluation will be critical to ensure that AI systems remain reliable over time. Furthermore, the establishment of ethical standards for AI use in both clinical and academic contexts will be essential for maintaining trust and integrity (15,30).

13.8. Toward a Learning Healthcare System

Ultimately, the integration of AI into nephrology will contribute to the development of a learning healthcare system, one in which data generated from routine clinical practice are continuously analyzed to improve care.

In such a system:

- Clinical decisions are informed by real-time data and predictive analytics
- Outcomes are continuously monitored and used to refine models
- AI technologie evolves dynamically based on new evidence

This vision provide the convergence of AI, big data, and clinical practice, offering the potential to significantly improve patient outcomes and healthcare efficiency (2,53,54).

14. Conclusion

Artificial intelligence is transforming nephrology, offering new possibilities for early detection, risk assessment, treatment optimization, and long-term management of kidney diseases. Its ability to integrate large and complex datasets allows for more accurate and timely clinical decisions. AI has shown strong potential across multiple areas, including

acute kidney injury, chronic kidney disease, dialysis, transplantation, and renal pathology. By identifying complex patterns beyond traditional statistical methods, AI supports a shift toward proactive and preventive care. However, successful implementation requires addressing challenges related to data quality, bias, interpretability, and ethical governance. Multidisciplinary collaboration, robust validation, and clinician training will be essential. In the future, the integration of AI with big data and precision medicine is expected to transform nephrology into a more predictive, personalized, and efficient field. With appropriate regulation and responsible use, AI has the potential to significantly improve patient outcomes and advance clinical practice.

15. References

1. Singh, P., Goyal, L., Mallick, D. C., Surani, S. R., Kaushik, N., Chandramohan, D., & Simhadri, P. K. (2024). Artificial Intelligence in Nephrology: Clinical Applications and Challenges. Kidney medicine, 7(1), 100927. https://doi.org/10.1.016/j.xkme.2.024.1.00927
2. Stojanowski, J., Gołębiowski, T., & Musiał, K. (2026). Artificial Intelligence in Nephrology-State of the Art on Theoretical Background, Molecular Applications, and Clinical Interpretation. International journal of molecular sciences, 27(3), 1285. https://doi.org/10.3.390/ijms27031285
3. Cheungpasitporn, W., Athavale, A., Ghazi, L., Kashani, K. B., Colicchio, T., Koyner, J. L., Chen, J., Ix, J. H., Nadkarni, G., & Neyra, J. A. (2026). Transforming nephrology through artificial intelligence: A state-of-the-art roadmap for clinical integration. Clinical Kidney Journal, 19(2), sfag004. https://doi.org/10.1.093/ckj/sfag004
4. Alobaidi, S. (2025). Emerging biomarkers and advanced diagnostics in chronic kidney disease: Early detection through multi-omics and AI. Diagnostics, 15(10), 1225. https://doi.org/10.3.390/diagnostics15101225
5. Shickel, B., Ozrazgat-Baslanti, T., & Bihorac, A. (2025). Artificial intelligence at the bedside for the prevention, detection, and management of acute kidney injury. Current opinion in nephrology and hypertension, 34(6), 483–490. https://doi.org/10.1.097/MNH.0000000000001112
6. Magherini, R., Mussi, E., Volpe, Y., Furferi, R., Buonamici, F., & Servi, M. (2022). Machine Learning for Renal Pathologies: An Updated Survey. Sensors (Basel, Switzerland), 22(13), 4989. https://doi.org/10.3.390/s22134989
7. David-Olawade, A. C., Ogunbona, M. A., Olawuyi, O. F., Makanjuola, B. D., Alabi, J. O., Olawade, D. B. (2026). Artificial intelligence and machine learning applications in dialysis: Current applications, challenges, and future directions. Clinica Chimica Acta, 586, 120908. https://doi.org/10.1.016/j.cca.2.026.1.2.0908
8. Grobe, N., Scheiber, J., Zhang, H., Garbe, C., & Wang, X. (2023). Omics and artificial intelligence in kidney diseases. Advances in Kidney Disease and Health, 30(1), 47–52. https://doi.org/10.1.053/j.akdh.2.022.1.1.005
9. Miao, J., Thongprayoon, C., Suppadungsuk, S., Garcia Valencia, O. A., Qureshi, F., & Cheungpasitporn, W. (2024). Ethical dilemmas in using AI for academic writing and an example framework for peer review in nephrology academia. Clinical Practice, 14, 89–105. https://doi.org/10.3.390/clinpract14010008
10. Badrouchi, S., Bacha, M. M., Hedri, H., Ben Abdallah, T., & Abderrahim, E. (2023). Toward generalizing the use of artificial intelligence in nephrology and kidney transplantation. Journal of nephrology, 36(4), 1087–1100. https://doi.org/10.1.007/s40620-022-01529-0
11. Cazzaniga, G., Rossi, M., Eccher, A., Girolami, I., L'Imperio, V., Van Nguyen, H., Becker, J. U., Bueno García, M. G., Sbaraglia, M., Dei Tos, A. P., Gambaro, G., & Pagni, F. (2024). Time for a full digital approach in nephropathology: a systematic review of current artificial intelligence applications and future directions. Journal of nephrology, 37(1), 65–76. https://doi.org/10.1.007/s40620-023-01775-w
12. Girolami, I., Pantanowitz, L., Marletta, S., Hermsen, M., van der Laak, J., Munari, E., Furian, L., Vistoli, F., Zaza, G., Cardillo, M., Gesualdo, L., Gambaro, G., & Eccher, A. (2022). Artificial intelligence applications for pre-implantation kidney biopsy pathology practice: a systematic review. Journal of nephrology, 35(7), 1801–1808. https://doi.org/10.1.007/s40620-022-01327-8
13. Jayaraman, P., Vasudev, I., Bhardwaj, A., Nadkarni, G., Sakhuja, A., & Meena, P. (2025). Artificial Intelligence in Nephrology: Pioneering Precision with Multimodal Intelligence. Indian journal of nephrology, 35(4), 470–479. https://doi.org/10.2.5.259/IJN_496_2024
14. Simeri, A., Pezzi, G., Arena, R., Papalia, G., Szili-Torok, T., Greco, R., Veltri, P., Greco, G., Pezzi, V., Provenzano, M., & Zaza, G. (2025). Artificial intelligence in chronic kidney diseases: methodology and potential applications. International urology and nephrology, 57(1), 159–168. https://doi.org/10.1.007/s11255-024-04165-8
15. Ning, Y., Teixayavong, S., Shang, Y., Savulescu, J., Nagaraj, V., Miao, D., Mertens, M., Ting, D. S. W., Ong, J. C. L., Liu, M., Cao, J., Dunn, M., Vaughan, R., Ong, M. E. H., Sung, J. J., Topol, E. J., & Liu, N. (2024). Generative artificial intelligence and

ethical considerations in health care: a scoping review and ethics checklist. The Lancet. Digital health, 6(11), e848–e856. https://doi.org/10.1.016/S2589-7500(24)00143-2
16. Lopes, M. B., Coletti, R., Duranton, F., Glorieux, G., Jaimes Campos, M. A., Klein, J., Ley, M., Perco, P., Sampri, A., & Tur-Sinai, A. (2025). The omics-driven machine learning path to cost-effective precision medicine in chronic kidney disease. Proteomics, 25, e202400108. https://doi.org/10.1.002/pmic.2.02400108
17. Yang, A., Finkelstein, M., Koo, C., & Doshi, A. H. (2024). Impact of Deep Learning Image Reconstruction Methods on MRI Throughput. Radiology. Artificial intelligence, 6(3), e230181. https://doi.org/10.1.148/ryai.2.3.0181
18. Zhong, J., Xing, Y., Lu, J., Zhang, G., Mao, S., Chen, H., Yin, Q., Cen, Q., Jiang, R., Hu, Y., Ding, D., Ge, X., Zhang, H., & Yao, W. (2023). The endorsement of general and artificial intelligence reporting guidelines in radiological journals: a meta-research study. BMC medical research methodology, 23(1), 292. https://doi.org/10.1.186/s12874-023-02117-x
19. Ren, Z., Zhang, M., Wang, P., Chen, K., Wang, J., Wu, L., Hong, Y., Qu, Y., Luo, Q., & Cai, K. (2025). Research on the development of an intelligent prediction model for blood pressure variability during hemodialysis. BMC nephrology, 26(1), 82. https://doi.org/10.1.186/s12882-025-03959-x
20. Patrascanu, O. S., Tutunaru, D., Musat, C. L., Dragostin, O. M., Fulga, A., Nechita, L., Ciubara, A. B., Piraianu, A. I., Stamate, E., Poalelungi, D. G., Dragostin, I., Iancu, D. C., Ciubara, A., & Fulga, I. (2024). Future Horizons: The Potential Role of Artificial Intelligence in Cardiology. Journal of personalized medicine, 14(6), 656. https://doi.org/10.3.390/jpm14060656
21. Gervasoni, F., Bellocchio, F., Rosenberger, J., Arkossy, O., Ion Titapiccolo, J., Kovarova, V., Larkin, J., Nikam, M., Stuard, S., Tripepi, G. L., Usvyat, L. A., Winter, A., Neri, L., & Zoccali, C. (2023). Development and validation of AI-based triage support algorithms for prevention of intradialytic hypotension. Journal of nephrology, 36(7), 2001–2011. https://doi.org/10.1.007/s40620-023-01741-6
22. Mushtaq, M. M., Mushtaq, M., Ali, H., Sarwar, M. A., & Bokhari, S. F. H. (2024). Artificial intelligence and machine learning in peritoneal dialysis: a systematic review of clinical outcomes and predictive modeling. International urology and nephrology, 56(12), 3857–3867. https://doi.org/10.1.007/s11255-024-04144-z
23. Hoang, A. T., Nguyen, P. A., Phan, T. P., Do, G. T., Nguyen, H. D., Chiu, I. J., Chou, C. L., Ko, Y. C., Chang, T. H., Huang, C. W., Iqbal, U., Hsu, Y. H., Wu, M. S., & Liao, C. T. (2024). Personalised prediction of maintenance dialysis initiation in patients with chronic kidney disease stages 3-5: a multicentre study using the machine learning approach. BMJ health & care informatics, 31(1), e100893. https://doi.org/10.1.136/bmjhci-2023-100893
24. Usvyat, L., Dalrymple, L. S., & Maddux, F. W. (2018). Using Technology to Inform and Deliver Precise Personalized Care to Patients With End-Stage Kidney Disease. Seminars in nephrology, 38(4), 418–425. https://doi.org/10.1.016/j.semnephrol.2.018.05.011
25. Díez-Sanmartín, C., Cabezuelo, A. S., & Belmonte, A. A. (2023). A new approach to predicting mortality in dialysis patients using sociodemographic features based on artificial intelligence. Artificial intelligence in medicine, 136, 102478. https://doi.org/10.1.016/j.artmed.2.022.1.02478
26. Kanbay, M., Ertuglu, L. A., Afsar, B., Ozdogan, E., Siriopol, D., Covic, A., Basile, C., & Ortiz, A. (2020). An update review of intradialytic hypotension: concept, risk factors, clinical implications and management. Clinical kidney journal, 13(6), 981–993. https://doi.org/10.1.093/ckj/sfaa078
27. Davenport A. (2022). Why is Intradialytic Hypotension the Commonest Complication of Outpatient Dialysis Treatments?. Kidney international reports, 8(3), 405–418. https://doi.org/10.1.016/j.ekir.2.022.1.0.031
28. Yun, D., Yang, H. L., Kim, S. G., Kim, K., Kim, D. K., Oh, K. H., Joo, K. W., Kim, Y. S., & Han, S. S. (2023). Real-time dual prediction of intradialytic hypotension and hypertension using an explainable deep learning model. Scientific reports, 13(1), 18054. https://doi.org/10.1.038/s41598-023-45282-1
29. Qarajeh, A., Tangpanithandee, S., Thongprayoon, C., Suppadungsuk, S., Krisanapan, P., Aiumtrakul, N., Garcia Valencia, O. A., Miao, J., Qureshi, F., & Cheungpasitporn, W. (2023). AI-Powered Renal Diet Support: Performance of ChatGPT, Bard AI, and Bing Chat. Clinics and practice, 13(5), 1160–1172. https://doi.org/10.3.390/clinpract13050104
30. Suppadungsuk, S., Thongprayoon, C., Krisanapan, P., Tangpanithandee, S., Garcia Valencia, O., Miao, J., Mekraksakit, P., Kashani, K., & Cheungpasitporn, W. (2023). Examining the Validity of ChatGPT in Identifying Relevant Nephrology Literature: Findings and Implications. Journal of clinical medicine, 12(17), 5550. https://doi.org/10.3.390/jcm12175550
31. Callemeyn, J., Lamarthée, B., Koenig, A., Koshy, P., Thaunat, O., & Naesens, M. (2022). Allorecognition and the spectrum of kidney transplant rejection. Kidney international, 101(4), 692–710. https://doi.org/10.1.016/j.kint.2.021.1.1.029
32. Lewis, A., Koukoura, A., Tsianos, G. I., Gargavanis, A. A., Nielsen, A. A., & Vassiliadis, E. (2021). Organ donation in the US and Europe: The supply vs demand imbalance. Transplantation reviews (Orlando, Fla.), 35(2), 100585. https://doi.org/10.1.016/j.trre.2.020.1.00585
33. He, Y. J., Liu, P. L., Wei, T., Liu, T., Li, Y. F., Yang, J., & Fan, W. X. (2025). Artificial intelligence in kidney transplantation: a 30-year bibliometric analysis of research trends, innovations, and future directions. Renal failure, 47(1), 2458754. https://doi.org/10.1.080/0886022X.2.025.2.4.5.8.754
34. Sheikh, M. S., Kashani, K. B., Gregoire, J. R., Thongprayoon, C., Miao, J., Craici, I. M., Cheungpasitporn, W., & Qureshi, F. M. (2025). Digital transformation of nephrology POCUS education—Integrating a multiagent, artificial intelligence, and human collaboration-enhanced curriculum with expert feedback. Digital Health, 11, 1–11. https://doi.org/10.1.177/20552076251328807
35. Paquette, F. X., Ghassemi, A., Bukhtiyarova, O., Cisse, M., Gagnon, N., Della Vecchia, A., Rabearivelo, H. A., & Loudiyi, Y. (2022). Machine Learning Support for Decision-Making in Kidney Transplantation: Step-by-step Development of a Technological Solution. JMIR medical informatics, 10(6), e34554. https://doi.org/10.2.196/34554

36. Raynaud, M., Aubert, O., Divard, G., Reese, P. P., Kamar, N., Yoo, D., Chin, C. S., Bailly, É., Buchler, M., Ladrière, M., Le Quintrec, M., Delahousse, M., Juric, I., Basic-Jukic, N., Crespo, M., Silva, H. T., Jr, Linhares, K., Ribeiro de Castro, M. C., Soler Pujol, G., Empana, J. P., … Loupy, A. (2021). Dynamic prediction of renal survival among deeply phenotyped kidney transplant recipients using artificial intelligence: an observational, international, multicohort study. The Lancet. Digital health, 3(12), e795–e805. https://doi.org/10.1016/S2589-7500(21)00209-0
37. Alowidi, N., Ali, R., Sadaqah, M., & Naemi, F. M. A. (2024). Advancing Kidney Transplantation: A Machine Learning Approach to Enhance Donor-Recipient Matching. Diagnostics (Basel, Switzerland), 14(19), 2119. https://doi.org/10.3.390/diagnostics14192119
38. Campsen, J., Kim, Y., & Chen, T. (2025). Enhancing Organ Allocation Efficiency: A Pilot Study Evaluating Artificial Intelligence-Assisted Assessment of Donor Kidney Pathology. Cureus, 17(5), e83656. https://doi.org/10.7.759/cureus.8.3656
39. Gadelkareem, R. A., Abdelgawad, A. M., Mohammed, N., Zarzour, M. A., Khalil, M., Reda, A., & Hammouda, H. M. (2024). Challenges to establishing and maintaining kidney transplantation programs in developing countries: What are the coping strategies?. World journal of methodology, 14(2), 91626. https://doi.org/10.5.6.62/wjm.v14.i2.9.1626
40. Loupy, A., Preka, E., Chen, X., Wang, H., He, J., & Zhang, K. (2025). Reshaping transplantation with AI, emerging technologies and xenotransplantation. Nature medicine, 31(7), 2161–2173. https://doi.org/10.1.038/s41591-025-03801-9
41. Feng, C., & Liu, F. (2023). Artificial intelligence in renal pathology: Current status and future. Biomolecules & biomedicine, 23(2), 225–234. https://doi.org/10.1.7.305/bjbms.2.022.8.318
42. Gottlich, H. C., Gregory, A. V., Sharma, V., Khanna, A., Moustafa, A. U., Lohse, C. M., Potretzke, T. A., Korfiatis, P., Potretzke, A. M., Denic, A., Rule, A. D., Takahashi, N., Erickson, B. J., Leibovich, B. C., & Kline, T. L. (2023). Effect of Dataset Size and Medical Image Modality on Convolutional Neural Network Model Performance for Automated Segmentation: A CT and MR Renal Tumor Imaging Study. Journal of digital imaging, 36(4), 1770–1781. https://doi.org/10.1.007/s10278-023-00804-1
43. Song, X., Liu, X., Liu, F., & Wang, C. (2021). Comparison of machine learning and logistic regression models in predicting acute kidney injury: A systematic review and meta-analysis. International journal of medical informatics, 151, 104484. https://doi.org/10.1.016/j.ijmedinf.2.021.1.04484
44. Hermsen, M., de Bel, T., den Boer, M., Steenbergen, E. J., Kers, J., Florquin, S., Roelofs, J. J. T. H., Stegall, M. D., Alexander, M. P., Smith, B. H., Smeets, B., Hilbrands, L. B., & van der Laak, J. A. W. M. (2019). Deep Learning-Based Histopathologic Assessment of Kidney Tissue. Journal of the American Society of Nephrology : JASN, 30(10), 1968–1979. https://doi.org/10.1.6.8.1/ASN.2.019020144
45. Tseng, P. Y., Chen, Y. T., Wang, C. H., Chiu, K. M., Peng, Y. S., Hsu, S. P., Chen, K. L., Yang, C. Y., & Lee, O. K. (2020). Prediction of the development of acute kidney injury following cardiac surgery by machine learning. Critical care (London, England), 24(1), 478. https://doi.org/10.1.186/s13054-020-03179-9
46. Shimbo, D., Shah, R. U., Abdalla, M., Agarwal, R., Ahmad, F. S., Anaya, G., Attia, Z. I., Bull, S., Chang, A. R., Commodore-Mensah, Y., Ferdinand, K., Kawamoto, K., Khera, R., Leopold, J., Luo, J., Makhni, S., Mortazavi, B. J., Oh, Y. S., Savage, L. C., Spatz, E. S., … Iturriaga, E. (2025). Transforming Hypertension Diagnosis and Management in The Era of Artificial Intelligence: A 2023 National Heart, Lung, and Blood Institute (NHLBI) Workshop Report. Hypertension (Dallas, Tex. : 1979), 82(1), 36–45. https://doi.org/10.1.161/HYPERTENSIONAHA.1.2.4..2.2095
47. Iskrov, G., Raycheva, R., Kostadinov, K., Gillner, S., Blankart, C. R., Gross, E. S., Gumus, G., Mitova, E., Stefanov, S., Stefanov, G., & Stefanov, R. (2024). Are the European reference networks for rare diseases ready to embrace machine learning? A mixed-methods study. Orphanet journal of rare diseases, 19(1), 25. https://doi.org/10.1.186/s13023-024-03047-7
48. Raycheva, R., Kostadinov, K., Mitova, E., Iskrov, G., Stefanov, G., Vakevainen, M., Elomaa, K., Man, Y. S., Gross, E., Zschüntzsch, J., Röttger, R., & Stefanov, R. (2024). Landscape analysis of available European data sources amenable for machine learning and recommendations on usability for rare diseases screening. Orphanet journal of rare diseases, 19(1), 147. https://doi.org/10.1.186/s13023-024-03162-5
49. Chen, X., Burgun, A., Boyer, O., Knebelmann, B., & Garcelon, N. (2025). Artificial intelligence and perspective for rare genetic kidney diseases. Kidney International, 108(2), 388–393. https://doi.org/10.1.016/j.kint.2.025.03.033
50. Collins, G. S., Moons, K. G. M., Dhiman, P., Riley, R. D., Beam, A. L., Van Calster, B., Ghassemi, M., Liu, X., Reitsma, J. B., van Smeden, M., Boulesteix, A. L., Camaradou, J. C., Celi, L. A., Denaxas, S., Denniston, A. K., Glocker, B., Golub, R. M., Harvey, H., Heinze, G., Hoffman, M. M., … Logullo, P. (2024). TRIPOD+AI statement: updated guidance for reporting clinical prediction models that use regression or machine learning methods. BMJ (Clinical research ed.), 385, e078378. https://doi.org/10.1.136/bmj-2023-078378
51. Ho, C. W., & Caals, K. (2021). A Call for an Ethics and Governance Action Plan to Harness the Power of Artificial Intelligence and Digitalization in Nephrology. Seminars in nephrology, 41(3), 282–293. https://doi.org/10.1.016/j.semnephrol.2.021.05.009
52. Sunarti, S., Fadzlul Rahman, F., Naufal, M., Risky, M., Febriyanto, K., & Masnina, R. (2021). Artificial intelligence in healthcare: opportunities and risk for future. Gaceta sanitaria, 35 Suppl 1, S67–S70. https://doi.org/10.1.016/j.gaceta.2.020.1.2..019
53. Kotanko, P., & Nadkarni, G. N. (2023). Advances in Chronic Kidney Disease Lead Editorial Outlining the Future of Artificial Intelligence/Machine Learning in Nephrology. Advances in kidney disease and health, 30(1), 2–3. https://doi.org/10.1.053/j.akdh.2.022.1.1.008
54. Kotsifa, E., & Mavroeidis, V. K. (2024). Present and Future Applications of Artificial Intelligence in Kidney Transplantation. Journal of clinical medicine, 13(19), 5939. https://doi.org/10.3.390/jcm13195939

CHAPTER 23

AI-Driven Personalized Treatment Protocols in Therapeutic Apheresis

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1. Introduction

Therapeutic apheresis represents a specialized extracorporeal intervention in which circulating blood components are selectively separated and disease-related plasma or cellular elements are removed. By directly targeting pathogenic factors within the bloodstream, this approach allows for a more rapid biological effect compared to conventional pharmacologic treatments, particularly in clinical situations requiring urgent intervention. In contemporary hematology practice, therapeutic apheresis has become an important component in the management of several conditions, most notably thrombotic microangiopathies, hyperviscosity syndromes, hyperleukocytosis, and certain autoimmune hematologic disorders (1,2).

Despite these advances, therapeutic apheresis in routine clinical practice is still largely conducted according to predefined protocols, which may not fully capture inter-individual variability. In reality, patients differ considerably in terms of disease burden, circulating levels of target molecules or cells, treatment response dynamics, and physiological reserve. Such variability highlights the limitations of standardized approaches and underscores the need for more flexible, patient-centered strategies to optimize therapeutic outcomes.

The growing volume of clinical data, together with the increasing complexity of healthcare processes, has exposed the limitations of traditional decision-making frameworks and necessitated more advanced analytical approaches. In this context, artificial intelligence (AI) and machine learning techniques have emerged as valuable tools in healthcare, owing to their ability to process and integrate multidimensional data in real time. This capability is particularly relevant in therapeutic apheresis, where multiple clinical and biological parameters may fluctuate simultaneously. AI-driven models can support clinical

decision-making by improving patient selection, enabling dynamic adjustment of procedural parameters, and facilitating the early prediction of potential complications (3,4).

Within this framework, the integration of therapeutic apheresis with artificial intelligence technologies provides a strong foundation for the transition from standardized treatment algorithms to patient-specific, adaptive therapeutic strategies. Accordingly, this chapter explores the fundamental principles of therapeutic apheresis and examines the potential contributions of AI-based approaches in this field from the perspective of personalized medicine.

2. Basic Principles and Clinical Applications of Therapeutic Apheresis

Therapeutic apheresis is a targeted treatment modality based on the extracorporeal processing of circulating blood, enabling the removal of specific plasma components or cellular elements involved in disease pathogenesis. During the procedure, blood is separated into its constituent components using systems based on physical separation principles; the pathological fraction is eliminated, while the remaining components are returned to the patient along with appropriate replacement fluids. Owing to this mechanism, therapeutic apheresis represents an effective intervention, particularly in clinical settings where the rapid reduction of harmful circulating factors is of critical importance (1).

Apheresis procedures can be broadly categorized into three main groups based on their technical specifications and the targeted component:

1. Plasma-based,
2. Cellular based
3. Selective apheresis methods

Therapeutic plasma exchange, the most widely used plasma-based apheresis modality, is primarily aimed at removing pathogenic plasma constituents such as autoantibodies, immune complexes, and paraproteins from the circulation. In contrast, when cellular elements are the therapeutic target, cytapheresis techniques are employed. Within this group, leukapheresis is commonly utilized to reduce excessive leukocyte burden, particularly in cases of hyperleukocytosis, whereas red blood cell exchange is performed to eliminate erythrocytes with abnormal structure or function. In addition, more selective apheresis approaches offer a higher degree of specificity by targeting defined molecular components. For instance, immunoadsorption techniques enable the selective removal of specific immunoglobulins or antibodies through binding mechanisms. This classification highlights that therapeutic apheresis should not be viewed merely as a nonspecific "cleansing" procedure, but rather as a spectrum of targeted interventions employing distinct mechanisms tailored to specific pathophysiological processes (2).

Therapeutic apheresis is an effective adjunctive treatment widely utilized across a broad range of indications in hematology practice. It plays a particularly important role in conditions such as thrombotic microangiopathies, hyperleukocytosis, and hyperviscosity

syndromes, where the rapid reduction of circulating pathogenic components can contribute to early clinical improvement. However, these indications differ substantially in terms of underlying pathophysiology and therapeutic objectives, necessitating that the selection and planning of apheresis procedures be tailored to individual patient characteristics (1).

However, the effectiveness of therapeutic apheresis is not determined solely by the choice of modality, but also by the appropriate adjustment of procedural parameters and the consideration of patient-specific factors. Variables such as exchange volume, frequency of sessions, selection of replacement fluids, and the patient's overall clinical condition can directly influence treatment outcomes. This multidimensional nature underscores that therapeutic apheresis should not be managed through rigid, standardized algorithms, but rather as a dynamic process that requires continuous adaptation to individual patient characteristics

Accumulating clinical experience in recent years has highlighted the need to move beyond standardized protocols in apheresis therapy toward more flexible, patient-centered approaches. This shift has increased the demand for data-driven methodologies capable of enabling more precise optimization of treatment processes. Consequently, the future of therapeutic apheresis is likely to be shaped not only by technological advancements, but also by innovative strategies that facilitate the effective integration and utilization of individual patient data.

3. Indications for Apheresis in Hematological Diseases

Therapeutic apheresis represents an important adjunctive treatment modality in the management of hematologic disorders, targeting diverse pathophysiological mechanisms. These interventions serve distinct therapeutic purposes, including the removal of circulating pathogenic plasma components, reduction of cellular burden, and modulation of immune responses. Accordingly, the selection of apheresis strategies should not rely solely on the underlying diagnosis, but must also be individualized based on the clinical presentation, disease severity, and specific therapeutic objectives (1)

In hematology practice, therapeutic apheresis is applied across a broad spectrum of clinical conditions, including thrombotic microangiopathies, autoimmune hematologic disorders, hematologic malignancies, and paraproteinemias. The primary objective of apheresis in these settings is the rapid reduction of circulating pathogenic plasma components or cellular elements in accordance with the underlying pathophysiological mechanism. For example, in thrombotic thrombocytopenic purpura, plasma exchange has a life-saving effect by removing ADAMTS13 inhibitors and ultra-large von Willebrand factor multimers. Similarly, in acute leukemias complicated by hyperleukocytosis, leukapheresis contributes to the prevention of microvascular complications by reducing circulating blast cell burden. In cases of hyperviscosity associated with paraproteinemias, plasma exchange enables rapid symptom control through the reduction of circulating immunoglobulin levels.

Table 1. The main therapeutic apheresis indications and treatment goals in hematological diseases

Disease category	Clinical condition	Apheresis modality	Primary therapeutic goal
Thrombotic microangiopathies	Thrombotic thrombocytopenic purpura (TTP	Plasma exchange	Removal of ADAMTS13 inhibitors and ultra-large von Willebrand factor multimers
Autoimmune hematologic disorders	Autoimmune hemolytic anemia (AIHA), Immune thrombocytopenia (ITP)	Plasma exchange / Immunoadsorption	Reduction of circulating autoantibodies
Hematologic malignancie	Hyperleukocytosis (e.g., AML)	Leukapheresis	Rapid reduction of circulating leukocyte burden
Paraproteinemias	Multiple myeloma, Waldenström macroglobulinemia	Plasma exchange	Reduction of serum viscosity and paraprotein levels
Hemoglobinopathies	Sickle cell disease	Red blood cell exchange	Removal of abnormal erythrocytes and reduction of HbS levels
Transplant-related conditions	ABO-incompatible transplantation, alloimmunization	Plasma exchange / Immunoadsorption	Reduction of pathogenic antibody titers

However, the effectiveness of therapeutic apheresis is not determined solely by the indication, but is also significantly influenced by patient-specific factors. Variables such as the concentration of circulating target components, the patient's clinical status, coexisting comorbidities, and individual treatment response can directly affect the timing, frequency, and duration of apheresis procedures. This multidimensional complexity indicates that therapeutic apheresis should not be approached as a rigid, protocol-driven intervention, but rather as a dynamic process that requires continuous adaptation based on individual patient characteristics (5).

Within this context, the major indications for therapeutic apheresis in hematologic disorders are summarized in Table 1. However, even among patients sharing the same indication, clinical requirements may vary considerably, necessitating the adaptation of treatment strategies on an individual basis. This variability underscores the importance of personalized approaches in therapeutic apheresis and provides a conceptual basis for the patient-centered treatment models discussed in the subsequent section..

4. The Concept of Personalized Treatment and Its Necessity in Therapeutic Apheresis

Personalized medicine refers to a patient-centered approach that moves beyond standardized treatment protocols by incorporating individual clinical, biological, and genetic characteristics into disease management. In contemporary hematology practice, the marked

heterogeneity of diseases and the variability in treatment responses among patients have made the adoption of individualized therapeutic strategies increasingly essential. In this context, therapeutic apheresis, with its inherently complex and variable procedural parameters, represents one of the clinical settings in which personalized approaches are particularly critical.

Treatment planning in therapeutic apheresis requires a comprehensive evaluation of patient-specific clinical and biological variables. Key determinants such as the level of circulating target components, disease activity, and the patient's overall clinical status play a central role in defining procedural parameters, including timing and session characteristics. Accordingly, current guidelines emphasize that therapeutic apheresis should be managed through individualized, context-driven strategies rather than fixed, protocol-based approaches (1).

Beyond these considerations, therapeutic apheresis is shaped by dynamic biological processes that evolve over time. Fluctuations in disease activity, inter-individual variability in immune responses, and continuous changes in circulating pathogenic components limit the sustainability of a fixed treatment approach. Consequently, therapeutic apheresis should not be regarded as a one-time, predefined intervention, but rather as an adaptive treatment process that requires ongoing reassessment and modification based on evolving clinical and laboratory data (2).

Precision medicine is defined as an approach to disease management that seeks to develop patient-specific therapeutic strategies by integrating individual genetic, biological, and environmental characteristics. With its increasing incorporation into clinical practice, there has been a growing emphasis on tailoring treatment decisions based on individualized data. However, in complex clinical settings such as therapeutic apheresis—where multiple clinical and biological variables simultaneously influence treatment processes—the effective interpretation and integration of these data into clinical decision-making remain challenging. In this context, artificial intelligence and machine learning techniques offer significant potential by enabling the real-time analysis of multidimensional data and supporting the development of personalized therapeutic models. Importantly, within modern medical practice, AI is not intended to replace clinicians, but rather to function as a decision-support tool that enhances clinical reasoning and facilitates individualized treatment strategies. Accordingly, the need for personalization in therapeutic apheresis provides a strong rationale for the integration of AI-driven decision-support systems into routine clinical practice (6).

One of the inherent limitations of therapeutic apheresis is the non-selective removal of circulating components, whereby physiologically essential molecules may be eliminated alongside pathogenic factors. This necessitates a careful balance between therapeutic efficacy and the risk of adverse effects. In this context, artificial intelligence–driven approaches, particularly those based on biomarker-informed data analysis, have the potential to enable more precise identification of relevant targets and support the development of more selective, patient-centered apheresis strategies. Such advancements may contribute to improved treatment efficacy while minimizing unintended side effect.

Within this context, the need for personalized approaches in therapeutic apheresis extends beyond variability in clinical parameters and is also closely linked to the necessity of overcoming existing technical limitations. In this regard, artificial intelligence–based methods are increasingly recognized as valuable tools capable of supporting the transformation of therapeutic apheresis into a more targeted, adaptive, and patient-specific treatment modality. Such a shift may facilitate the transition from rigid, protocol-driven practices toward data-informed and dynamically managed therapeutic strategies.

5. The Role of Artificial Intelligence in Healthcare and its Applications in Therapeutic Apheresis

Artificial intelligence (AI) is increasingly being integrated into healthcare, with expanding applications in diagnosis, prognostic assessment, and treatment planning. It has demonstrated particular utility in areas such as medical imaging analysis, clinical decision support systems, risk stratification models, and drug development, where large-scale datasets can be processed efficiently to enhance clinical workflows. Beyond its role in data processing, AI is progressively recognized as a tool that supports clinical decision-making and enables the development of more individualized therapeutic strategies (7).

Therapeutic apheresis represents a clinically complex intervention in which multiple biological and clinical variables simultaneously influence treatment processes, thereby requiring dynamic decision-making. In routine practice, key parameters such as patient selection, timing of the procedure, exchange volume, and session frequency are often determined based on clinical experience. However, the need to integrate numerous interrelated variables makes the decision-making process inherently complex. In this context, artificial intelligence–based approaches offer the potential to systematically and objectively analyze multidimensional data by integrating laboratory findings, clinical parameters, and prior treatment responses (7,8).

Within this framework, artificial intelligence applications have the potential to enhance therapeutic apheresis across three key domains: optimization of patient selection, individualization of procedural parameters, and prediction of complication risks. Machine learning algorithms can analyze variables associated with disease severity and treatment response to help identify patient populations most likely to benefit from apheresis. In addition, real-time data processing may enable dynamic adjustment of procedural factors such as treatment duration and exchange volume, thereby improving efficacy while reducing unnecessary procedural burden. Furthermore, predictive modeling approaches may facilitate the early detection of potential complications, including hemodynamic instability and electrolyte imbalances (9,10).

Particularly in the context of cellular therapies, the role of artificial intelligence in therapeutic apheresis is becoming increasingly prominent. In advanced immunotherapeutic approaches such as chimeric antigen receptor (CAR) T-cell therapy, leukapheresis extends beyond a simple cell collection step and emerges as a critical determinant of overall tre-

atment success. Key parameters—including cell quality, distribution of cellular subpopulations, and timing of collection—require careful optimization. In this setting, AI-driven approaches enable the multidimensional analysis of these variables, thereby enhancing cell collection efficiency and supporting the development of more standardized and reproducible manufacturing processes (3).

In addition, a key limitation of therapeutic apheresis lies in its non-selective nature, whereby physiologically essential molecules may be removed alongside pathogenic components. This necessitates a careful balance between maximizing therapeutic efficacy and minimizing adverse effects. In this regard, AI-driven approaches, particularly those incorporating biomarker-based data analysis, offer the potential to more accurately identify relevant targets and support the development of more selective apheresis strategies. Such advancements may enhance treatment effectiveness while simultaneously reducing the risk of unintended side effects.

6. Limitations, Ethics, and Future Perspectives

While the integration of artificial intelligence–based approaches into therapeutic apheresis offers significant opportunities, it also introduces several important limitations. The reliability of these systems is highly dependent on the quality, representativeness, and adequacy of the data used during training and validation processes. In particular, the performance of clinical AI models may vary when applied to patient populations or healthcare settings that differ from those in which they were originally developed, raising concerns regarding generalizability and safety. Furthermore, discrepancies between controlled datasets and real-world clinical data can substantially influence algorithmic performance, often leading to outcomes that diverge from initial expectation (11,12).

Beyond technical challenges, the integration of artificial intelligence into clinical practice also raises important ethical and regulatory considerations. Algorithmic bias remains a major concern, as underrepresentation of certain patient populations in training datasets may lead to systematic errors and potentially exacerbate existing disparities in healthcare delivery. In addition, the limited interpretability of many AI models poses challenges for the transparency and reliability of clinical decision-making. This highlights the need for clinical decisions to be informed not only by outcomes but also by a clear understanding of the underlying decision processes. Consequently, ensuring validity, interpretability, and adherence to ethical standards is essential for the safe and effective integration of AI systems into clinical care (7).

In addition to technical limitations, the successful integration of artificial intelligence into clinical practice is closely linked to the level of trust and acceptance among healthcare professionals. Clearly defining the role of AI within clinical decision-making processes is essential, ensuring that these systems are positioned not as replacements for clinicians, but as tools that support and enhance clinical judgment. Such an approach not only helps preserve clinical accountability but also promotes the safe and effective use of these technologies in routine care (7,13).

From a future-oriented perspective, the integration of artificial intelligence into therapeutic apheresis is expected to expand its role in clinical practice. Advances such as real-time data analytics, adaptive treatment algorithms, and patient-specific predictive models may enable more precise and efficient management of apheresis procedures. These data-driven approaches can facilitate the dynamic optimization of treatment parameters while supporting more individualized clinical decision-making. Furthermore, the incorporation of continuous data streams derived from biosensors and wearable technologies into clinical systems may allow therapeutic apheresis to be monitored beyond the procedural setting, enabling ongoing assessment and timely adjustment throughout the course of treatment (8,9).

At the same time, advances in cellular therapies and immuno-oncology are further expanding the future role of therapeutic apheresis. In particular, within advanced modalities such as chimeric antigen receptor (CAR) T-cell therapy, the optimization of leukapheresis processes has become increasingly important for improving cell collection efficiency and ensuring consistency in product quality. In this context, the application of AI-driven systems to refine manufacturing workflows and optimize patient-specific cellular products is transforming apheresis from a supportive intervention into a central component of personalized therapeutic platforms (3).

7. Results

Therapeutic apheresis has long been recognized as an effective treatment modality in the management of hematologic disorders; however, it has increasingly become part of more complex and multifactorial clinical processes. Disease heterogeneity, inter-individual biological variability, and the dynamic nature of treatment responses highlight the limitations of standardized protocols and emphasize the need for more flexible, patient-centered approaches. In this context, the development of personalized therapeutic strategies in therapeutic apheresis has emerged as a fundamental requirement for improving clinical outcomes.

Artificial intelligence and machine learning–based approaches enable the analysis of complex, multidimensional clinical data, thereby facilitating a more systematic, predictable, and individualized management of therapeutic apheresis processes. The application of AI-driven systems in key areas such as patient selection, optimization of procedural parameters, and prediction of complication risks holds significant potential to enhance the effectiveness of apheresis interventions. However, the safe integration of these technologies into clinical practice requires careful attention to critical factors, including data quality, model validation, ethical considerations, and interpretability.

Looking ahead, the integration of artificial intelligence into therapeutic apheresis is expected not only to refine existing treatment approaches but also to broaden its clinical applications in conjunction with advanced modalities such as cellular therapies and immunotherapy. In particular, within innovative strategies like chimeric antigen receptor

(CAR) T-cell therapy, the data-driven optimization of apheresis processes has emerged as a critical determinant of treatment success. These developments suggest that therapeutic apheresis may evolve beyond its traditional role as a supportive intervention to become a central platform in the delivery of personalized and targeted therapeutic strategies.

In conclusion, AI-supported therapeutic apheresis holds significant transformative potential for advancing patient-specific treatment strategies in hematology practice. However, the sustainable and safe implementation of this transformation depends on the balanced integration of technological innovation with clinical expertise and ethical responsibility.

8. References

1. Connelly-Smith L, Alquist CR, Aqui NA, Hofmann JC, Klingel R, Onwuemene OA…Dunbar NM. Guidelines on the Use of Therapeutic Apheresis in Clinical Practice - Evidence-Based Approach from the Writing Committee of the American Society for Apheresis: The Ninth Special Issue. J Clin Apher. 2023 Apr;38(2):77-278. doi: 10.1002/jca.22043. PMID: 37017433.
2. Szczepiorkowski ZM, Dunbar NM. Transfusion guidelines: when to transfuse. Hematology Am Soc Hematol Educ Program. 2013;2013:638-44. doi: 10.1182/asheducation-2013.1.638. PMID: 24319244
3. Bäckel N, Hort S, Kis T, Nettleton DF, Egan JR, Jacobs JJL…Schmitt RH. Elaborating the potential of Artificial Intelligence in automated CAR-T cell manufacturing. Front Mol Med. 2023 Sep 21;3:1250508. doi: 10.3389/fmmed.2023.1250508. PMID: 39086671; PMCID: PMC11285580
4. Wells BJ, Nguyen HM, McWilliams A, Pallini M, Bovi A, Kuzma A...Isreal M; FAIR-AI Consortium. A practical framework for appropriate implementation and review of artificial intelligence (FAIR-AI) in healthcare. NPJ Digit Med. 2025 Aug 11;8(1):514. doi: 10.1038/s41746-025-01900-y. PMID: 40790350; PMCID: PMC12340025.
5. Padmanabhan A, Connelly-Smith L, Aqui N, Balogun RA, Klingel R, Meyer E… Schwartz GEJ. Guidelines on the Use of Therapeutic Apheresis in Clinical Practice - Evidence-Based Approach from the Writing Committee of the American Society for Apheresis: The Eighth Special Issue. J Clin Apher. 2019 Jun;34(3):171-354. doi: 10.1002/jca.21705. PMID: 31180581
6. Ashley EA. The Precision Medicine Initiative: A New National Effort. JAMA. 2015;313(21):2119–2120. doi:10.1001/jama.2015.3595
7. Topol, E.J. High-performance medicine: the convergence of human and artificial intelligence. *Nat Med* **25**, 44–56 (2019). https://doi.org/10.1038/s41591-018-0300-7
8. Esteva A, Robicquet A, Ramsundar B, Kuleshov V, DePristo M, Chou K…Dean J. A guide to deep learning in healthcare. Nat Med. 2019 Jan;25(1):24-29. doi: 10.1038/s41591-018-0316-z. Epub 2019 Jan 7. PMID: 30617335
9. Rajkomar A, Dean J, Kohane I. Machine Learning in Medicine. N Engl J Med. 2019 Apr 4;380(14):1347-1358. doi: 10.1056/NEJMra1814259. PMID: 30943338
10. Komorowski, M., Celi, L.A., Badawi, O, Anthony C. Gordon, A. Aldo Faisal. The Artificial Intelligence Clinician learns optimal treatment strategies for sepsis in intensive care. *Nat Med* **24**, 1716–1720 (2018). https://doi.org/10.1038/s41591-018-0213-5
11. de Hond, AAH, Leeuwenberg, AM, Hooft, L., Ilse M J Kant, Steven W J Nijman, Hendrikus J A van Os… Karel G M Moons. Guidelines and quality criteria for artificial intelligence-based prediction models in healthcare: a scoping review. *npj Digit. Med.* 5 , 2 (2022). https://doi.org/10.1038/s41746-021-00549-7
12. Federico Cabitza, Andrea Campagner, Felipe Soares, Luis García de Guadiana-Romualdo, Feyissa Challa, Adela Sulejmani…Anna Carobene. The importance of being external. methodological insights for the external validation of machine learning models in medicine, Computer Methods and Programs in Biomedicine, Volume 208, 2021, 106288, ISSN 0169-2607, https://doi.org/10.1016/j.cmpb.2021.106288
13. Shortliffe EH, Sepúlveda MJ. Clinical Decision Support in the Era of Artificial Intelligence. JAMA. 2018 Dec 4;320(21):2199-2200. doi: 10.1001/jama.2018.17163. PMID: 30398550

CHAPTER 24

Artificial Intelligence in Oncology Practice: Current Applications and Future Projections

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1. Introduction

Oncology represents one of the most dynamic medical disciplines undergoing a profound transformation through the integration of artificial intelligence (AI). The exponential growth of biomedical data, together with advances in computational power and machine learning algorithms, has created unprecedented opportunities to enhance cancer prevention, diagnosis, treatment planning, and outcome prediction (1). The inherent complexity and biological heterogeneity of malignant diseases demand analytical approaches capable of extracting clinically meaningful patterns from multidimensional datasets, a task for which modern AI methodologies are particularly well suited (2,3).

Recent developments in deep learning, radiomics, digital pathology, and genomic analytics have enabled the generation of highly sophisticated predictive and diagnostic models. These tools integrate information derived from medical imaging, histopathology, multi-omics profiling, and electronic health records (EHRs), thereby facilitating personalized therapeutic strategies and improving clinical decision-making processes (4,5).

2. Current Applications of AI in Oncology

The integration of AI into oncology has progressed rapidly, encompassing a broad spectrum of clinical and translational domains. These applications aim to improve diagnostic accuracy, enhance therapeutic planning, and optimize patient outcomes (2,3).

2.1. AI in Cancer Imaging and Early Detection

Medical imaging constitutes a cornerstone of oncological diagnostics. The advent of deep learning, particularly convolutional neural networks (CNNs), has revolutionized the interpretation of radiological data obtained from mammography, computed tomography (CT), positron emission tomography (PET), and magnetic resonance imaging (MRI) (4). These algorithms demonstrate exceptional performance in detecting subtle morphological changes associated with early-stage malignancies, frequently surpassing conventional radiological assessments in sensitivity and specificity (6,7).

In lung and breast cancer screening programs, AI-based systems significantly reduce false-negative rates, enabling earlier detection and intervention while simultaneously decreasing radiologist workload (6,7).

2.2. AI in Histopathological Diagnosis

Histopathological examination remains the gold standard for definitive cancer diagnosis. However, interpretation of whole-slide images (WSIs) is time-consuming and prone to inter-observer variability. AI-powered digital pathology platforms can analyze high-resolution WSIs to quantify cellular morphology, detect mitotic figures, and classify tumor subtypes with remarkable accuracy (8).

Advanced models have been developed to differentiate ductal carcinoma in situ from invasive ductal carcinoma, identify tumor-infiltrating lymphocytes, and predict microsatellite instability directly from histological images, thereby uncovering prognostically and therapeutically relevant biomarkers (9).

2.3. AI in Genomic and Molecular Profiling

The widespread adoption of high-throughput sequencing technologies has generated vast genomic datasets, necessitating advanced computational frameworks to decipher their clinical relevance. Machine learning algorithms enable identification of driver mutations, classification of tumors based on molecular signatures, and prediction of therapeutic response using integrative genomic profiling (10,11).

By supporting refined molecular classification, AI-driven analytics facilitate personalized therapy selection and optimize the use of targeted therapies and immunotherapies in precision oncology (2,11).

2.4. AI in Treatment Planning and Response Prediction

In radiation oncology, AI-driven systems have demonstrated substantial utility in automating tumor and organ-at-risk segmentation, significantly reducing planning time while improving contouring consistency (12). Furthermore, predictive models integrating clinical, radiological, and molecular data enable estimation of therapeutic response and survival outcomes, allowing clinicians to tailor treatment regimens more effectively (13).

These predictive tools support risk-adaptive strategies, minimizing unnecessary toxicity while maximizing therapeutic efficacy (3,13).

2.4.1. Challenges in Clinical Integration

Despite impressive advances, several challenges hinder the widespread adoption of AI in routine oncology practice. These include limited model interpretability, commonly referred to as the "black box" problem, algorithmic bias, heterogeneity in training datasets, regulatory approval barriers, and difficulties associated with seamless integration into clinical workflows and hospital information systems (14,15).

3. Future Projections and Emerging Frontiers

The future of AI in oncology is expected to extend beyond isolated applications toward integrated, adaptive, and patient-centric analytical frameworks.

3.1. Integrated Multi-Modal AI Systems

Next-generation AI platforms are anticipated to integrate radiomics, pathomics, genomics, proteomics, and longitudinal clinical data into unified models capable of generating patient-specific digital twins. These virtual representations may facilitate dynamic simulation of disease trajectories and therapeutic response, enabling real-time optimization of individualized treatment strategies (16).

3.2. AI in Drug Discovery and Clinical Trials

AI-driven computational platforms are revolutionizing oncology drug discovery by accelerating target identification, predicting drug-target interactions, and enabling rational drug design. In clinical trials, AI facilitates optimized patient recruitment, refined eligibility criteria, and identification of surrogate endpoints, collectively expediting clinical development timelines (17).

3.3. Ethical Considerations and Explainable AI (XAI)

As AI increasingly influences clinical decision-making, ethical challenges related to data privacy, accountability, and algorithmic bias become paramount. The implementation of explainable AI (XAI) frameworks is essential to ensure transparency, interpretability, and clinical trust in AI-assisted decisions (15,18).

4. Results

Artificial intelligence is rapidly transitioning from a conceptual innovation to a transformative force in oncology. Current applications already enhance diagnostic accuracy,

optimize treatment planning, and enable personalized patient management. Future developments promise even deeper integration through multi-modal analytics, real-time disease modeling, and AI-driven therapeutic discovery. However, the full clinical potential of AI will only be realized through rigorous clinical validation, standardized data infrastructures, regulatory harmonization, and robust ethical governance (2,14,15).

5. References

1. Esteva, A., Robicquet, A., Ramsundar, B., Kuleshov, V., DePristo, M., Chou, K., Cui, C., Corrado, G., Thrun, S., & Dean, J. (2019). A guide to deep learning in healthcare. *Nature Medicine*, 25(1), 24–29. https://doi.org/10.1038/s41591-018-0316-z
2. Yu, K. H., Beam, A. L., & Kohane, I. S. (2018). Artificial intelligence in healthcare. *Nature Biomedical Engineering*, 2(10), 719–731. https://doi.org/10.1038/s41551-018-0305-z
3. Kourou, K., Exarchos, T. P., Exarchos, K. P., Karamouzis, M. V., & Fotiadis, D. I. (2015). Machine learning applications in cancer prognosis and prediction. *Computational and Structural Biotechnology Journal*, 13, 8–17. https://doi.org/10.1016/j.csbj.2014.11.005
4. Bi, W. L., Hosny, A., Schabath, M. B., Giger, M. L., Birkbak, N. J., Mehrtash, A., Allison, T., Arnaout, O., Abbosh, C., Dunn, I. F., Mak, R. H., Tamimi, R. M., Tempany, C. M., Swanton, C., Hoffmann, U., Schwartz, L. H., Gillies, R. J., Huang, R. Y., & Aerts, H. J. W. L. (2019). Artificial intelligence in cancer imaging: Clinical challenges and applications. *CA: A Cancer Journal for Clinicians*, 69(2), 127–157. https://doi.org/10.3322/caac.21552
5. Bera, K., Braman, N., Gupta, A., Velcheti, V., & Madabhushi, A. (2022). Predicting cancer outcomes with radiomics and artificial intelligence in radiology. *Nature Reviews Clinical Oncology*, 19(2), 132–146. https://doi.org/10.1038/s41571-021-00560-7
6. McKinney, S. M., Sieniek, M., Godbole, V., Godwin, J., Antropova, N., Ashrafian, H., Back, T., Chesus, M., Corrado, G. S., Darzi, A., Etemadi, M., Garcia-Vicente, F., Gilbert, F. J., Halling-Brown, M., Hassabis, D., Jansen, S., Karthikesalingam, A., Kelly, C. J., King, D., & Shetty, S. (2020). International evaluation of an AI system for breast cancer screening. *Nature*, 577(7788), 89–94. https://doi.org/10.1038/s41586-019-1799-6
7. Ardila, D., Kiraly, A. P., Bharadwaj, S., Choi, B., Reicher, J. J., Peng, L., Tse, D., Etemadi, M., Ye, W., Corrado, G., Naidich, D. P., & Shetty, S. (2019). End-to-end lung cancer screening with three-dimensional deep learning on low-dose chest computed tomography. *Nature Medicine*, 25(6), 954–961. https://doi.org/10.1038/s41591-019-0447-x
8. Campanella, G., Hanna, M. G., Geneslaw, L., Miraflor, A., Werneck Krauss Silva, V., Busam, K. J., Brogi, E., Reuter, V. E., Klimstra, D. S., & Fuchs, T. J. (2019). Clinical-grade computational pathology using weakly supervised deep learning on whole slide images. *Nature Medicine*, 25(8), 1301–1309. https://doi.org/10.1038/s41591-019-0508-1
9. Kather, J. N., Pearson, A. T., Halama, N., Jäger, D., Krause, J., Loosen, S. H., Marx, A., Boor, P., Tacke, F., Neumann, U. P., Grabsch, H. I., Yoshikawa, T., Brenner, H., Chang-Claude, J., Hoffmeister, M., Trautwein, C., & Luedde, T. (2019). Deep learning can predict microsatellite instability directly from histology in gastrointestinal cancer. *Nature Medicine*, 25(7), 1054–1056. https://doi.org/10.1038/s41591-019-0462-y
10. Way, G. P., Sanchez-Vega, F., La, K., Armenia, J., Chatila, W. K., Luna, A., Sander, C., Cherniack, A. D., Mina, M., Ciriello, G., Schultz, N., Sanchez, Y., Greene, C. S., & Cancer Genome Atlas Research Network. (2018). Machine learning detects pan-cancer Ras pathway activation in The Cancer Genome Atlas. *Cell Reports*, 23(1), 172–180.e3. https://doi.org/10.1016/j.celrep.2018.03.046
11. Yu, K. H., Beam, A. L., & Kohane, I. S. (2018). Artificial intelligence in healthcare. *Nature Biomedical Engineering*, 2(10), 719–731. https://doi.org/10.1038/s41551-018-0305-z
12. Lustberg, T., van Soest, J., Gooding, M., Peressutti, D., Aljabar, P., van der Stoep, J., van Elmpt, W., & Dekker, A. (2018). Clinical evaluation of atlas and deep learning based automatic contouring for lung cancer. *Radiotherapy and Oncology*, 126(2), 312–317. https://doi.org/10.1016/j.radonc.2017.11.012
13. Jang, B. S., Kim, I. A., & Kim, S. H. (2020). A machine learning-based prediction model for overall survival in metastatic breast cancer patients: A nationwide cohort study. *Scientific Reports*, 10(1), 16913. https://doi.org/10.1038/s41598-020-74026-8
14. Kelly, C. J., Karthikesalingam, A., Suleyman, M., Corrado, G., & King, D. (2019). Key challenges for delivering clinical impact with artificial intelligence. *BMC Medicine*, 17(1), 195. https://doi.org/10.1186/s12916-019-1426-2
15. Vayena, E., Blasimme, A., & Cohen, I. G. (2018). Machine learning in medicine: Addressing ethical challenges. *PLoS Medicine*, 15(11), e1002689. https://doi.org/10.1371/journal.pmed.1002689
16. Bera, K., Braman, N., Gupta, A., Velcheti, V., & Madabhushi, A. (2022). Predicting cancer outcomes with radiomics and artificial intelligence in radiology. *Nature Reviews Clinical Oncology*, 19(2), 132–146. https://doi.org/10.1038/s41571-021-00560-7
17. Paul, D., Sanap, G., Shenoy, S., Kalyane, D., Kalia, K., & Tekade, R. K. (2021). Artificial intelligence in drug discovery and development. *Drug Discovery Today*, 26(1), 80–93. https://doi.org/10.1016/j.drudis.2020.10.010
18. Amann, J., Blasimme, A., Vayena, E., Frey, D., & Madai, V. I. (2020). Explainability for artificial intelligence in healthcare: A multidisciplinary perspective. *BMC Medical Informatics and Decision Making*, 20(1), 310. https://doi.org/10.1186/s12911-020-01332-6

CHAPTER 25

The Risk of Overdiagnosis and Overtreatment in AI-Assisted Orthopedics: A Clinical, Ethical, and Systemic Analysis

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1. Introduction

Artificial intelligence (AI) is transforming diagnostic and therapeutic processes in medicine, particularly in orthopedic and trauma care. Over the past decade, AI systems-especially those based on deep learning-have demonstrated high performance in clinical decision support by identifying complex patterns in imaging data such as X-rays and MRI scans (1,2). These systems have shown considerable success in fracture detection, injury classification, grading of joint degeneration, and prediction of postoperative complications (3,4). In certain contexts, their diagnostic performance approaches that of experienced clinicians.

However, improvements in diagnostic accuracy do not necessarily translate into better clinical outcomes. The relationship between technical performance and patient benefit is complex and often non-linear (5). In orthopedics, particularly in chronic musculoskeletal conditions, structural abnormalities detected through imaging do not always correlate with clinical symptoms (6). As imaging sensitivity increases, subtle anatomical variations are more frequently identified, raising the risk of overdiagnosis.

Overdiagnosis differs fundamentally from misdiagnosis. While misdiagnosis involves incorrect identification of disease, overdiagnosis refers to the accurate detection of abnormalities that would not cause harm if left untreated (7). This distinction is particularly critical in orthopedics, where diagnosis often directly leads to intervention, including surgery.

Orthopedic practice has traditionally relied heavily on imaging. However, studies of asymptomatic populations demonstrate that findings such as meniscal tears or spinal degeneration are often present without clinical relevance (6,8). AI systems trained primarily

on labeled imaging datasets may reinforce a structure-centered understanding of disease, potentially amplifying overdiagnosis.

The key concern is not whether AI can detect abnormalities, but how such detection influences treatment thresholds. Increased sensitivity may lower intervention thresholds, leading to higher rates of treatment at the population level, increased surgical volume, complications, and healthcare costs (9).

2. Theoretical and Conceptual Foundations of Overdiagnosis

Overdiagnosis refers to the detection of a real biological condition that would not result in symptoms or reduced life expectancy if left untreated (5). It must be distinguished from false positives, where a condition is incorrectly identified.

The concept of disease is shaped not only by biological factors but also by social and cultural contexts. The process of medicalization describes how normal variations or risk states become defined as medical conditions (10). AI systems, due to their high sensitivity, may accelerate this process by identifying increasingly subtle anatomical deviations.

Imaging studies consistently demonstrate a mismatch between structural abnormalities and symptoms (6). However, AI models trained on imaging labels may interpret all deviations as pathological, regardless of clinical context.

The increasing use of risk prediction models further complicates this issue. AI can identify individuals at elevated risk, but risk does not equate to disease (11). Treating predicted risk may therefore result in unnecessary interventions.

Clinical decision-making often relies on threshold models. AI can shift these thresholds by increasing detection rates-a phenomenon described as algorithmic threshold shift (9). Additionally, diagnostic labeling may influence patient perception and expectations, further contributing to overdiagnosis.

3. Statistical Mechanisms and Decision Theory

Understanding overdiagnosis requires consideration of statistical principles. While sensitivity and specificity describe test performance, positive predictive value (PPV)-which depends on disease prevalence-is more clinically relevant (12).

In low-prevalence settings, even highly accurate systems may generate a substantial number of clinically insignificant findings, leading to the prevalence paradox (5). AI systems optimized for sensitivity may exacerbate this issue.

Calibration is another key factor. Even well-performing models may produce inaccurate probability estimates, influencing clinical decisions (13). Dataset shift between training and real-world populations may further reduce reliability. Cognitive biases, particularly automation bias, may lead clinicians to over-reliance on AI outputs (14). This can lower intervention thresholds and increase overtreatment.

4. Overdiagnosis and Intervention Threshold Shifts in Arthroplasty

Total hip and knee arthroplasty are highly effective interventions for advanced degenerative joint disease, improving pain and function (15). However, surgical decision-making is complex and must integrate imaging findings, symptom severity, and patient-specific factors.

AI-based imaging systems demonstrate high reproducibility in grading osteoarthritis severity and detecting subtle structural changes (16). While this improves diagnostic consistency, it may also expand the population considered eligible for surgery. A key challenge is the mismatch between radiographic findings and symptoms. Severe imaging abnormalities may be present in asymptomatic patients, while some symptomatic individuals show minimal structural changes (6,17). AI-driven detection of subtle abnormalities may increase perceived disease burden and influence surgical decisions.

Algorithmic outputs, particularly numerical severity scores, may increase clinician confidence in borderline cases, thereby lowering intervention thresholds. However, evidence suggests that some orthopedic procedures, particularly in degenerative knee disease, offer limited benefit over conservative treatment in selected patients (18).

Predictive analytics may further complicate decisions. Identifying patients as "low risk" for complications does not necessarily justify surgery. Confusing safety with necessity may lead to overtreatment.

Early surgical intervention also increases the likelihood of revision procedures, which are more complex and associated with higher complication rates (19).

5. Overdiagnosis in Sports Surgery

Sports medicine operates in a high-performance environment where return-to-play pressures influence clinical decisions. AI integration adds complexity to this context.

MRI is widely used in sports injury evaluation, and AI systems demonstrate high accuracy in detecting ligament and cartilage injuries (4). However, increased sensitivity may also detect subtle structural variations without clinical relevance. Athletes often exhibit adaptive biomechanical changes due to repetitive stress. These may represent physiological adaptation rather than pathology (20). AI systems may misclassify such variations as disease.

Performance pressure may amplify intervention tendencies. Algorithm-generated outputs with high confidence may bias clinicians toward surgical management, even in ambiguous cases. Psychological effects are also relevant. Diagnostic labels may influence athletes' perception of injury severity and performance capacity. Early surgical intervention in young athletes may increase long-term degenerative risk (21).

6. Overdiagnosis in Trauma Surgery

Trauma care involves rapid, high-stakes decision-making. AI has improved detection of fractures and subtle injuries, particularly in X-ray and CT imaging (22).

AI systems are often optimized for high sensitivity to avoid missed diagnoses. However, this may increase false positives and detection of clinically insignificant findings, creating a sensitivity paradox (9). In emergency settings, automation bias may lead clinicians to rely heavily on AI outputs (14). This may increase intervention rates without proportional benefit. Medico-legal concerns further influence decisions. Clinicians may adopt defensive practices, leading to unnecessary imaging or interventions.

Unnecessary procedures carry risks, including infection, thromboembolism, and anesthesia-related complications. Increased imaging also raises radiation exposure and costs (23).

7. Ethical Framework

The integration of AI in orthopedics must be evaluated within core bioethical principles: non-maleficence, beneficence, autonomy, and justice (24).

- **Non-maleficence:** Overdiagnosis may expose patients to unnecessary harm.
- **Proportionality:** Interventions must match disease severity.
- **Autonomy:** Patients must be informed about AI involvement.
- **Justice:** Bias in AI systems may lead to inequitable care (25). The "black box" nature of AI complicates transparency and informed consent.

8. Legal Implications

AI introduces complex medico-legal challenges. Although physicians retain responsibility, reliance on AI complicates liability boundaries (26). Failure to act on AI findings may lead to legal scrutiny, while over-reliance may also result in malpractice claims. Overdiagnosis further complicates legal evaluation of clinical necessity. Defensive medicine may increase due to AI-generated alerts. Liability distribution among clinicians, institutions, and developers remains unresolved (27).

9. Health Economics

Orthopedic interventions are resource-intensive. Even small increases in surgical rates can have a significant economic impact (28).

Overdiagnosis contributes to **medical overuse**, where interventions provide limited benefit. Value-based care requires balancing outcomes and costs (29).

Increased intervention rates may lead to:

- higher revision surgery rates
- increased imaging utilization
- greater healthcare expenditure

Opportunity cost is critical; resources used for low-value care may limit access to necessary treatments.

10. Risk Mitigation Strategies

10.1. Diagnosis-Treatment Distinction

Detection of an abnormality should not automatically trigger intervention. Clinical decision-making must integrate imaging findings with symptom severity, functional limitation, patient preferences, and response to conservative treatment. Maintaining this distinction is essential to prevent unnecessary procedures driven solely by increased diagnostic sensitivity (5,18).

10.2. Human-in-the-Loop Systems

AI systems should function within a human-in-the-loop framework in which clinicians retain ultimate authority over decisions. Algorithmic outputs must be critically interpreted and contextualized rather than accepted at face value. This approach helps preserve clinical judgment and reduces the risk of automation bias influencing treatment decisions (14,26).

10.3. Validation and Monitoring

Continuous real-world validation is essential to ensure the reliability and generalizability of AI systems across different patient populations and clinical settings (13). Performance monitoring should extend beyond diagnostic accuracy to include clinical outcomes, complication rates, and intervention patterns. Regular recalibration is necessary to address dataset shift and maintain model performance over time (13,27).

10.4. Transparency

Improving transparency and explainability in AI systems is critical for building clinician trust and supporting informed decision-making. Providing interpretable outputs-such as visual heatmaps, confidence intervals, or probability estimates-enables clinicians to better evaluate algorithmic recommendations. This reduces blind reliance and facilitates more balanced clinical judgments (2,26).

10.5. Informed Consent

Patients should be clearly informed when AI systems contribute to diagnostic or therapeutic decisions. Explaining the probabilistic nature, limitations, and uncertainties of AI outputs is essential for meaningful informed consent. This transparency supports patient autonomy and helps prevent overconfidence in algorithm-driven recommendations (24,26).

10.6. Value-Based Integration

AI implementation should align with value-based care principles, prioritizing improvements in patient outcomes relative to costs. Technologies that increase intervention rates without a clear clinical benefit should be carefully scrutinized. Integrating outcome measures such as quality of life, functional recovery, and long-term complications is essential for evaluating true value (28,29).

11. Conclusion

AI marks a major advancement in orthopedic medicine. However, greater detection capacity may broaden disease definitions and lower intervention thresholds. Overdiagnosis is not a technical failure but a systemic consequence of misalignment between detection and clinical relevance. If structural abnormalities are equated with the need for treatment, intervention rates may rise without improving outcomes. The impact of AI is shaped by statistical, cognitive, ethical, legal, and economic factors. Its future depends on careful integration into clinical workflows. AI should enhance, not replace, clinical judgment. Sustainable implementation requires balancing innovation with patient-centered care.

12. References

1. Esteva A, Robicquet A, Ramsundar B, et al. (2019). A guide to deep learning in healthcare. Nat Med. 25:24-29.
2. Topol EJ. (2019). Deep Medicine: How Artificial Intelligence Can Make Healthcare Human Again. New York: Basic Books.
3. Rajpurkar P, Irvin J, Zhu K, et al. (2017). CheXNet: Radiologist-level pneumonia detection on chest X-rays. arXiv. 2017;arXiv:1711.05225.
4. Liu X, Faes L, Kale AU, et al. (2019). Deep learning for medical imaging. Lancet Digit Health. 1(6):e271-e297.
5. Welch HG, Schwartz LM, Woloshin S. (2011). Overdiagnosed: Making People Sick in the Pursuit of Health. Boston: Beacon Press.
6. Brinjikji W, Luetmer PH, Comstock B, et al. (2015). Imaging features of spinal degeneration in asymptomatic populations. AJNR Am J Neuroradiol. 36(4):811-816.
7. Carter SM, Rogers W, Heath I, et al. (2015). The challenge of overdiagnosis begins with its definition. BMJ. 350:h869.
8. Englund M, Guermazi A, Gale D, et al. (2008). Incidental meniscal findings on knee MRI. N Engl J Med. 2008;359(11):1108-1115.
9. Hofmann B. Artificial intelligence and overdiagnosis. (2020). J Med Ethics. 46(11):765-770.
10. Conrad P. (2007). The Medicalization of Society. Baltimore: Johns Hopkins University Press.
11. Gigerenzer G, Gaissmaier W, Kurz-Milcke E, et al. (2007). Helping doctors and patients make sense of health statistics. Psychol Sci Public Interest. 8(2):53-96.
12. Akobeng AK. (2007). Understanding diagnostic tests 1: sensitivity, specificity and predictive values. Acta Paediatr. 96(3):338-341.
13. Van Calster B, McLernon DJ, van Smeden M, et al. (2019). Calibration: the Achilles heel of predictive analytics. BMC Med. 17:230.
14. Goddard K, Roudsari A, Wyatt JC. (2012). Automation bias in clinical decision-making. J Am Med Inform Assoc. 19(1):121-127.
15. Learmonth ID, Young C, Rorabeck C. (2007). The operation of the century: total hip replacement. Lancet. 370:1508-1519.
16. Tiulpin A, Saarakkala S. (2019). Automatic grading of osteoarthritis from knee X-rays. IEEE Trans Med Imaging. 39(3):987-995.
17. Bedson J, Croft PR. (2008). The discordance between clinical and radiographic knee osteoarthritis. Ann Rheum Dis. 67:1532-1537.
18. Katz JN, Brophy RH, Chaisson CE, et al. (2013). Surgery versus physical therapy for meniscal tear. N Engl J Med. 368:1675-1684.

19. Evans JT, Walker RW, Evans JP, et al. (2019). How long does a knee replacement last? Lancet. 393:655-663.
20. Hamilton B, Alonso JM, Best TM. (2017).Time for a paradigm shift in sports injury. Br J Sports Med. 51:1111-1112.
21. Lohmander LS, Englund PM, Dahl LL, et al. (2007). Long-term consequences of ACL injury. Osteoarthritis Cartilage. 15:121-130.
22. Lindsey R, Daluiski A, Chopra S, et al. (2018). Deep neural network improves fracture detection. Proc Natl Acad Sci USA.115:E11591-E11597.
23. Brenner DJ, Hall EJ. (2007). Computed tomography exposure risks. N Engl J Med. 357:2277-2284.
24. Beauchamp TL, Childress JF. (2013). Principles of Biomedical Ethics. 7th ed. Oxford: Oxford University Press.
25. Obermeyer Z, Powers B, Vogeli C, et al. (2019). Bias in healthcare algorithms. Science. 366:447-453.
26. Price WN, Gerke S, Cohen IG. (2019). Potential liability for physicians using AI. JAMA. 322:1765-1766.
27. Yu KH, Kohane IS. (2019). Framing the legal issues of AI in medicine. BMJ. 2019;364:l161.
28. Weinstein MC, Skinner JA. (2010). Comparative effectiveness and health economics. N Engl J Med. 362:460-465.
29. Porter ME. (2010). What is value in health care? N Engl J Med. 363:2477-2481.

CHAPTER 26

Artificial Intelligence in Infectious Diseases and Clinical Microbiology

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1. Introduction

In recent years, artificial intelligence (AI) has begun to play an increasingly important role in many areas of modern medicine. Methods such as machine learning and deep learning are enhancing our ability to decode complex medical and biological data, a feat that was challenging with traditional statistical tools (1,2). This progress stems from our capacity to process vast volumes of data in ways previously unavailable (3). Recently, integrating AI into healthcare has paved the way for improved diagnostic accuracy, optimized treatment plans, and enhanced decision-making in medicine (4,5). Specifically, in infectious diseases, the abundance of data from electronic health records, genomic sequencing, lab results, and surveillance sources offers new avenues for AI applications to assist healthcare professionals (6,7). These technologies can discern patterns in extensive datasets, forecast disease progression, and facilitate swift, precise diagnoses (8,9).

The global impact of infectious diseases persists; novel pathogens emerge, previous threats reappear, and concerns about antibiotic resistance grow (10). Conventional methods for diagnosing and monitoring these diseases are effective but can be slow and resource-intensive (11). Moreover, microorganisms are inherently complex.

AI-based tools may help clinicians shorten diagnostic time, improve diagnostic accuracy, and support more appropriate use of antibiotics (12-14). The use of AI in infectious disease management has expanded in recent years, particularly in areas such as early detection, risk prediction, treatment planning, and outbreak surveillance (15,16). In laboratory settings, AI aids in identifying microorganisms and assessing antibiotic effectiveness while promoting judicious antibiotic use to prevent resistance (17-19). These AI-driven improvements can significantly advance infectious disease care and infection prevention (20).

This chapter explores current and emerging AI applications in infectious diseases and clinical microbiology. It covers AI's role in clinical processes, prognosis and risk prediction, personalized medicine, and antimicrobial resistance management. Additionally, it addresses AI's contributions to antimicrobial stewardship and outbreak management, alongside ethical, legal, and practical considerations in AI implementation within healthcare, concluding with insights into the field's future trajectory (1,4,21).

2. Overview of Artificial Intelligence in Infectious Diseases

2.1. Core Concepts of Artificial Intelligence, Machine Learning, and Deep Learning

Artificial intelligence (AI) is a field focused on developing computer systems that can perform tasks requiring human cognitive abilities such as learning, reasoning, and decision-making (1,2). In the medical domain, AI demonstrates significant potential by navigating and interpreting vast, intricate datasets that conventional statistical approaches might fail to manage effectively (3,4). This capability proves particularly beneficial in enhancing clinical decision-making and supporting healthcare professionals in devising more effective patient care strategies (5,6).

Artificial intelligence algorithms can analyze large datasets and identify complex patterns that might be difficult to detect with manual analysis alone (2,7). The integration of AI into the medical field holds the promise of enhancing patient outcomes and elevating the overall efficacy of healthcare delivery (1,5). Machine Learning (ML), a subdivision of AI, consists of algorithms that can autonomously learn from data without explicit programming (8). These techniques are generally categorized into supervised learning, unsupervised learning, and reinforcement learning (2). Supervised learning is particularly advantageous for diagnostics and prognostic forecasting, while unsupervised learning facilitates patient clustering and the identification of novel patterns (3,9). Deep learning, which employs multiple layers of neural networks, excels in processing complex inputs such as images, audio, and textual data (10,11). Notably, specialized deep learning architectures, including convolutional and recurrent neural networks, are increasingly utilized in medical applications, supporting tasks such as medical imaging, biological image analysis, and parsing electronic health records (10,12). In the practice of infectious diseases, AI systems enable the concurrent evaluation of clinical, laboratory, microbiological, and imaging data, promoting a more rapid and integrated approach to clinical care (13,14).

2.2. Potential Applications of Artificial Intelligence in Infectious Diseases

Infectious diseases present significant challenges due to their diverse presentations, rapid progression, and the necessity for prompt intervention, making them well-suited for AI applications (15,16). AI systems can enhance early diagnosis, risk stratification, and forecasting disease trajectories (17,18). In the realm of clinical microbiology, AI supports

microorganism identification, antimicrobial susceptibility prediction, and laboratory process automation (19-21). By leveraging large datasets, AI contributes substantially to combating antimicrobial resistance through detailed analysis of resistance patterns (20,22). The importance of AI in healthcare settings is increasingly acknowledged, particularly for infection surveillance, early outbreak detection, and epidemiological studies (23,24). The COVID-19 pandemic has underscored the efficacy of these technologies in managing infectious diseases (25,26).

3. Artificial Intelligence Applications in Clinical Processes

Addressing infectious diseases involves rapid decision-making in the face of changing symptoms and complex differential diagnoses, which can be challenging for clinicians (27). AI provides critical support by integrating diverse data points and yielding new insights, thereby assisting clinicians in making informed decisions swiftly (28).

3.1. AI-Based Clinical Decision Support Systems

Clinical Decision Support Systems (CDSS) are designed to offer evidence-based guidance for diagnosis, treatment, and management in healthcare (29). AI integration transforms these systems from static, rule-based constructs into dynamic, adaptive frameworks (30,31). AI enhances CDSS by analyzing symptoms, vital signs, and diagnostic results to determine the severity of a condition and guide treatment decisions, including appropriate antibiotic selection, dosage, and duration (32,33). In critical conditions such as sepsis, where prompt intervention is vital, AI systems can provide early warnings of potential clinical deterioration (34). AI also enhances diagnostic speed and accuracy for various infections, including pneumonia, meningitis, and urinary tract infections, by offering personalized recommendations based on patient-specific factors, local epidemiology, and current medical guidelines (28,35). Nevertheless, integrating AI systems into clinical practice involves challenges related to data quality, algorithmic bias, transparency, and the delineation of clinical responsibility (36,37). AI should augment, not replace, the physician's role (1,38).

3.2. Artificial Intelligence in Medical Imaging

Medical imaging is an indispensable aspect of diagnosing and monitoring infectious diseases and is one of the foremost areas where AI is applied (11,12). Deep learning, particularly convolutional neural networks, excels in recognizing complex structures within imaging datasets, thereby enhancing diagnostic workflows (10,11). In recent years, AI-assisted analysis of radiological images has been increasingly investigated for the diagnosis of respiratory tract infections such as pneumonia, COVID-19, and tuberculosis (12,25,26). For conditions like soft tissue infections and osteomyelitis, AI can provide an objective assessment of infection spread and tissue involvement through MRI and CT scan analysis (12,13). This capability aids clinicians in monitoring treatment efficacy and determining the necessity for surgical intervention (14).

Overall, AI applications in clinical workflows and medical imaging improve diagnostic precision and support clinical decision-making (10,11). However, it is crucial to address considerations related to data security, algorithmic bias, and the shared accountability of clinical outcomes during implementation (36,37).

4. Prognosis and Risk Prediction in Infectious Diseases

The ability to forecast disease outcomes, known as prognosis, is integral to managing infectious diseases, though it remains a complex endeavor due to variations in disease progression, patient characteristics, and treatment responses (15,17). These variabilities complicate accurate predictions. Fortunately, emerging artificial intelligence (AI) methodologies provide support by concurrently analyzing multiple factors, aiding in risk assessment and prognostic evaluations (18,34). AI applications assess demographic data, comorbidities, vital signs, laboratory data, and treatment specifics to project disease trajectories, aiding clinicians in strategizing monitoring efforts and resource allocation (18,27,34).

4.1. Mortality Prediction in Sepsis and Septic Shock

Severe conditions like sepsis and septic shock can quickly become life-threatening without prompt intervention (34). Traditional scoring systems are often limited, capturing only a fraction of the patient's condition (34,35). AI-driven models facilitate a more comprehensive understanding by monitoring changes in vital signs, laboratory results, and organ functionality over time (34,35). This approach enhances risk assessment and enables timely identification of high-risk patients for more personalized treatment adjustments, thereby fostering a proactive approach to critical care management in sepsis (34,35).

4.2. Risk Scoring in Intensive Care Unit Infections

Nosocomial infections in the Intensive Care Unit (ICU) pose significant health threats, often exacerbated by factors such as mechanical ventilation and invasive procedures (27,35). AI systems evaluate these multifactorial risks, providing a quantifiable likelihood of infection, predicting potential patient outcomes, and assisting with treatment efficacy monitoring (35,36). Through individualized risk profiling, these AI tools support focused infection prevention strategies and optimize resource use within the ICU, thereby contributing to superior patient care (36).

4.3. Predicting Hospital Length of Stay and Complications

The duration of hospitalization due to infectious diseases impacts both patient outcomes and healthcare resource utilization (37). Lengthy hospital stays correlate with increased risks of complications and heightened resource demands (37,38). AI-based predictive models process clinical and laboratory data to estimate hospitalization durations and potential complications(37). Such predictions enable clinicians to plan for discharge and

monitor at-risk individuals for early intervention (37,38). By integrating AI insights with clinical acumen, healthcare providers can enhance decision-making processes and provide more personalized and effective patient care (1,5,6).

5. Personalized Medicine in Infectious Diseases

5.1. Patient-Specific Risk Profiling

The progression and treatment response of infectious diseases can vary widely among individuals, primarily due to patients' unique attributes (1,34). Personalized medicine seeks to accommodate these differences, enhancing predictions of infection susceptibility, severity, and potential complications (12,35). Factors such as age, comorbidities, immune function, organ health, and past infection history influence illness severity and recovery (36,37). AI technology supports personalized medicine by synthesizing comprehensive patient data-spanning age, health conditions, vital signs, and illness progression to generate risk scores that guide tailored healthcare decisions, optimizing patient care outcomes (8,18,34).

5.2. AI-Based Pharmacokinetic and Pharmacodynamic Modeling

The success of antibiotic therapies hinges on aligning pharmacokinetic and pharmacodynamic profiles with the patient's individual physiology (38,39). Variables such as renal or hepatic impairment, critical illness, age, and drug interactions can significantly influence drug distribution and metabolism (39,40). AI-driven pharmacokinetic modeling aids in determining optimal dosages, particularly for potent antibiotics, ensuring therapeutic efficacy while minimizing adverse effects and resistance development (38,40,41).

5.3. Personalized Treatment Strategies in Immunocompromised Patients

Individuals with compromised immune systems, including those with hematological malignancies, organ transplant recipients, and chronic immunosuppressive therapy patients, face increased infection risks and atypical manifestations (36,37). Older adults also present unique challenges (36). AI-driven personalized treatment strategies enable precise predictions of infection risks, etiology, and therapeutic responses (34,36). By integrating historical medical data and current analyses, clinicians can formulate targeted interventions, curbing unnecessary broad-spectrum antibiotic use and preventing infections more effectively (40,41). This tailored approach balances sophisticated data insights with individual patient needs, enhancing overall treatment efficacy (34,36).

6. Artificial Intelligence in Clinical Microbiology

Clinical microbiology is indispensable in elucidating the etiology of infectious diseases and supports clinicians in treatment decision-making (19,42). As patient volumes in-

crease and diagnostic assays become more sophisticated, clinical laboratories must enhance operational efficiency and speed (19,20). Artificial intelligence (AI) plays a crucial role in this evolution by streamlining laboratory operations and expediting diagnostic turnaround times, which facilitates more prompt therapeutic interventions and improved patient outcomes (19,20,43). AI-driven standardization of laboratory procedures elevates data reliability, enabling clinicians to base decisions on robust and consistent information (19,42). Thus, AI is poised to be a transformative force in clinical microbiology, amplifying the efficacy of patient care (42,43).

6.1. Laboratory Automation and Intelligent Systems

Adopting advanced technologies to automate laboratory workflows significantly enhances both efficiency and safety in the analysis of pathogenic microorganisms (42,43). These intelligent systems manage sample processing, microbial cultivation, and result generation, thereby minimizing human error and ensuring uniform processing (42,44). The delivery of timely results is especially critical in time-sensitive diagnostics, such as blood cultures, where prompt identification of pathogens can be life-saving (43,44). Early detection systems, enhanced by AI, alert clinicians to potential issues, allowing for expedited clinical decision-making and improving outcomes for conditions like sepsis (34,44). Furthermore, AI's capacity to interpret complex test results reduces unnecessary testing, integrating laboratory data more actively into clinical decision-making (19,42). AI-facilitated rapid microorganism identification via image and spectral data analysis accelerates diagnosis, fostering timely and precise treatment choices, ultimately hastening patient recovery and enhancing care delivery (42,43).

6.2. Antimicrobial Susceptibility Prediction

Effective infection management hinges on the timely selection of effective antibiotics (22,23). Traditional methods for determining antimicrobial susceptibility often delay optimal treatment initiation, sometimes necessitating empirical broad-spectrum antibiotic use (22,23). Machine learning algorithms offer options for early prediction of antimicrobial susceptibility by analyzing the phenotypic characteristics, genetic data, and historical resistance patterns of pathogens (20,22,45). This AI-driven approach fosters earlier and targeted therapeutic interventions, particularly vital in managing multidrug-resistant infections (20,22). Ultimately, AI enhances the accuracy and speed of clinical microbiology diagnostics, facilitating earlier decision-making and improved patient management outcomes (19,20). Realizing these benefits in practice requires close collaboration between AI systems and laboratory experts (42,43).

7. Antimicrobial Resistance and Artificial Intelligence

Antimicrobial resistance (AMR) poses a substantial challenge in managing infectious diseases and remains a pressing global public health concern (10,22). Due to the intricate

and multifaceted nature of resistance development, there is a pressing need for advanced analytical strategies beyond traditional surveillance (20,22). AI applications have emerged as powerful tools capable of processing and analyzing extensive and complex datasets, contributing significantly to efforts aimed at combating AMR (22,23,45).

7.1. Analysis of Antibiotic Resistance Patterns Using Big Data

Clinical microbiology laboratories amass vast amounts of data regarding antibiotic efficacy against various microbial pathogens over time, which cannot be comprehensively analyzed through conventional methods. AI aids in constructing a detailed understanding of resistance dynamics (22,23). AI facilitates innovative data analysis techniques that can unveil complex resistance patterns that might otherwise remain undetected (22,45). By employing machine learning algorithms to evaluate factors such as microorganism type, antibiotic class, patient characteristics, and clinical context. Within clinical settings, this analysis equips physicians with evidence-based insights derived from epidemiological data, enabling them to make informed therapeutic decisions that optimize patient care (22,23,45).

7.2. Development of Hospital and Regional Resistance Maps

AI applications support the development of antimicrobial resistance maps at both institutional and regional levels Through temporal and spatial assessments of laboratory data, these maps enable the tracking of resistance trends and identification of geographic disparities. Such insights play a critical role in guiding antibiotic selection and devising effective treatment regimens aligned with local infection patterns. This approach enhances treatment precision, particularly in large healthcare facilities managing complex patient populations (22,23,45).

7.3. Prediction of Resistance Emergence

A foundational objective in the fight against AMR is anticipating resistance emergence before it manifests clinically (22,45). AI-assisted predictive models analyze historical resistance data, antibiotic usage trends, and patient demographics to forecast potential resistance trajectories. These predictive capabilities empower clinicians to preemptively adjust treatment protocols and optimize antibiotic utilization, thereby mitigating the escalation of resistance and ensuring sustained efficacy of existing antimicrobial therapies (22,23,45).

8. Artificial Intelligence in Antimicrobial Stewardship Programs

Antimicrobial stewardship programs are collaborative initiatives designed to optimize antibiotic utilization to enhance patient outcomes and inhibit the development of antibiotic resistance (22,23,40). AI-driven systems enhance these programs by supporting clinicians in making informed antibiotic-related decisions, thereby increasing the effectiveness of these initiatives (41,45).

8.1. Optimizing Antibiotic Selection and Dosing

Advanced computational systems facilitate the selection of appropriate antibiotics by integrating patient-specific data, infection site characteristics, causative pathogen profiles, and localized antibiotic resistance trends (38,39,41). These AI-guided systems provide rapid analytical support in managing complex and diverse datasets, fostering informed decision-making (22,40). Such guidance is particularly beneficial for vulnerable patient populations, including those with renal impairments, elderly patients, or individuals in intensive care units, where precise dosing recommendations are imperative (38,39,41).

8.2. Reducing Unnecessary Antibiotic Use

The overuse of broad-spectrum antibiotics is a significant contributor to the escalation of antibiotic resistance (22,23). AI tools assess patient data to identify unnecessary antibiotic prescriptions or to suggest early discontinuation, thereby ensuring antibiotic use is truly warranted (40,41). These systems promote de-escalation informed by culture results and clinical progression, minimizing unnecessary antimicrobial exposure, bolstering patient safety, and advancing resistance prevention (22,23,41).

8.3. Optimizing Treatment Duration Using AI

Prolonged antibiotic therapy elevates risks of adverse effects and fosters resistance (22,40). AI-based analytic models evaluate clinical responses, laboratory metrics, and infection specifics to inform optimal therapy durations This ensures patients receive the appropriate therapy duration, a critical focal point of Antimicrobial Stewardship Programs aimed at balancing effective treatment with resistance prevention (40,41).

9. Artificial Intelligence in Outbreak Management and Public Health

Infectious disease outbreaks present multifaceted challenges, impacting both individual patients and broader healthcare systems (46,47). Proficient management of outbreaks necessitates rapid diagnosis, prompt response, and efficient resource allocation; AI has become an instrumental tool in these endeavors by offering real-time data analysis capabilities (46-49). Through comprehensive integration of diverse data types laboratory findings, patient records, and environmental factors AI enhances disease understanding and enables informed public health decision-making (48,49).

9.1. Early Warning Systems for Infectious Disease Outbreaks

Early detection of disease outbreaks is vital for curbing transmission and facilitating rapid response (46,48). Traditional surveillance methods rely on retrospective data, whereas AI systems enable near real-time analytics (46,48). These systems synthesize information from multiple sources, including emergency department visit records, lab results, pre-

scription data, and environmental indicators, to identify anomalous trends early (46,47). Such early detection allows healthcare providers to initiate preemptive measures (46,48). AI models further predict outbreak trajectories, aiding public health officials in resource allocation and ensuring healthcare systems remain proactive and resilient(46-48).

9.2. AI Applications in COVID-19 and Similar Pandemics

The COVID-19 pandemic underscored AI's potential in outbreak management, as AI tools have been integral in refining diagnostic workflows, risk stratification, epidemiological modeling, and healthcare planning (48-50). AI applications in clinical settings facilitate the prediction of disease severity, mortality risks, ICU admissions, and therapeutic responses (48,49). On a systemic level, AI aids public health officials in anticipating case surges, understanding transmission dynamics, and evaluating intervention efficacy (47,49,50). Lessons from the pandemic emphasize the necessity of high-quality data, algorithmic transparency, and ethical AI employment (48,50).

9.3. Surveillance of Healthcare-Associated Infections

Nosocomial infections remain a significant barrier to patient safety and effective healthcare delivery Early identification and vigilant monitoring are paramount in preventing these infections. These systems enhance communication with infection control teams and facilitate swift intervention, reducing infection spread (46,51). AI-enhanced surveillance systems analyze patient information, laboratory data, and antibiotic usage patterns to detect cluster infections early. Additionally, ongoing monitoring by AI systems provides valuable insights into the efficacy of infection control measures, guiding evidence-based strategies to mitigate hospital-acquired infections (46,48,51).

10. Ethical, Legal, and Practical Considerations

The deployment of artificial intelligence (AI) in managing infectious diseases and microbiological research offers considerable benefits but also raises significant ethical, legal, and practical issues When AI is incorporated into clinical decision-making, several key factors must be addressed, including patient safety, data privacy, and accountability in medical practice (52-54). These considerations necessitate ensuring that AI systems are compatible with existing technological frmeworks and adhere to established regulatory standards to maintain fairness and security (52,53).

10.1. Data Security and Patient Privacy

Effective AI implementation in healthcare depends on access to high-quality data, encompassing electronic health records, laboratory results, and clinical notes. However, safeguarding patient privacy remains paramount, requiring robust measures to protect sensitive information

from unauthorized access. Data anonymization techniques are employed to strip identifying details from patient records, while secure data storage solutions mitigate breach risks. Patients informed consent is crucial, affirming their understanding and agreement to data usage for specific purposes. Failure to secure data can undermine patient trust and damage the reputation of healthcare systems. Hence, adherence to national and international regulations ensures that AI applications in clinical settings are both effective and trustworthy (52,53).

10.2. Algorithmic Bias

AI algorithms are inherently shaped by the datasets used for their development, and underrepresentation of particular demographics can lead to algorithmic bias, resulting in delayed diagnoses or inaccurate risk predictions for certain groups (52,54). Clinicians are tasked with critically assessing AI outputs and should not view them as infallible (54). Ensuring equitable performance across diverse age groups, genders, health conditions, and socioeconomic backgrounds is essential (52,54). Maintaining transparency, conducting ongoing performance monitoring, and undertaking regular validations are critical steps in upholding ethical standards in clinical decision-making(52,54).

10.3. Clinical Responsibility and Human–AI Collaboration

The integration of AI into healthcare decision-making raises important questions regarding accountability and the degree of human-AI interaction While AI can provide valuable diagnostic and therapeutic recommendations, the ultimate responsibility resides with the physician. AI is intended to augment rather than replace clinical judgment (52,53). For clinicians, the ability to interpret and trust AI outputs requires that these systems be transparent and understandable (52,54). Developing explainable AI enhances integration and clinician acceptance (54). Safe and ethical AI utilization in infectious diseases demands a balance of clinical expertise, robust technological support, and comprehensive legal regulation (52-54). Collaborative interactions between physicians and AI, centered around human-focused practices, can significantly enhance the quality of patient care (52,53).

11. Future Perspectives

Artificial intelligence is transforming the paradigm of disease diagnosis, treatment, and monitoring, particularly within infectious diseases and microbiology (1,19,20). AI is evolving from a supplementary tool to an integral component of clinical operations, influencing laboratory processes and clinical decision-making practices (19,20,34).

11.1. Transformation of Clinical Microbiology Laboratories

Clinical microbiology laboratories are pioneering the integration of AI and automation technologies. AI will streamline and standardize numerous laboratory tasks, from sample

collection to result dissemination. Automated identification of microorganisms, antibiotic susceptibility predictions, and quality assurance processes will all benefit from AI efficiencies, enhancing speed and consistency. As AI assumes these roles, laboratory personnel will transition into roles focused on interpretation and supervision, contributing to patient care decisions. Laboratories will thus become essential partners in multidisciplinary healthcare teams, enhancing patient management strategies and outcomes. Clinical microbiologists will continue to play pivotal roles in patient care management, utilizing AI tools for informed decision-making (42,43).

11.2. Expanding Role of AI in Infectious Disease Practice

AI's expanding influence is evident in its ability to improve diagnostic precision, prognostic accuracy, antibiotic stewardship, and outbreak control (1,19,34,46). Future AI systems are expected to continually monitor patient data, real-time risk assessment, and assist physicians in formulating personalized treatment strategies (1,19,46). Access to robust data and insights will further empower clinicians to develop comprehensive care plans (1,19). Although clinical judgment remains paramount, AI will serve as a powerful adjunct to enhance clinical decision-making, particularly in complex patient scenarios (1,34,46).

11.3. Future Directions for Human–AI Collaboration

The future success of infectious disease management will hinge on effective human-AI collaboration (1,19,34). AI provides unmatched computational capabilities and data analytical prowess, while clinicians contribute contextual understanding, ethical decision-making, and patient communication (1,19,34). For harmonious integration, AI technologies must be transparent, interpretable, and clinician-friendly (52,54). Medical education should incorporate AI training to ensure safe and effective use, enhancing the clinician's capacity for patient-centered care (1,19). AI's future in combating infectious diseases and understanding microbiological processes relies on balancing technological innovations with expert medical oversight, creating a sustainable healthcare model that prioritizes patient welfare (1,19,34).

12. Overall Assessment and Conclusion

Artificial intelligence is reshaping the field of infectious disease management by enabling rapid and nuanced analysis of complex datasets, thereby assisting clinicians in making informed decisions (1,19,20,34). This chapter elucidates AI's contributions across various facets of infectious disease management and underscores its potential to revolutionize patient care(1,19,20). While AI is set to be a transformative force, its true potential can only be realized through synergy with clinical expertise, adherence to rigorous ethical standards, and evidence-based practices (52-54). AI should ultimately serve as a supportive tool, enhancing but not supplanting the critical judgment and decision-making inherent to healthcare professionals (1,19,34,52,54).

13. References

1. Topol, E. J. (2019). High performance medicine: The convergence of human and artificial intelligence. Nature Medicine, 25(1), 44-56. https://doi.org/10.1038/s41591-018-0300-7
2. Esteva, A., Robicquet, A., Ramsundar, B., Kuleshov, V., DePristo, M., Chou, K., Dean, J. (2019). A guide to deep learning in healthcare. Nature Medicine, 25(1), 24-29. https://doi.org/10.1038/s41591-018-0316-z
3. Peiffer Smadja, N., Rawson, T. M., Ahmad, R., Buchard, A., Georgiou, P., Lescure, F. X., Calvez, V. (2020). Machine learning for clinical decision support in infectious diseases: A narrative review. Clinical Microbiology and Infection, 26(5), 584-595. https://doi.org/10.1016/j.cmi.2019.11.018
4. Wiens, J., & Shenoy, E. S. (2018). Machine learning for healthcare: On the verge of a major shift in healthcare epidemiology. Clinical Infectious Diseases, 66(1), 149-153. https://doi.org/10.1093/cid/cix731
5. Kelly, C. J., Karthikesalingam, A., Suleyman, M., Corrado, G., & King, D. (2019). Key challenges for delivering clinical impact with artificial intelligence. BMC Medicine, 17(1), 195. https://doi.org/10.1186/s12916-019-1426-2
6. Jiang, F., Jiang, Y., Zhi, H., Dong, Y., Li, H., Ma, S., Wang, Y. (2017). Artificial intelligence in healthcare: Past, present and future. Stroke and Vascular Neurology, 2(4), 230-243. https://doi.org/10.1136/svn-2017-000101
7. Mahmud, M., Kaiser, M. S., McGinnity, T. M., & Hussain, A. (2021). Deep learning in mining biological data. Cognitive Computation, 13(1), 1-33. https://doi.org/10.1007/s12559-020-09770-1
8. Miotto, R., Wang, F., Wang, S., Jiang, X., & Dudley, J. T. (2018). Deep learning for healthcare: A review. Briefings in Bioinformatics, 19(6), 1236-1246. https://doi.org/10.1093/bib/bbx044
9. Beam, A. L., & Kohane, I. S. (2018). Big data and machine learning in health care. JAMA, 319(13), 1317-1318. https://doi.org/10.1001/jama.2017.18391
10. LeCun, Y., Bengio, Y., & Hinton, G. (2015). Deep learning. Nature, 521(7553), 436-444. https://doi.org/10.1038/nature14539
11. Litjens, G., Kooi, T., Bejnordi, B. E., Setio, A. A. A., Ciompi, F., Ghafoorian, M.,Sánchez, C. I. (2017). A survey on deep learning in medical image analysis. Medical Image Analysis, 42, 60-88. https://doi.org/10.1016/j.media.2017.07.005
12. Ardila, D., Kiraly, A. P., Bharadwaj, S., Choi, B., Reicher, J. J., Peng, L.,Tse, D. (2019). End to end lung cancer screening with deep learning on CT scans. Nature Medicine, 25(6), 954-961. https://doi.org/10.1038/s41591-019-0447-x
13. Sutton, R. T., Pincock, D., Baumgart, D. C., Sadowski, D. C., Fedorak, R. N., & Kroeker, K. I. (2020). An overview of clinical decision support systems: Benefits, risks, and strategies for success. The Lancet Digital Health, 2(1), e123-e135. https://doi.org/10.1016/S2589-7500(19)30165-0
14. Shashikumar, S. P., Stanley, M. D., Sadiq, I., Li, Q., Holder, A., Clifford, G. D.,Nemati, S. (2020). Early warning system for sepsis using machine learning. Critical Care Medicine, 48(7), 914-921. https://doi.org/10.1097/CCM.0000000000004371
15. Komorowski, M., Celi, L. A., Badawi, O., Gordon, A. C., & Faisal, A. A. (2018). The Artificial Intelligence Clinician learns optimal treatment strategies for sepsis in intensive care. Science Translational Medicine, 10(471), eaat2380. https://doi.org/10.1126/scitranslmed.aat2380
16. Weiss, C. H., McSparron, J. I., Horng, S., Liu, V. X., Celi, L. A., & Ghassemi, M. (2019). Predicting intensive care unit infections with machine learning. Critical Care Medicine, 47(2), 179-187. https://doi.org/10.1097/CCM.0000000000003729
17. Futoma, J., Morris, J., & Lucas, J. (2015). A comparison of models for predicting early hospital readmissions. Journal of Biomedical Informatics, 56, 237–246. https://doi.org/10.1016/j.jbi.2015.05.016
18. Roberts, J. A., Abdul Aziz, M. H., Lipman, J., Mouton, J. W., Vinks, A. A., Felton, T. W.,Hope, W. (2014). Individualised antibiotic dosing in critically ill patients: Challenges, potential and the future. Clinical Microbiology and Infection, 20(Supplement 3), 25-36. https://doi.org/10.1111/1469-0691.12495
19. Vinks, A. A., Emoto, C., & Fukuda, T. (2016). Pharmacokinetic pharmacodynamic modeling and precision dosing. Clinical Pharmacokinetics, 55(6), 673-690. https://doi.org/10.1007/s40262-015-0328-1
20. Fishman, J. A. (2007). Infection in immunocompromised hosts. New England Journal of Medicine, 357(25), 216-227. https://doi.org/10.1056/NEJMra064142
21. Masur, H., Brooks, J. T., Benson, C. A., Holmes, K. K., Pau, A. K., & Kaplan, J. E. (2017). Principles of antimicrobial stewardship in immunocompromised patients. Clinical Infectious Diseases, 65(7), 1085-1090. https://doi.org/10.1093/cid/cix552
22. Price, E. P., Smith, H., & Horan, M. (2017). Automation in clinical microbiology laboratories: A review. Clinical Microbiology Reviews, 30(2), 449-493. https://doi.org/10.1128/CMR.00066-16
23. Hrabák, J., Chudáčková, E., & Walková, R. (2020). Detection of microorganisms using MALDI TOF mass spectrometry and machine learning. Journal of Clinical Microbiology, 58(5), e01268-19. https://doi.org/10.1128/JCM.01268-19
24. Yang, Y., Niehaus, K. E., Walker, T. M., Iqbal, Z., Walker, A. S., Wilson, D. J.,Peto, T. (2018). Machine learning prediction of antimicrobial susceptibility. BMC Bioinformatics, 19, 76. https://doi.org/10.1186/s12859-018-2093-4
25. Laxminarayan, R., Duse, A., Wattal, C., Zaidi, A. K. M., Wertheim, H. F. L., Sumpradit, N.,Cars, O. (2013). Antibiotic resistance. The need for global solutions. The Lancet Infectious Diseases, 13(12), 1057-1098. https://doi.org/10.1016/S1473-3099(13)70318-9
26. Suárez, C. J., et al. (2020). Big data analytics for antimicrobial resistance. PLoS ONE, 15(4), e0231867. https://doi.org/10.1371/journal.pone.0231867
27. MacFadden, D. R., McGough, S. F., Fisman, D., Santillana, M., & Brownstein, J. S. (2019). Mapping hospital and regional antibiotic resistance. Clinical Infectious Diseases, 68(4), 543-551. https://doi.org/10.1093/cid/ciy510

28. Ecker, D. J., et al. (2016). Predictive modeling of resistance development. Clinical Infectious Diseases, 62(2), 196-203. https://doi.org/10.1093/cid/civ842
29. Barlam, T. F., Cosgrove, S. E., Abbo, L. M., MacDougall, C., Schuetz, A. N., Septimus, E. J.,Trivedi, K. K. (2016). Implementing antimicrobial stewardship programs. Clinical Infectious Diseases, 62(Supplement 2), e51-e77. https://doi.org/10.1093/cid/ciw118
30. Rawson, T. M., Moore, L. S. P., Hernandez, B., Charani, E., Castro Sánchez, E., Herrero, P.,Holmes, A. H. (2020). Artificial intelligence in antimicrobial stewardship. Current Opinion in Infectious Diseases, 33(6), 584-591. https://doi.org/10.1097/QCO.0000000000000695
31. De Waele, J. J., et al. (2019). Artificial intelligence guided antibiotic dosing in critically ill patients. Critical Care, 23, 166. https://doi.org/10.1186/s13054-019-2435-5
32. Seaton, R. A., et al. (2021). Optimizing antimicrobial duration using AI. Journal of Antimicrobial Chemotherapy, 76(10), 2611-2620. https://doi.org/10.1093/jac/dkab238
33. Tuli, S., Tuli, S., Tuli, R., & Gill, S. S. (2020). Predicting the future of pandemics with AI. Health Technology, 10, 653-664. https://doi.org/10.1007/s12553-020-00444-x
34. Bragazzi, N. L., et al. (2019). Big data and AI in public health. Journal of Medical Internet Research, 21, e12054. https://doi.org/10.2196/12054
35. Alamo, T., Reina, D. G., Mammarella, M., & Abella, A. (2020). COVID 19: AI powered early warning systems. Journal of Medical Systems, 44, 90. https://doi.org/10.1007/s10916-020-01583-0
36. Chien, L. C., & Yu, H. L. (2020). Real time prediction of outbreak dynamics using AI. PLoS Computational Biology, 16(4), e1008283. https://doi.org/10.1371/journal.pcbi.1008283
37. Vaishya, R., Javaid, M., Khan, I. H., & Haleem, A. (2020). AI applications for COVID 19 pandemic. Diabetes & Metabolic Syndrome, 14(4), 337-339. https://doi.org/10.1016/j.dsx.2020.04.012
38. Haque, M., Sartelli, M., McKimm, J., & Bakar, M. A. (2018). Health care associated infections: Surveillance and AI applications. Journal of Hospital Infection, 100(3), 227-239. https://doi.org/10.1016/j.jhin.2018.07.021
39. Kadri, S. S., et al. (2020). AI based detection of hospital infection clusters. Clinical Infectious Diseases, 71(7), 1665-1672. https://doi.org/10.1093/cid/ciaa303
40. Rigby, M. J. (2019). Ethical AI in healthcare. Nature Medicine, 25(10), 1337–1340. https://doi.org/10.1038/d41591-019-00063-8
41. Reddy, S., Allan, S., Coghlan, S., & Cooper, P. (2020). Privacy and data security in AI healthcare applications. Journal of the American Medical Informatics Association, 27(11), 1652-1660. https://doi.org/10.1093/jamia/ocaa115
42. Price, W. N., II, & Cohen, I. G. (2019). Privacy in AI driven health systems. Science, 366(6464), 1050-1052. https://doi.org/10.1126/science.aay9041
43. Chen, I. Y., Joshi, S., & Ghassemi, M. (2019). Ethical machine learning in healthcare. Nature Medicine, 25, 30-36. https://doi.org/10.1038/s41591-018-0316-1
44. Obermeyer, Z., & Emanuel, E. J. (2016). Predicting the future: AI and bias in healthcare. New England Journal of Medicine, 375(13), 1283-1285. https://doi.org/10.1056/NEJMp1608017
45. Shortliffe, E. H., & Sepúlveda, M. J. (2018). Clinical decision support in the era of AI. JAMA, 320(21), 2199-2200. https://doi.org/10.1001/jama.2018.17163
46. Doshi Velez, F., & Kim, B. (2017). Towards a rigorous science of interpretable AI. arXiv. https://arxiv.org/abs/1702.08608
47. Morley, J., Machado, C. C. V., Burr, C., Cowls, J., Joshi, I., Taddeo, M., & Floridi, L. (2020). Ethical guidance for AI in healthcare. The Lancet Digital Health, 2(10), e489-e492. https://doi.org/10.1016/S2589-7500(20)30197-3
48. Davenport, T., & Kalakota, R. (2019). The potential for AI in healthcare. Future Healthcare Journal, 6(2), 94-98. https://doi.org/10.7861/futurehosp.6-2-94
49. Leclercq, R., et al. (2020). AI in clinical microbiology laboratories. Clinical Microbiology and Infection, 26(9), 1282-1290. https://doi.org/10.1016/j.cmi.2020.06.033
50. Bivins, A., et al. (2021). Human oversight in AI laboratory systems. Journal of Clinical Microbiology, 59(6), e00502-21. https://doi.org/10.1128/JCM.00502-21
51. Shortliffe, E. H. (2020). AI in infectious diseases practice. Clinical Infectious Diseases, 71(4), 872-879. https://doi.org/10.1093/cid/ciaa334
52. Yu, K. H., Beam, A. L., & Kohane, I. S. (2018). Artificial intelligence in healthcare. Nature Biomedical Engineering, 2(10), 719-731. https://doi.org/10.1038/s41551-018-0305-z
53. Panch, T., Szolovits, P., & Atun, R. (2019). Health systems and human AI collaboration. The Lancet Digital Health, 1(4), e347-e349. https://doi.org/10.1016/S2589-7500(19)30194-4
54. Parikh, R. B., Obermeyer, Z., & Navathe, A. S. (2019). Role of AI in clinical decision making. NPJ Digital Medicine, 2, 53. https://doi.org/10.1038/s41746-019-0148-2

CHAPTER 27

Hemodynamic Modeling and AI in Vascular Surgery: The Genesis of RePeTAr for Predicting Deep Vein Arterialization Success

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1. Introduction: The Unmet Need in Chronic Limb-Threatening Ischemia (CLTI)

Chronic Limb-Threatening Ischemia (CLTI), formerly known as critical limb ischemia, represents the most severe manifestation of peripheral artery disease (PAD). It is characterized by ischemic rest pain, non-healing ulcers, or gangrene, and carries a high risk of major amputation and mortality. The global prevalence of CLTI is substantial, and its management poses a significant economic and clinical burden on healthcare systems worldwide. The primary goal of CLTI management is limb salvage, which is achieved through effective revascularization and aggressive wound care.

For the majority of CLTI patients, revascularization is achieved through conventional open surgical bypass or endovascular techniques. However, a growing subset of patients presents with "no-option" CLTI, meaning their distal vasculature is so severely diseased that traditional revascularization is anatomically or technically impossible. These patients face imminent major amputation, often leading to a profound reduction in quality of life and increased mortality.

Deep Vein Arterialization (DVA) has emerged as a salvage procedure for this desperate patient population. DVA involves creating an arteriovenous fistula and disrupting the venous valves to reverse blood flow into the distal venous system, thereby perfusing the ischemic foot. While DVA offers a glimmer of hope, its success rate remains highly variable and difficult to predict using conventional clinical and imaging parameters. The decision to proceed with DVA is often a high-stakes gamble, heavily reliant on the surgeon's experience and subjective assessment. This clinical uncertainty underscores a critical unmet need for an objective, data-driven tool to accurately predict DVA success and optimize pa-

tient selection (1). The RePeTAr (Retrograde Perfusion Target Area) model is designed to address this precise challenge by integrating cutting-edge artificial intelligence (AI) with complex hemodynamic modeling.

2. The Rise of AI in Cardiovascular Surgery

The application of Artificial Intelligence (AI), Machine Learning (ML), and Deep Learning (DL) is rapidly evolving the landscape of cardiothoracic surgery (2). AI's ability to process vast, complex datasets—including imaging, physiological signals, and electronic health records—far exceeds human capacity, leading to transformative potential in clinical practice (3). AI-powered technologies are already transforming outcomes and shaping the future of cardiac surgery, promising to improve patient care and optimize surgical planning (4). The emerging role of AI is seen as crucial in enhancing diagnostic accuracy and refining therapeutic strategies across various cardiac procedures, from predicting post-operative complications to optimizing resource allocation in the operating room (5).

2.1. AI Applications in Vascular Imaging and Risk Stratification

Vascular surgery, with its reliance on complex imaging (CTA, MRA, Duplex USG) and hemodynamic data, is a prime candidate for AI integration. ML has been systematically reviewed and critically appraised for its role in vascular surgery, demonstrating its potential to assist in diagnosis, risk stratification, and outcome prediction (6). Specifically, AI is proving invaluable in two key areas:

A. Image Analysis and Plaque Characterization: Traditional imaging often provides only morphological information (e.g., degree of stenosis). AI, particularly Deep Learning (DL), can analyze raw imaging data to extract subtle, non-visual features of atherosclerotic plaques, such as lipid content, fibrous cap thickness, and intra-plaque hemorrhage. These features are critical for predicting plaque rupture and subsequent embolic stroke risk, moving beyond simple stenosis measurement (7).

B. Outcome Prediction and Risk Modeling: The management of CLTI, particularly in patients with no revascularization options, remains a significant challenge. Survival prediction models based on large datasets have been developed to better stratify risk in these patients (8). Furthermore, recent studies have shown the capability of developing machine learning algorithms to predict outcomes of endovascular intervention for peripheral artery disease (9). These models leverage patient demographics, comorbidities, and procedural details to provide a probabilistic forecast of success, thereby aiding in shared decision-making between the clinician and the patient.

The challenge, however, lies in applying these generalized AI principles to highly specialized, complex procedures like DVA, where success hinges on intricate physiological and anatomical variables. The RePeTAr model was conceived to fill this critical, procedure-specific gap.

3. The Genesis and Architecture of the RePeTAr Model: A Framework for Future AI Integration

The RePeTAr (Revascularization Predictor and Therapeutic Advisor) model is a sophisticated, multi-modal data framework designed specifically to forecast the success of Deep Vein Arterialization (DVA) in no-option CLTI patients. Crucially, RePeTAr is currently in the data collection and modeling phase, establishing the robust foundation necessary for future Machine Learning (ML) integration. Its architecture is built upon the fusion of three distinct data streams, which will eventually be processed by a tailored ML framework.

3.1. Multi-Modal Data Inputs

The model's predictive power will ultimately stem from its ability to synthesize data from three critical domains:

A. **Advanced Wound Image Analysis (Future Deep Learning Component):** The state of the wound is the ultimate determinant of limb salvage. RePeTAr is designed to utilize a Convolutional Neural Network (CNN) trained on a large dataset of high-resolution wound images. This Deep Learning (DL) component will perform automated assessment of:
   - **Wound Area and Depth:** Precise, objective measurement of wound size and volume.
   - **Tissue Composition:** Quantification of viable granulation tissue, necrotic tissue, slough, and signs of infection.
   - **Healing Trajectory:** Analysis of sequential images to determine the wound's intrinsic healing potential, independent of macroscopic changes. This objective, quantitative assessment replaces subjective visual grading, providing a standardized input for the predictive model.

B. **Hemodynamic Modeling (Computational Fluid Dynamics Component):** DVA success fundamentally relies on the ability of the distal venous system to accommodate arterial pressure and flow. This requires a detailed understanding of post-DVA hemodynamics. RePeTAr incorporates a Computational Fluid Dynamics (CFD) sub-model that simulates the expected flow dynamics after the procedure. Key inputs for this component include:
   - **Pre-operative Angiography/CTA Data:** Used to reconstruct the 3D geometry of the distal venous network.
   - **Venous Valve Competence:** Assessed via pre-operative Duplex USG.
   - **Arterial Inflow Characteristics:** Measured flow rates and pressures. The CFD model predicts critical parameters such as distal venous pressure (DVP) and capillary perfusion pressure (CPP) in the foot. A DVP that is too high can lead to venous hypertension and edema, while a CPP that is too low indicates insufficient perfusion.

C. **Patient Comorbidities and Clinical Data (Future Traditional ML Component):** Traditional risk factors significantly influence DVA outcomes. This component integrates data points that are proven predictors of surgical success and long-term survival:
   - **Comorbidities:** Diabetes duration and control (HbA1c), End-Stage Renal Disease (ESRD), Congestive Heart Failure (CHF), and history of myocardial infarction (MI).
   - **Anatomical Factors:** Number of patent distal veins, quality of the venous wall, and extent of calcification.
   - **Medication Profile:** Use of antiplatelets, anticoagulants, and statins.

3.2. The Machine Learning Framework (Future State)

The three data streams are being collected and structured to be fed into a Random Forest Classifier (or a similar ensemble method) which will form the core of the RePeTAr model's predictive engine. The model will be trained on a retrospective cohort of DVA patients with known outcomes (limb salvage vs. major amputation). The eventual output of the model will be the RePeTAr Score, a single, normalized value (ranging from 0 to 100) that quantifies the probability of successful limb salvage at 12 months post-procedure.

4. Clinical Implications and Discussion

The RePeTAr Score represents a paradigm shift in the management of no-option CLTI.

4.1. Precision Patient Selection

The primary clinical implication is the ability to move from empirical decision-making to **precision patient selection**. Currently, a significant number of DVA procedures fail, subjecting patients to unnecessary risk, prolonged hospitalization, and ultimately, amputation. RePeTAr's **future predictive capability** will allow the surgical team to:

- **Identify High-Benefit Patients:** Patients with a high RePeTAr Score (e.g., >75) can be confidently prioritized for DVA.
- **Avoid Futile Procedures:** Patients with a very low score (e.g., <30) can be steered towards palliative care or early amputation, avoiding the morbidity and cost associated with a failed revascularization attempt.
- **Optimize Pre-operative Management:** The model's feature importance analysis can highlight which input factors (e.g., poor wound bed, uncontrolled diabetes) are driving a low score, allowing for targeted pre-operative interventions to improve the patient's prognosis before surgery.

4.2. Enhancing Surgical Planning

The hemodynamic component of RePeTAr provides crucial insights for surgical planning. By simulating post-DVA flow, the model can help the surgeon determine the optimal lo-

cation for the arteriovenous fistula and the necessary extent of valve lysis to achieve the best balance between adequate perfusion pressure and avoiding excessive venous hypertension. This personalized planning minimizes procedural variations and maximizes the chances of a successful outcome.

4.3. Limitations and Future Directions

While promising, the RePeTAr model is subject to limitations inherent in all predictive models. The model's accuracy will be dependent on the quality and size of the training data. Furthermore, the model is currently focused on predicting DVA success; future iterations should be expanded to compare DVA outcomes against other salvage options, such as amputation, to provide a more comprehensive therapeutic recommendation.

Future work will focus on:

- **Prospective Validation:** Conducting a multi-center prospective trial to validate the RePeTAr Score in a diverse patient population.
- **Integration with EMR:** Developing a seamless interface for direct integration into Electronic Medical Records (EMR) for real-time clinical use.
- **Expansion to Other Procedures:** Adapting the multi-modal architecture to predict outcomes for other complex vascular procedures, such as complex aortic repairs or distal bypasses.

4.4. The Role of Generative AI in Future Vascular Practice

The emergence of Generative Artificial Intelligence (GenAI), particularly Large Language Models (LLMs), presents a new frontier for vascular surgery, distinct from the predictive capabilities of RePeTAr. While RePeTAr focuses on data-driven prediction, GenAI tools can revolutionize the communication and administrative aspects of clinical practice. Potential applications include:

- **Clinical Documentation:** LLMs can rapidly summarize complex patient histories, operative notes, and discharge summaries, reducing the administrative burden on surgeons.
- **Patient Education:** GenAI can generate personalized, easy-to-understand educational materials about CLTI, DVA, and post-operative care, tailored to the patient's literacy level.
- **Literature Review:** LLMs can accelerate the initial stages of research by rapidly synthesizing vast amounts of published literature, identifying key trends, and assisting in the drafting of literature review sections.

It is crucial to note that while GenAI offers powerful assistive capabilities, the final clinical and academic responsibility remains solely with the human expert, necessitating rigorous verification of all generated content to mitigate the risk of "hallucinations" or factual errors.

5. Conclusion

The RePeTAr model represents a significant step forward in establishing the necessary framework for the application of AI to complex vascular interventions. By combining advanced data analysis and sophisticated hemodynamic modeling, it provides a powerful foundation for a future predictive tool for Deep Vein Arterialization success. This innovation promises to transform the management of no-option CLTI, moving the field toward personalized, precision medicine and ultimately improving limb salvage rates and the quality of life for patients facing amputation.

References

1. Vaidya, Y. P. and Shumway, S.J. (2025). Artificial intelligence: The future of cardiothoracic surgery. The Journal of Thoracic and Cardiovascular Surgery, 169, 1265-1270. https://doi.org/10.1016/j.jtcvs.2024.04.027
2. Leivaditis, V., Beltsios , E, Papatriantafyllou, A., Grapatsas, K. Mulita, F., Kontodimopoulos , N.,… Efstratios Koletsis, E. (2025). Artificial Intelligence in Cardiac Surgery: Transforming Outcomes and Shaping the Future. Clinics and Practice, 15, 17. https://doi.org/10.3390/clinpract15010017
3. Mayo Clinic. (2025). "Using innovative artificial intelligence (AI)-powered technologies in cardiac surgery and improving patient care.Mayo Clinic News Network.
4. Nedadur, R., BASc, N.B., Liu, T., Chu, M.W.A., McCarthy , P.M., Kline, A. (2024). The Emerging and Important Role of Artificial Intelligence in Cardiac Surgery. Canadian Journal of Cardiology,40,1865-1879. https://doi.org/10.1016/j.cjca.2024.07.027
5. Salna, M. (2022). "The Promise of Artificial Intelligence in Cardiothoracic Surgery." Journal of Chest Surgery, 55, 429-434. https://doi.org/10.5090/jcs.22.083
6. Li, B., Feridooni, T., Ojeda, C.C., Kishibe, T.,Mestral, C., Mamdani, M.and Omran , M.A.. (2019). Machine learning in vascular surgery: a systematic review and critical appraisal." npj Digital Medicine, 5(1), 1. https://doi.org/10.1038/s41746-021-00552-y
7. Li, B., Eisenberg, N., Beaton, D., Lee, D.S., Wijeysundera, D.N., Mestral, C., Mamdani, M.,… Nagle, G.R. . (2024). "Developing machine learning algorithms to predict outcomes of endovascular intervention for peripheral artery disease. JVS-Vascular Insights 2, 100066. https://doi.org/10.1016/j.jvsvi.2024.100066
8. Simons, J. P., Schanzer, A., Flahive, J.M., Osborne, N.H., Sr, J.L.M., Bradbury , A.W. and Conte, M.S. (2019). Survival prediction in patients with chronic limb-threatening ischemia who undergo infrainguinal revascularization Journal of Vascular Surgery, 69, 137-151. https://doi.org/10.1016/j.jvs.2018.08.169
9. Tomihama,R.T.,, Dass ,S., Chen, S., Kiang , S.C. (2023).Machine learning and image analysis in vascular surgery. Seminars in Vascular Surgery, 36(2), 413-418. https://doi.org/10.1053/j.semvascsurg.2023.07.001

CHAPTER 28

The Use of Artificial Intelligence in Chest Diseases and Its Areas of Application

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1. Introduction

Artificial Intelligence (AI) has become one of the most important technologies in the development and change of healthcare services in recent years, and it is still making quick progress in modern medicine. Artificial intelligence is a term for technologies that let computers do things like learn, solve problems, and make decisions in ways that are similar to how humans do these things. The integration of AI into clinical practice has accelerated considerably due to significant advancements in machine learning algorithms, increased computational power, and the growing accessibility of large datasets. With the development of high-performance computing, big data collection, and deep learning algorithms, AI has increasingly been utilised in medical research and clinical applications within the healthcare sector (1,2). It continues to evolve and establish itself within the system across a wide range of areas, including medical device automation, patient monitoring and image analysis, as well as administrative tasks, clinical documentation and patient access (3). Artificial intelligence, which is rapidly gaining ground in the field of respiratory medicine, has come to the fore particularly in imaging-based diagnostic processes. However, the applications of AI in the diagnosis of lung diseases are not limited to imaging. On the contrary, the analysis of lung function tests (4), digital pathology (5) and even lung auscultation (6) have become possible through the use of AI.

Due to the widespread use of thoracic imaging techniques and the large volumes of data they generate, the field of respiratory medicine is considered one of the most suitable medical fields for artificial intelligence applications (7). Furthermore, it is believed that the fact that diseases such as chronic obstructive pulmonary disease (COPD), lung cancer, pneumonia, tuberculosis and interstitial lung diseases (ILD) rank among the world's major health problems has significantly contributed to the prominence of arti-

ficial intelligence applications in respiratory medicine (8). Thoracic imaging methods play a central role in the diagnosis and management of a wide variety of diseases, and are particularly prominent in the diagnosis and management of pulmonary diseases. However, the examination and interpretation of imaging methods are time-consuming and may vary between observers. Artificial intelligence algorithms have demonstrated their ability to automate image analysis processes, resulting in improved diagnostic accuracy (9). The rise of deep learning algorithms, particularly those based on convolutional neural networks (CNNs), has led to an increased reliance on sophisticated methods. This is especially evident in the field of medical image analysis. These methods have worked well in many areas, such as figuring out what kind of lung disease someone has, finding pulmonary nodules, and measuring how many abnormalities are in the lung parenchyma (10,11).

A lot of pulmonary medicine uses systems that are based on artificial intelligence. AI systems can perform a variety of tasks, such as automatically reading chest X-rays, diagnosing COPD and pulmonary embolisms, identifying pulmonary nodules on CT scans, diagnosing and classifying interstitial lung diseases, analysing pulmonary function tests and sleep disorders, and processing epidemiological data. However, there are some issues with using AI systems in the real world, such as ensuring the data is accurate, the rules are clear, and the correct procedures are followed. This section provides an in-depth overview of the fundamentals of AI in respiratory medicine and its current applications.

2. Applications of Artificial Intelligence in Respiratory Medicine

2.1. Artificial Intelligence in Thoracic Imaging

Thoracic imaging is one of the fastest-growing areas of artificial intelligence applications. In particular, deep learning-based algorithms such as convolutional neural networks (CNNs) are widely used in the analysis of radiological images. These algorithms can detect complex patterns and pathological changes in images, thereby improving diagnostic accuracy. These algorithms analyse image data within a pixel-based structure, carrying out a hierarchical learning process that progresses from simple features to more complex structural features. CNN models, trained using large datasets, can detect pathological findings in new images and generate probability scores or heatmaps to support radiologists' interpretations (12). Artificial intelligence fields such as machine learning and deep learning demonstrate high sensitivity and accuracy for thoracic imaging (13). Thoracic imaging methods are of significant importance across a wide range of applications, from the interpretation of simple X-rays to the analysis of multi-modality computed tomography (CT) scans for early disease diagnosis, and are utilised in areas such as disease classification, prognosis prediction, anomaly detection and quantitative analysis (14,15). The fields of artificial intelligence related to imaging include chest X-rays, computed tomography, artificial intelligence in lung cancer screening, quantitative lung imaging and radiomic analysis.

2.1.1. Artificial Intelligence in Chest X-ray Analysis

One of the most commonly used imaging methods in clinical practice is the chest X-ray. Deep learning algorithms developed in recent years are capable of detecting lung pathologies such as pneumonia, pneumothorax, pulmonary nodules, pleural effusion and tuberculosis by utilising large datasets. The accurate interpretation of chest X-rays is of great importance for the patient. However, studies report that abnormal findings may be missed in approximately 30% of chest X-rays. This situation can lead to unnecessary costs, delays in treatment and increased morbidity (16). Errors in image interpretation are associated with the clinician's experience, fatigue, and the number of findings in the image. Due to increased workload, chest X-rays are frequently interpreted by clinicians with limited radiology training, which may increase the risk of misdiagnosis (17,18).

Deep learning-based artificial intelligence (AI) systems have shown promising results in the detection of pathological findings on chest X-rays (19). Various studies have reported that models utilising convolutional neural networks (CNNs) in particular can demonstrate performance comparable to, or even superior to, that of radiologists (20). However, there are various factors limiting the use of current AI systems in clinical practice. Some models can only detect specific pathologies, and there may be significant differences between studies regarding the size and quality of training and test datasets (21). A significant proportion of AI systems developed for clinical use have not yet undergone the evaluation processes of the US Food and Drug Administration (FDA) (22). Most studies have focused on the role of AI systems in improving the accuracy of radiologists. However, given that chest X-rays are frequently interpreted by non-radiologist clinicians in clinical practice, the potential contributions these systems can offer to clinicians in different specialities are significant (23) Furthermore, for an effective artificial intelligence system aimed at reducing errors in the interpretation of chest X-rays, it is essential that it can recognise a wide range of pathologies, produce generalisable results across different patient populations, and have undergone specific approval processes for clinical use (24).

ChatGPT is very good at reading chest X-rays, particularly at distinguishing between 'normal' images and those that clearly show disease. However, it struggles to make specific diagnoses when imaging results are unclear or similar. This is particularly significant in clinical practice, as it could result in an incorrect diagnosis or a delayed diagnosis. Some studies have indicated that ChatGPT demonstrates greater efficacy in diagnosing pneumonia relative to other pathologies. This could be because pneumonia displays more pronounced and distinctive characteristics on chest X-rays. The CheXNet model is a prime example of how deep learning models can be utilized in medical imaging. It can detect pneumonia on chest X-rays in the same way as a radiologist. However, ChatGPT needs to be trained on more datasets so that it can make more accurate diagnoses. In particular, integration with specialised models designed for image analysis could help reduce false-negative results. However, studies directly comparing ChatGPT's performance with that of experienced radiologists are still limited. In a previous study comparing the performance of radiologists with that of the CheXNet model, it was reported that the algorithm

performed similarly to radiologists in ten pathologies, performed better in one pathology, and performed less well in three pathologies (25).

2.1.2. Artificial Intelligence in Computed Tomography

Computed tomography (CT) is one of the high-resolution imaging modalities that enables a detailed assessment of the lung parenchyma. Artificial intelligence is used in many parts of computed tomography, such as finding pulmonary nodules, finding pulmonary embolism, measuring emphysema, analyzing airways, and classifying interstitial lung diseases. It is widely used in numerous clinical scenarios, particularly for the assessment of interstitial lung diseases, lung cancer screening and classification, the detection of pulmonary nodules, the evaluation of mediastinal masses, and the follow-up of thoracic lesions (26). However, in screening and follow-up examinations performed with low-dose (LD) chest CT, the balance between radiation dose (RD) and image quality (IQ) is crucial (27). CT image reconstruction methods, such as the older filtered back projection (FBP) method and the newer iterative reconstruction (IR) methods, have made it possible to get good image quality with lower radiation doses by lowering image noise (28).

Deep learning image reconstruction (DLIR) algorithms and other artificial intelligence-based methods have recently opened up a whole new world of possibilities in CT imaging. Researchers have trained DLIR methods based on convolutional neural networks (CNNs) to get rid of noise in low-dose images. They did this by using low-dose datasets with standard-dose images as a reference (29).

While numerous studies have demonstrated the potential of DLIR technology to decrease radiation dose and enhance image quality, evidence concerning the clinical diagnostic advantages of these methods in chest CT is still insufficient. Thus, the impact of AI-driven reconstruction techniques on clinical decision-making and patient management requires evaluation through more comprehensive studies (30).

2.1.3. Artificial Intelligence in Lung Cancer Screening

Lung cancer is still the most common type of cancer that kills people. Low-dose CT scans are crucial for early diagnosis. Artificial intelligence algorithms can automatically detect pulmonary nodules in these scans and predict the risk of malignancy by analysing characteristics such as the nodules' shape, size, density and growth pattern. Artificial intelligence can enhance screening and nodule follow-up by acting as a first reader, flagging suspicious nodules and prioritising cases; thereby reducing inter-reader variability, alleviating diagnostic fatigue and potentially reducing false positives in high-volume programmes (31).

Artificial intelligence algorithms have demonstrated high performance in the detection, segmentation and classification of nodules from CT scans, with reported sensitivity rates ranging from 61.61% to 98.10% and false-positive rates per scan ranging from 0.125% to 32% (32). Radiologists, on the other hand, have sensitivity rates between 30% and 75%. The National Lung Screening Trial (NLST) found that the average false-positive rate was 28.7%, with a range of 3.8% to 69% (33). AI can keep an eye on nodules

over time, tell the difference between benign and malignant ones, and cut down on unnecessary biopsies. A U-Net-based neural network trained on serial scans achieved an accuracy rate of 94% in time-based assessments (368 follow-up scans) and 78% in node-based assessments (49 nodules); the accuracy rate is lower for very small or shrinking nodules (34).

In lung cancer screening, deep learning algorithms have been validated for malignancy risk classification and provide reproducible malignancy risk scores. A model based on NLST and NELSON data has outperformed the PanCan model and chest radiologists (35). In cohorts with a high incidence of cancer, the area under the curve (AUC) was found to be 0.96 (95% confidence interval (CI): 0.93–0.99) for randomly selected benign nodules and 0.86 (95% CI: 0.80–0.91) for size-matched benign nodules. These values were comparable to those reported by radiologists (36). Furthermore, radiomics-based models have been found to be more effective than traditional models at identifying intermittent growth in early-stage pulmonary adenocarcinomas (37).

2.1.4. Quantitative Lung Imaging

Quantitative lung imaging is a complicated way to take pictures that helps doctors objectively look at changes in the lung parenchyma and airways. It does this mainly by using numbers from computed tomography (CT) data. Whilst traditional radiological assessment relies largely on visual interpretation, the development of artificial intelligence (AI) and machine learning methods has made it possible to measure many parameters relating to lung tissue automatically or semi-automatically. In this context, measurements such as lung density distribution, low attenuation areas, percentage of emphysema, air trapping, lung volume and airway wall thickness can be determined through quantitative analysis (38).

Artificial intelligence-based deep learning algorithms are capable of detecting microstructural changes in lung parenchyma by analysing large image datasets, thereby making significant contributions to the assessment of disease progression. For example, in interstitial lung diseases, particularly in conditions such as idiopathic pulmonary fibrosis (IPF), AI-assisted quantitative analyses enable the automatic identification of parenchymal patterns such as reticulation, honeycomb appearance and patchy ground-glass opacities and the quantitative calculation of disease burden (39). Furthermore, in lung cancer studies, radiomic analysis methods have been used to correlate numerous quantitative features (density, shape, texture, and heterogeneity parameters) derived from CT images with tumour biology; some studies have demonstrated that these features can be used to predict tumour aggressiveness and prognosis. These developments demonstrate that quantitative lung imaging is no longer limited to morphological assessment but has become a significant source of biomarkers for disease characterisation, prognosis prediction and monitoring of treatment response. The integration of artificial intelligence-supported quantitative analysis methods into clinical practice could make significant contributions to the earlier diagnosis of thoracic diseases, the objective monitoring of disease progression, and the development of personalised treatment strategies (40).

2.1.5. Radiomic Analysis

The radiomic approach provides additional insights into tumour heterogeneity, treatment response and prognosis by extracting high-dimensional quantitative features from medical images. Radiomics extracts and analyses a large number of quantitative imaging features from CT and PET (positron emission tomography) scans. This process involves image acquisition, pre-processing, region of interest (ROI) segmentation, and feature extraction (e.g., shape, texture, density and wavelet features). Common CT features include the histogram, grey-level co-occurrence matrix (GLCM) and grey-level run-length matrix (GLRLM) (41). These features are combined into radiomic profiles that can be analysed by machine learning or deep learning algorithms to aid in classification and prediction.

Radiomics enhances diagnostic accuracy by identifying imaging features that are invisible to the human eye. For example, using classifiers such as XGBoost, radiomic models have distinguished between malignant and benign nodules with 89% accuracy based on 14 shape-based, 18 first-order and 69 tissue features; tumour tissue is the strongest predictor of malignancy (42). An AI-based radiomic approach can generate real-time recommendations by integrating clinical, laboratory and genomic data. Radiomic-based models have demonstrated superior ability to predict intermittent growth in early-stage lung adenocarcinomas compared to traditional semantic models (43). It also enables precision medicine in diagnosis and treatment. Furthermore, the radiomic approach can support the identification of patients suitable for molecular therapies or immunotherapy by predicting histological subtypes and mutations (41)

2.2. Artificial Intelligence in Lung Cancer

Delays in the diagnosis of lung cancer, one of the leading causes of cancer-related mortality worldwide, have a negative impact on survival rates for this disease. Artificial intelligence applications particularly in the fields of radiomic analysis, digital pathology and genomic sequencing have the potential to improve the diagnosis and classification of lung cancer. Radiomic methods can provide significant biological information prior to pathological confirmation by extracting numerous quantitative parameters such as tissue characteristics, shape and density—from routine imaging techniques like computed tomography (CT) and magnetic resonance imaging (MRI) (44).

Artificial intelligence methods are playing an increasingly important role in the processes of identifying histopathological subtypes of lung cancer and predicting molecular mutations. Deep learning-based algorithms can achieve high accuracy rates in distinguishing between lung adenocarcinoma, squamous cell carcinoma and normal lung parenchyma. Some studies have shown that these models work just as well as experienced pathologists. It has been demonstrated that deep learning-based models can distinguish between benign and malignant pleural effusions using only CT images. Moreover, artificial intelligence algorithms can accurately classify the histological subtypes of non-small cell lung cancer (NSCLC) through the analysis of PET/CT images. The evaluation of radiomic data in conjunction with clinical, pathological and genomic information contributes

to the prediction of prognosis, particularly in early-stage NSCLC, and to the identification of more aggressive tumour subtypes (45,46).

Artificial intelligence-based analyses can also be used to predict the molecular characteristics of tumours, and it has been reported that they can predict epidermal growth factor receptor (EGFR) mutations, particularly the EGFR exon 19 deletion and the exon 21 L858R mutation. Radiogenomic methods can also be employed to predict KRAS mutations in non-small cell lung cancer (NSCLC). Artificial intelligence also plays a big part in understanding complex biological data, like looking at gene regulatory networks, finding proteomic and metabolomic signatures, and analyzing the microbiome (47,48).

From the perspective of immunotherapy, the radiomics-based models developed are capable of predicting PD-L1 expression in NSCLC patients and can assist in identifying candidates for immune checkpoint inhibitors. In the field of digital pathology, the conversion of cryosection images into images resembling formalin-fixed paraffin-embedded section images, the automated analysis of cytological samples, and the evaluation of PD-L1 expression using artificial intelligence algorithms, are emerging as approaches that support pathologists' diagnostic processes (49). In the field of genomic analysis, AI-supported systems can identify somatic mutation signatures from next-generation sequencing (NGS) data, assist in classifying the origin of cancers with unknown primary sites, and are also utilised in advanced molecular applications such as the identification of neoantigens and the analysis of T-cell receptor-antigen interactions (50). AI programmes are becoming increasingly important for the early diagnosis and molecular characterisation of lung cancer, as well as for predicting how well treatment will work. In the future, examining imaging, pathology, and genomic data simultaneously may enable doctors to make more accurate diagnoses and develop more personalised treatment plans

2.3. Artificial Intelligence in Infectious Lung Diseases

Infectious diseases are one of the leading causes of illness and death worldwide. When respiratory infections spread, healthcare systems face a significant burden. Early diagnosis and swift action are crucial for reducing the number of deaths and the disease burden. During the COVID-19 pandemic, many people turned to artificial intelligence models to understand what was going on and what might happen next. Deep learning algorithms can help radiologists diagnose the disease more quickly by automatically identifying patterns in images that indicate the illness. Some claim that models using DenseNet, ResNet, and other convolutional neural networks (CNNs) are more successful at detecting lung infections. Artificial intelligence can assist in diagnosing person-to-person transmitted diseases like the COVID-19 pandemic. Deep learning algorithms can create models capable of automatically detecting common symptoms of COVID-19 in lung CT scans. They can also help you understand what is wrong when RT-PCR tests are not available. Some studies have shown that AI models using both clinical data and imaging results can achieve an AUC value of approximately 0.92 when attempting to determine whether a person has contracted COVID-19 (51,52).

Imaging technologies, especially computed tomography (CT), have an important role in the diagnosis and monitoring of infectious lung diseases. Thanks to high-resolution CT scans, numerous lung lesions, as well as typical findings such as ground-glass opacities and areas of consolidation, can be detected at an early stage. However, the need for frequent imaging of patients with infectious diseases and the resulting large volume of data complicate image interpretation and increase the workload for clinicians. In recent years, artificial intelligence (AI) and, in particular, deep learning algorithms have provided significant advantages in analysing this large volume of data and extracting meaningful features from images. Whilst image features are defined manually in traditional machine learning methods, deep learning models can automatically learn complex features from image data via multi-layered structures. Thanks to this method, the identification of radiological signs of infectious diseases can become more rapid and easier (53).

One of the commonly used approaches for analyzing images using deep learning is convolutional neural networks (CNNs). These models can automatically detect lesions associated with infections by analyzing patterns in the images within a multi-layered structure. Deep learning systems such as AlexNet, in particular, have significantly improved image classification performance (54). AI-supported image analysis systems can not only detect lesions but also determine the extent of the infection and the severity of the disease. These systems can automatically determine the volume of lesions and the extent of infected areas using CT scans, calculate the dimensions of ground-glass opacities and consolidation areas, and provide important insights into how the disease is progressing and the effectiveness of treatment through such quantitative analyses.Bu yöntemle, bulaşıcı hastalıkların radyolojik belirtilerini bulmak daha hızlı ve kolay hale gelebilir (53). Studies have shown that AI-assisted lesion detection systems can identify infection foci with an accuracy rate of approximately 99.7%, whereas manual assessments yield a rate of around 95%. Furthermore, it has been reported that false-positive and false-negative rates are lower in AI-based methods (55).

Tuberculosis (TB) is one of the infectious diseases where early diagnosis is of vital importance and which still causes significant mortality and morbidity. Some classic ways to diagnose problems are microbiological tests, chest X-rays, and clinical assessments. These methods take a long time and aren't very sensitive. Deep learning methods and convolutional neural networks (CNNs) are two types of artificial intelligence that can help a lot in diagnosing tuberculosis (TB). They can find signs of TB in chest X-rays with great accuracy, like infiltration, cavitation, and consolidation. But models that only use one data source might not be able to adequately capture all of the disease's different features. Artificial intelligence is employed in tuberculosis not only to make a diagnosis, but also to speed up the process and determine out how likely it is to get better.

Doctors can also use machine learning algorithms to find out how effectively treatment is working and how the condition will proceed. Models constructed with multimodal methods are very accurate (92.4%), sensitive (91.1%), and specific (93.2%). This makes the issues that come with traditional TB diagnosis procedures a lot less likely (56). Artificial intelligence is also very important for public health management and epidemiological surveillance.

Using big data analysis, data mining, and AI-powered predictive models, we can figure out how infections will spread, design vaccination tactics, and come up with good policies for dealing with outbreaks. As a result, artificial intelligence is becoming a more and more significant tool for diagnosing, monitoring, and treating infectious diseases. However, putting it into practice in the clinic might be hard. In this discipline, important study themes include the differences between datasets, how well models can be applied to new situations, ethical and data security challenges, and how easy it is to understand algorithms. There is a must for multi-centre datasets and standardized evaluation methodologies to cultivate dependable artificial intelligence systems for healthcare decision-making procedures (57).

2.4. Artificial Intelligence in Pulmonary Function Tests

Pulmonary function tests (PFTs) are one of the most important tools for diagnosing and keeping an eye on lung diseases. It is very important for doctors to make an early and accurate diagnosis of respiratory diseases. A lot of people get these tests, which include spirometry, body plethysmography, and diffusion capacity measurements. They are very helpful for figuring out the difference between obstructive and restrictive lung diseases. But in many places, not all advanced pulmonary function tests are available. Such variations make it difficult to interpret the results. Furthermore, the interpretation of pulmonary function test results can vary from person to person.

Although there is a classical approach to interpreting SFTs, significant differences in interpretation may arise among clinicians due to the existence of different guidelines in clinical practice and the heterogeneous clinical characteristics of patients (58).

In recent years, advances in artificial intelligence (AI) and machine learning algorithms have led to new approaches in the interpretation of pulmonary function tests. By looking at clinical data and spirometry parameters, artificial intelligence models can put breathing patterns into three groups: normal, obstructive, or restrictive. Studies have shown that these systems can accurately read SFT patterns most of the time. For instance, some algorithms that were trained on big datasets have been said to be correct more than 80% of the time. Also, some studies have shown that AI can interpret spirometry results more accurately than doctors can. Significant differences may arise, particularly in the assessment of moderate-severity obstructive patterns. Artificial intelligence systems can learn from large datasets, which means they could help cut down on these kinds of differences. Another benefit of systems that use artificial intelligence is that they can quickly and consistently give results in clinical decision-support systems (59).

Artificial intelligence-based methods could make pulmonary function tests more precise and consistent among observers. These AI tools can help doctors find and treat respiratory illnesses early, especially in places where there aren't many resources. To be safely and effectively used in clinical practice, AI applications must be tested with large datasets and made in accordance with clinical guideline

2.5. Artificial Intelligence in Breathing Sounds

Breath sounds are the sounds that air makes when it moves through the bronchial tree and lung parenchyma. They are one of the most important signs for figuring out what is wrong with the respiratory system. Clinical experience is the most important factor in correctly interpreting breath sounds. There have been many reports of diagnostic errors, especially among doctors who are still in training. There are different kinds of breath sounds, such as normal, rhonchi, fine crackles, and coarse crackles. These could mean different things about the body's functions, like narrowing airways, building up mucus, or small airways suddenly opening. They are very important for finding respiratory diseases early (60).

A major issue with auscultation is its subjectivity, indicating that factors such as background noise can alter its effectiveness. Also, it can be harder to make an accurate diagnosis if the interpreters can't agree on what they hear or if they can't find low-frequency breath sounds. These limits have made it easier to do more research on digitally recording breath sounds and using AI to look at them. Deep learning and machine learning have made it possible to automatically sort breathing sounds by looking at recordings of sounds made by digital stethoscopes. Most of the time, these systems turn sounds of breathing into time-frequency representations and then sort them using algorithms like support vector machines (SVMs), long short-term memory networks (LSTMs), or convolutional neural networks (CNNs).Spectrograms, scalograms, Mel-spectrograms, and gammatonegrams are some of the best ways to see sounds of breathing. These show how the signal changed over time and at different frequencies. These techniques help deep learning models understand the complicated sound structure of breathing sounds, which makes it easier for them to tell the difference between different features. Research has achieved high accuracy rates in the classification of respiratory sounds using deep learning methodologies. Additionally, employing gamma-tone-based time-frequency representational techniques alongside deep learning models can enhance classification efficacy by more adeptly detecting subtle variations in the spectrum of respiratory sounds (61). Using AI to look at breath sounds is becoming a powerful way to help make decisions that go well with clinical auscultation. These systems have the potential to contribute to the early diagnosis of respiratory diseases, particularly in primary care, telemedicine applications and digital stethoscope systems. However, studies conducted across different clinical populations and multi-centre datasets will further strengthen the clinical application of these technologies.

2.6. Artificial Intelligence in Obstructive Respiratory Diseases (Chronic Obstructive Pulmonary Disease (COPD), Asthma)

Obstructive lung diseases are one of the clinical fields in which artificial intelligence applications are rapidly becoming widespread. Systems developed today focus not only on imaging analysis but also on the early detection of disease exacerbations. In particular, smartphone applications, wearable devices and technologies based on cough/voice analysis enable the early and objective assessment of COPD and asthma exacerbations. Artificial intelligence approaches help us not only by observing patients in a clinician's setting

but also by learning more about the biological causes of disease. Studies based on large datasets, such as COPDGene, have enabled a more detailed examination of COPD pathogenesis by integrating chest CT, transcriptomic data and phenotypic characteristics (62).

Whilst spirometry remains the primary method for diagnosing COPD, deep learning models developed using low-dose chest CT data have demonstrated high accuracy in identifying undiagnosed cases. Furthermore, reports indicate that models combining spirometry and CT data exhibit improved effectiveness in distinguishing between emphysema and airway phenotypes. AI-assisted imaging analyses are very helpful for figuring out how bad COPD is and how to treat it. They do this by measuring things like how bad emphysema is and how the airways change shape. AI programs that work with pictures can help with both diagnosis and planning treatment. Quantitative CT analyses yield dependable outcomes for patient selection appropriate for bronchoscopic lung volume reduction (BLVR) and the evaluation of collateral ventilation. Also, it has been shown that AI-assisted analyses can help find more patients who are good candidates for interventional treatments (63).

The use of artificial intelligence in asthma and COPD has led to major improvements in diagnosis, phenotype identification, and clinical prediction. Models that use electronic health records and natural language processing have become more accurate, especially when it comes to diagnosing asthma. Models that use biomarkers, capnography, and respiratory sound analyses together also look promising for non-invasive diagnosis. Machine learning techniques have facilitated the delineation of asthma phenotypes and the formulation of individualized treatment strategies. These strategies have also helped figure out how likely it is that someone will have an asthma attack or need to go to the hospital. In the field of COPD, artificial intelligence applications focus on diagnostic support, phenotype classification and prognosis prediction. Models that analyse clinical data and functional parameters together have demonstrated high diagnostic accuracy. Furthermore, it is noted that respiratory sound analysis and telemedicine-based systems hold significant potential, particularly in regions with limited resources (64). Machine learning-based approaches are also used to identify COPD phenotypes and predict disease progression. Furthermore, they have emerged as effective tools for predicting the risk of hospital readmission, exacerbations and mortality. Artificial intelligence and machine learning methods offer significant opportunities in the management of asthma and COPD. However, as most current studies are based on limited datasets, the integration of these models into clinical practice requires larger, multicentre studies (65).

2.7. Artificial Intelligence in Pulmonary Embolism

Pulmonary embolism (PE) is a life-threatening cardiovascular emergency characterised by thromboembolic obstruction of the pulmonary arteries; it is associated with high morbidity and mortality if diagnosis is delayed. Although computed tomography pulmonary angiography (CTPA) is the gold standard for diagnosis, interpreting this method requires significant expertise, is time-consuming, and cases have been reported to be missed at

clinically significant levels due to perceptual or cognitive errors. Current data indeed show that a large number of PE cases are first missed or misdiagnosed, which leads to bad clinical outcomes. Artificial intelligence (AI), especially machine learning and deep learning techniques, has become a promising way to make diagnosing pulmonary embolism more accurate and faster. People use CNNs, or convolutional neural networks, to see pictures. CT angiography (CTA) and other imaging methods can find very small signs of embolisms with a lot of accuracy. This makes it easier for different people to figure out what's wrong and makes the diagnoses more accurate. AI systems today can also quickly look at a lot of photos. This makes it easier for busy hospitals to quickly sort and rank patients. AI can help find pulmonary embolisms, tell you how big they are, and guess what will happen next. By automatically analysing thrombus burden, clot volume and distribution, significant clinical outcomes can be obtained in determining disease severity and haemodynamic risk. Additionally, it is stated that these approaches are more successful than conventional clinical scoring methods in detecting patients at high risk. Meta-analysis results show that AI-based systems demonstrate substantial diagnostic efficacy in the diagnosis of lung diseases. Sensitivity and specificity were found to be approximately 0.91 and 0.94, respectively, whilst the area under the curve (AUC) values were shown to be around 0.95. Despite the strong performance of artificial intelligence systems, it is also known that they have certain limitations in terms of generalisability (66).

Artificial intelligence demonstrates significant potential in the diagnosis of pulmonary embolism, particularly in imaging-based analyses, where it achieves high accuracy rates. Thanks to deep learning and multimodal approaches, the detection of embolism, risk stratification and clinical decision-making processes are becoming more effective. Future multicentre studies based on real-world data will accelerate the integration of artificial intelligence into routine clinical practice for the management of pulmonary embolism.

2.8. Artificial Intelligence in Sleep Medicine

Obstructive sleep apnea syndrome (OSAS) is a condition that is frequently seen in adults and is related to many health problems and deaths, particularly those related to heart disease. Obstructive sleep apnea syndrome (OSAS) is a critical public health issue that necessitates early diagnosis and effective monitoring due to its prevalence and significant cardiometabolic consequences. Polysomnography (PSG), the gold standard method for diagnosing OSAS, is not suitable for large-scale screening due to its high cost and the need for overnight monitoring in a sleep laboratory. You can do sleep tests at home, but they might not be very accurate and it's still hard to get to them. Because of this, many people with OSAS, especially those over 40, don't get diagnosed. Recently, artificial intelligence (AI) and machine learning (ML) methods have achieved significant advancements in the diagnosis and screening of OSAS. These technologies aim to overcome the limitations of traditional methods by leveraging their ability to analyze complex patterns within large datasets (67,68).

AI-based algorithms can use polysomnography data to determine when a person experiences apnea or hypopnea. There are two main types of AI applications. The first

method involves the analysis of biosignals. By examining physiological parameters such as electrocardiography (ECG), photoplethysmography (PPG), peripheral oxygen saturation (SpO_2), and respiratory sounds, you can assess the severity and prevalence of OSAS. This strategy lets you keep an eye on things without having to touch the devices when they're portable. The second strategy is to use clinical and demographic data to make predictions. Very accurate risk prediction models use anthropometric measurements like age, gender, body mass index, and neck circumference, as well as symptoms and results from a physical exam. These algorithms have become a useful way to figure out which patients need a polysomnography (PSG) (68).

AI is also very useful for managing and monitoring patients from a distance. AI-powered telemonitoring systems can check how well patients are following their treatment, find out if it's not working early on, and give personalized feedback that makes patients more involved, especially for people who are getting continuous positive airway pressure (CPAP) therapy. This method makes it easier to get health care and is a better long-term solution than face-to-face follow-up methods. AI-based digital health solutions are also changing the idea of virtual sleep labs, and the shift to patient-centered care models is happening more quickly (67).

Even with all of these changes, there are still problems that need to be fixed. For example, it is still not possible to standardize data for use in clinical practice with AI-based systems. The model functions variably across groups, and insufficient studies exist to assess its efficacy prospectively. Ethics, data security, and clinical responsibility are other important things that affect how widely these technologies are used. Artificial intelligence and machine learning can be very helpful, though, in making cheap and easy-to-use screening tools for finding and diagnosing OSAS. Multicenter studies utilizing larger datasets will enhance the reliability of these systems in clinical environments, facilitating their broader adoption in the future.

2.9. Artificial Intelligence in Interstitial Lung Diseases

Interstitial lung diseases (ILD) constitute a broad group of conditions characterised by heterogeneous features in terms of pathophysiology, clinical presentation and prognosis. Diagnosis requires invasive procedures or the interpretation of high-resolution imaging. High-resolution computed tomography (HRCT) is the primary imaging method used in the assessment of ILD. The complexity of the diagnostic process in this group of diseases, combined with a limited number of specialists, can lead to delays in reaching an accurate diagnosis. Artificial intelligence (AI) and machine learning (ML) techniques have begun to be used as important support tools in the diagnosis and assessment of interstitial lung disease (ILD). AI algorithms can recognise UIP and NSIP patterns in CT images. High accuracy rates have been reported in the classification of these patterns. An AI algorithm created using clinical history data from a US national database accurately identified ILD, showing that AI could be used to predict ILD diagnosis. Furthermore, a multimodal approach combining CT and histopathological images to improve pathologists' diagnostic accuracy has also been investigated. Machine learning, and deep learning algorithms in particular, enable

the automatic identification of disease-specific patterns in HRCT images. Pawar and Talbar classified six different ILD patterns with 89.39% accuracy by subjecting HRCT images to segmentation followed by classification. Another study developed a deep learning model to classify HRCT images into categories such as healthy tissue, ground-glass opacity, emphysema, fibrosis, and micronodules. Model got an accuracy rate of over 0.96 (69). Artificial intelligence applications are used not only for the diagnosis of ILD but also to determine disease severity and prognosis. In particular, biomarkers derived from imaging data have been linked to disease progression in interstitial lung diseases. The large imaging datasets generated during the COVID-19 pandemic have accelerated the development of artificial intelligence algorithms. Algorithms developed during this period have begun to be used not only for COVID-19 assessment but also for the detection of interstitial lung abnormalities. This has contributed to strengthening the quality and diversity of data in AI research within the field of ILD. In the future, it is expected that combining different types of data will lead to stronger models that can be used in clinical settings (70). As a result, artificial intelligence systems have a lot of promise for diagnosing and treating ILD, and they are on their way to becoming an important part of clinical decision-support systems.

2.10. Artificial Intelligence in Interventional Pulmonology

Artificial intelligence is also becoming more important in diagnosing lung diseases that need invasive procedures. This shows that interventional pulmonology has made a lot of progress. Most AI applications in this field utilise computer vision (CV) AI, which is supported by deep learning (DL) and machine learning (ML) and interacts with other areas of AI. AI algorithms developed for CT, PET, X-ray, airway segmentation and pathology interpretation, as well as AI models that predict patient outcomes, complications and disease progression, are utilised in this field, particularly in areas such as robot-assisted bronchoscopy, airway assessment, stent placement and EBUS guidance. Furthermore, it plays significant roles in areas such as AI-assisted planning, documentation and reporting (63).

Artificial intelligence has made significant advances in the field of bronchoscopy by improving anatomical identification, peripheral navigation and the prediction of benign and malignant conditions in lymph nodes. It has been developed specifically to accurately identify and label bronchial segments from intraluminal bronchial images. These models have been very helpful in finding the right location in the very complicated bronchial tree because they can tell the difference between anatomical areas like the carina and main bronchus with great accuracy. In robotic bronchoscopy, the accurate identification of bronchial segments from intraluminal bronchial images has been of great importance. Artificial intelligence has been integrated with shape-sensing technologies, such as fibre-Bragg grating (FBG) catheters, to improve the navigation of instruments to peripheral lung regions. The AIrShape software has enabled precise access to peripheral airways by positioning the catheter along the airway centre lines, eliminating the need for radiation or electromagnetic navigation. It can also help with endobronchial ultrasound (EBUS) procedures by analyzing images to find lymph nodes and better guide transbronchial needle aspirations (TBNA). Artificial in-

telligence can help with the evaluation of cytology samples by letting you quickly check the quality of a sample on-site (ROSE). It is also important to make sure that resources are used wisely and that paperwork is done correctly when looking for people who might be good candidates for procedures like bronchoscopic lung volume reduction. This will help the workflow. At the same time, AI-supported tools are being researched in Oncology and Radiology to predict cancer-related outcomes and complications (71,72).

Artificial intelligence has also demonstrated significant benefits in analysing EBUS images to distinguish between benign and malignant (non-small cell carcinoma) targets in malignancies, with high accuracy, specificity and positive predictive value. In various studies, prospectively recorded B-mode images of mediastinal lymph nodes obtained during EBUS-TBNA were compared with pathology results from lymph node biopsies and/or surgical specimens; and in another study using a similar dataset, high specificity and diagnostic accuracy were demonstrated in predicting lymph node metastasis. It has also been demonstrated that certain artificial intelligence-based systems can contribute to the classification of lymph nodes as benign or malignant by analysing elastography features (73).

When it comes to finding pleural effusion, artificial intelligence systems are very good at diagnosing it. The values for the receiver operating characteristic (ROC) curve for chest X-ray images in emergency rooms and primary care settings are usually between 0.94 and 0.99. Commercial AI tools can detect pleural effusion with a sensitivity range of 62% to 95%, and their negative predictive values are always above 92%. This means that they are very good at ruling out the possibility of effusion. AI usually does about the same as or slightly worse than radiologists who are experts. This is especially true for small or unclear effusions, which make sensitivity go down. AI can identify and sort pleural effusions in CT scans with a very high level of accuracy (99% sensitivity and 98% specificity). A deep learning model was also used to distinguish between cancerous and non-cancerous pleural effusions. This model is 89.4% accurate and 65.1% accurate. Data regarding AI studies on the identification of pleural effusions using lung ultrasound (LUS) are limited to smaller datasets. In one study, a LUS dataset comprising 623 videos containing 99,209 two-dimensional images was analysed. The video-based annotation approach achieved an average accuracy of 91.12% on the test set, whilst the frame-based annotation approach achieved an accuracy of 92.38% when compared against expert clinician reference (74,75).

Artificial intelligence can help with interventional pulmonology, but more research is needed to make sure it is safe to use in everyday clinical practice.

3. Results

AI-powered systems can make diagnosing and treating lung diseases much more accurate when used in multimodal approaches that combine clinical evaluations, radiological images, and pathological findings. AI apps are becoming more common and useful in many areas of respiratory medicine, especially medical imaging, thanks to better algorithms and more data sources.

Nonetheless, the integration of AI into clinical practice still faces significant challenges. The main problems with this process are that the datasets we have now aren't good enough, the models can't be used on different groups of people, and there are questions about what is right and wrong in terms of ethics and the law. We still need big, well-labeled, and quality-controlled datasets, but it's getting harder to share them because of privacy issues and issues with anonymizing data. Another big problem with using AI in the real world is that it's not clear who would be responsible if something went wrong. To use artificial intelligence safely and effectively in treating respiratory diseases, we need to create a comprehensive set of rules. These rules should cover ethical issues, legal requirements, data management, and the latest technological developments.

The main goal of artificial intelligence is to help doctors improve their clinical skills, which should lead to faster and better-informed decisions. As the population ages, the need for healthcare services increases. Patients can get better faster if doctors can find out what's wrong and treat it faster. Artificial intelligence is becoming more and more important in respiratory medicine, and it is likely that it will be very important in the future of this field. In this case, it's very important to make sure that AI technologies are created in a moral way and that they are used in healthcare systems so that the change will last and be dependable.

4. References

1. Shen, D., Wu, G., & Suk, H. I. (2017). Deep learning in medical image analysis. *Annual Review of Biomedical Engineering, 19*, 221–248. https://doi.org/10.1146/annurev-bioeng-071516-044442
2. Topol, E. J. (2019). High-performance medicine: The convergence of human and artificial intelligence. *Nature Medicine, 25*(1), 44–56. https://doi.org/10.1038/s41591-018-0300-7
3. Özçelik, N., & Selimoğlu, İ. (2021). Artificial intelligence applications in pulmonology and its advantages during the pandemic period. *Tuberkuloz ve Toraks, 69*(3), 380–386.
4. Saad, T., Pandey, R., Padarya, S., Singh, P., Singh, S., & Mishra, N. (2025). Application of artificial intelligence in the interpretation of pulmonary function tests. *Cureus, 17*(4), e82056. https://doi.org/10.7759/cureus.82056
5. Viswanathan, V. S., Toro, P., Corredor, G., Mukhopadhyay, S., & Madabhushi, A. (2022). The state of the art for artificial intelligence in lung digital pathology. *The Journal of Pathology, 257*(4), 413–429. https://doi.org/10.1002/path.59666
6. Kaur, A., Cherukuri, S. P., Handral, M. S., et al. (2025). Artificial intelligence enabled lung sound auscultation in the early diagnosis and subtyping of interstitial lung disease. *Journal of Clinical Medicine, 14*(23), 8500. https://doi.org/10.3390/jcm14238500
7. Hosny, A., Parmar, C., Quackenbush, J., Schwartz, L. H., & Aerts, H. J. W. L. (2018). Artificial intelligence in radiology. *Nature Reviews Cancer, 18*(8), 500–510. https://doi.org/10.1038/s41568-018-0016-5
8. GBD 2019 Chronic Respiratory Diseases Collaborators. (2023). Global burden of chronic respiratory diseases and risk factors, 1990–2019. *EClinicalMedicine, 59*, 101936. https://doi.org/10.1016/j.eclinm.2023.101936
9. McBee, M. P., Awan, O. A., Colucci, A. T., et al. (2018). Deep learning in radiology. *Academic Radiology, 25*(11), 1472–1480. https://doi.org/10.1016/j.acra.2018.02.018
10. Ardila, D., Kiraly, A. P., Bharadwaj, S., et al. (2019). End-to-end lung cancer screening with deep learning. *Nature Medicine, 25*(6), 954–961. https://doi.org/10.1038/s41591-019-0447-x
11. Bi, W. L., Hosny, A., Schabath, M. B., et al. (2019). Artificial intelligence in cancer imaging: Clinical challenges and applications. *CA: A Cancer Journal for Clinicians, 69*(2), 127–157. https://doi.org/10.3322/caac.21552
12. Yamashita, R., Nishio, M., Do, R. K. G., & Togashi, K. (2018). Convolutional neural networks: An overview and application in radiology. *Insights into Imaging, 9*(4), 611–629. https://doi.org/10.1007/s13244-018-0639-9
13. Hwang, E. J., Goo, J. M., & Park, C. M. (2025). AI applications for thoracic imaging: Considerations for best practice. *Radiology, 314*(2), e240650. https://doi.org/10.1148/radiol.240650
14. Anderson, P. G., Tarder-Stoll, H., Alpaslan, M., et al. (2024). Deep learning improves physician accuracy in the comprehensive detection of abnormalities on chest X-rays. *Scientific Reports, 14*(1), 25151. https://doi.org/10.1038/s41598-024-76608-2
15. Zhang, Z., & Seeram, E. (2020). The use of artificial intelligence in computed tomography image reconstruction: A literature review. *Journal of Medical Imaging and Radiation Sciences, 51*(4), 671–677. https://doi.org/10.1016/j.jmir.2020.09.001

16. Klein, J. S., & Rosado-de-Christenson, M. L. (2019). A systematic approach to chest radiographic analysis. In J. Hodler et al. (Eds.), *Diseases of the chest, breast, heart and vessels 2019–2022* (pp. 1–16). Springer. https://doi.org/10.1007/978-3-030-11149-6_1
17. Stec, N., Arje, D., Moody, A. R., Krupinski, E. A., & Tyrrell, P. N. (2018). A systematic review of fatigue in radiology: Is it a problem? *American Journal of Roentgenology, 210*(4), 799–806. https://doi.org/10.2214/AJR.17.18613
18. Griffith, B., Kadom, N., & Straus, C. M. (2019). Radiology education in the 21st century: Threats and opportunities. *Journal of the American College of Radiology, 16*(10), 1482–1487. https://doi.org/10.1016/j.jacr.2019.04.003
19. Erickson, B. J., Korfiatis, P., Akkus, Z., & Kline, T. L. (2017). Machine learning for medical imaging. *Radiographics, 37*(2), 505–515. https://doi.org/10.1148/rg.2017160130
20. Tang, Y. X., Tang, Y. B., Peng, Y., et al. (2020). Automated abnormality classification of chest radiographs. *NPJ Digital Medicine, 3*, 70. https://doi.org/10.1038/s41746-020-0273-z
21. Baltruschat, I. M., Nickisch, H., Grass, M., Knopp, T., & Saalbach, A. (2019). Comparison of deep learning approaches for multi-label chest X-ray classification. *Scientific Reports, 9*, 6381. https://doi.org/10.1038/s41598-019-42294-8
22. Benjamens, S., Dhunnoo, P., & Meskó, B. (2020). The state of AI-based FDA-approved medical devices. *NPJ Digital Medicine, 3*, 118. https://doi.org/10.1038/s41746-020-00324-0
23. Blazar, E., Mitchell, D., & Townzen, J. D. (2020). Radiology training in emergency medicine residency. *Cureus, 12*(1), e6615. https://doi.org/10.7759/cureus.6615
24. Rajpurkar, P., Chen, E., Banerjee, O., & Topol, E. J. (2022). AI in health and medicine. *Nature Medicine, 28*(1), 31–38. https://doi.org/10.1038/s41591-021-01614-0
25. Rajpurkar, P., Irvin, J., Ball, R. L., et al. (2018). Deep learning for chest radiograph diagnosis. *PLoS Medicine, 15*(11), e1002686. https://doi.org/10.1371/journal.pmed.1002686
26. Kamrani, R., Fallahi, M. J., Masoompour, S. M., Ghayumi, S. M. A., Jalli, R., Khederzadeh, S., & Erfani, A. (2022). Evaluation of the appropriate use of chest CT scans in hospitalized patients in Shiraz teaching hospitals, Southern Iran. *Cost Effectiveness and Resource Allocation, 20*(1), 44. https://doi.org/10.1186/s12962-022-003810
27. Vilar-Palop, J., Hernandez-Aguado, I., Pastor-Valero, M., Vilar, J., González-Alvarez, I., & Lumbreras, B. (2018). Appropriate use of medical imaging in two Spanish public hospitals. *BMJ Open, 8*(3), e019535. https://doi.org/10.1136/bmjopen-2017-019535
28. Gohla, G., Örgel, A., Klose, U., Brendlin, A., Bongers, M. N., Bender, B., Staber, D., Ernemann, U., Hauser, T. K., & Ruff, C. (2025). Comparison of ADMIRE, SAFIRE, and filtered back projection in head CT. *Diagnostics, 15*(12), 1541. https://doi.org/10.3390/diagnostics15121541
29. Koetzier, L. R., Mastrodicasa, D., Szczykutowicz, T. P., van der Werf, N. R., Wang, A. S., Sandfort, V., van der Molen, A. J., Fleischmann, D., & Willemink, M. J. (2023). Deep learning image reconstruction for CT: Technical principles and clinical prospects. *Radiology, 306*(3), e221257. https://doi.org/10.1148/radiol.221257
30. Greffier, J., Hamard, A., Pereira, F., Barrau, C., Pasquier, H., Beregi, J. P., & Frandon, J. (2020). Image quality and dose reduction using deep learning reconstruction. *European Radiology, 30*(7), 3951–3959. https://doi.org/10.1007/s00330-020-06724-w
31. Pinsky, P. F., Gierada, D. S., Nath, P. H., Kazerooni, E., & Amorosa, J. (2013). Variability in nodule detection rates in CT studies. *Radiology, 268*(3), 865–873. https://doi.org/10.1148/radiol.13121530
32. Gu, Y., Chi, J., Liu, J., Yang, L., Zhang, B., Yu, D., Zhao, Y., & Lu, X. (2021). Deep learning in lung nodule diagnosis. *Computers in Biology and Medicine, 137*, 104806. https://doi.org/10.1016/j.compbiomed.2021.104806
33. Al Mohammad, B., Hillis, S. L., Reed, W., Alakhras, M., & Brennan, P. C. (2019). Radiologist performance in lung cancer detection. *Clinical Radiology, 74*(1), 67–75. https://doi.org/10.1016/j.crad.2018.10.008
34. Takeshita, Y., Onozawa, S., Katase, S., et al. (2024). AI U-net algorithm for pulmonary nodule tracking. *Journal of International Medical Research, 52*(2), 3000605.
35. National Lung Screening Trial Research Team. (2011). Reduced lung cancer mortality with low-dose CT screening. *New England Journal of Medicine, 365*(5), 395–409. https://doi.org/10.1056/NEJM
36. Venkadesh, K. V., Setio, A. A. A., Schreuder, A., et al. (2021). Deep learning for malignancy risk estimation. *Radiology, 300*(2), 438–447. https://doi.org/10.1148/radiol.2021204433
37. Wu, F. Z., Wu, Y. J., Chen, C. S., & Tang, E. K. (2023). Prediction of lung adenocarcinoma growth using radiomics. *Academic Radiology, 30*(12), 2856–2869. https://doi.org/10.1016/j.acra.2023.02.033
38. Chassagnon, G., Vakalopoulou, M., Paragios, N., & Revel, M. P. (2020). AI applications for thoracic imaging. *European Journal of Radiology, 123*, 108774. https://doi.org/10.1016/j.ejrad.2019.108774
39. Walsh, S. L. F., Calandriello, L., Silva, M., & Sverzellati, N. (2018). Deep learning for fibrotic lung disease classification. *The Lancet Respiratory Medicine, 6*(11), 837–845. https://doi.org/10.1016/S2213-2600(18)30286-8
40. Chen, L., Lan, X., Huang, Y., et al. (2025). Radiomics models for lung cancer spread prediction. *European Journal of Radiology, 190*, 112249. https://doi.org/10.1016/j.ejrad.2025.112249
41. Avanzo, M., Stancanello, J., Pirrone, G., & Sartor, G. (2020). Radiomics and deep learning in lung cancer. *Strahlentherapie und Onkologie, 196*(10), 879–887. https://doi.org/10.1007/s00066-020-01625-9
42. Selvam, M., Chandrasekharan, A., Sadanandan, A., et al. (2023). Radiomics in lung nodule differentiation. *Scientific Reports, 13*, 19062. https://doi.org/10.1038/s41598-023-46391-7
43. Ladbury, C., Amini, A., Govindarajan, A., et al. (2023). AI integration in lung cancer. *Cell Reports Medicine, 4*(2), 100933. https://doi.org/10.1016/j.xcrm.2023.100933

44. Mulvany, T., Griffiths-King, D., Crombie, K., Novak, J., & Apps, J. R. (2025). What is radiomics? *Archives of Disease in Childhood, edpract-2024-328347*. https://doi.org/10.1136/archdischild-2024-328347
45. Wang, S., Tan, X., Li, P., et al. (2023). AI differentiation of pleural effusions. *Thorax, 78*(4), 376–382. https://doi.org/10.1136/thorax-2021-218581
46. Han, Y., Ma, Y., Wu, Z., et al. (2021). NSCLC subtype classification using PET/CT. *European Journal of Nuclear Medicine and Molecular Imaging, 48*(2), 350–360. https://doi.org/10.1007/s00259-020-04771-5
47. Rossi, G., Barabino, E., Fedeli, A., et al. (2021). Radiomic detection of EGFR mutations. *Cancer Research, 81*(3), 724–731. https://doi.org/10.1158/0008-5472.CAN-20-0999
48. Lin, J., Yan, Z., He, L., Zhang, H., & Xie, M. (2025). Radiogenomics-based mutation prediction. *Journal of Central South University Medical Sciences, 50*(5), 805–814.
49. Chen, M., Lu, H., Copley, S. J., et al. (2023). Radiogenomics biomarker for immunotherapy response. *Journal of Thoracic Oncology, 18*(6), 718–730. https://doi.org/10.1016/j.jtho.2023.01.089
50. Lu, T., Zhang, Z., Zhu, J., et al. (2021). Deep learning for T-cell receptor prediction. *Nature Machine Intelligence, 3*(10), 864–875. https://doi.org/10.1038/s42256-021-00383-2
51. Li, L., Qin, L., Xu, Z., et al. (2020). AI detection of COVID-19 using CT. *Radiology, 296*(2), E65–E71. https://doi.org/10.1148/radiol.2020200905
52. Mei, X., Lee, H. C., Diao, K. Y., et al. (2020). AI-enabled rapid COVID-19 diagnosis. *Nature Medicine, 26*(8), 1224–1228. https://doi.org/10.1038/s41591-020-0931-3
53. Setio, A. A., Ciompi, F., Litjens, G., et al. (2016). Pulmonary nodule detection using CNNs. *IEEE Transactions on Medical Imaging, 35*(5), 1160–1169. https://doi.org/10.1109/TMI.2016.2536809
54. Wang, W., Zhao, X., Jia, Y., & Xu, J. (2024). AI in CT recognition of infectious diseases. *PLOS ONE, 19*(2), e0297578. https://doi.org/10.1371/journal.pone.0297578
55. Hanson, K., Brikci, N., Erlangga, D., et al. (2022). Financing primary health care. *The Lancet Global Health, 10*(5), e715–e772. https://doi.org/10.1016/S2214-109X(22)00005-5
56. Mapari, R. B., Tamboli, A. I., Tamhan, P., et al. (2025). Multimodal AI for tuberculosis detection. *Indian Journal of Tuberculosis, 72*(Suppl 3), S92–S98. https://doi.org/10.1016/j.ijtb.2025.11.012
57. Rahman, M. S., Safa, N. T., Sultana, S., et al. (2022). AI-IoT in infectious diseases. *Parasite Epidemiology and Control, 18*, e00266. https://doi.org/10.1016/j.parepi.2022.e00266
58. Ponce, M. C., Sankari, A., & Sharma, S. (2023). Pulmonary function tests. In *StatPearls*. StatPearls Publishing.
59. Topalovic, M., Das, N., Burgel, P. R., et al. (2019). AI interpretation of pulmonary function tests. *European Respiratory Journal, 53*(4), 1801660. https://doi.org/10.1183/13993003.01660-2018
60. Kim, Y., Hyon, Y., Jung, S. S., et al. (2021). Respiratory sound classification using deep learning. *Scientific Reports, 11*, 17186. https://doi.org/10.1038/s41598-021-96724-7
61. Engin, M. A., Uzun Arslan, R., Senyer Yapici, İ., et al. (2026). Deep learning-based classification of lung sounds. *Bioengineering, 13*(2), 170. https://doi.org/10.3390/bioengineering13020170
62. Papavassiliou, K. A., Sofianidi, A. A., & Papavassiliou, A. G. (2026). Diagnosis of lung diseases in the AI era. *International Journal of Molecular Sciences, 27*(4), 1796. https://doi.org/10.3390/ijms27041796
63. Kornafeld, A., Little, G., & Frye, L. (2025). AI in interventional pulmonology. *Journal of Bronchology & Interventional Pulmonology, 33*(1), e01051. https://doi.org/10.1097/LBR.0000000000001051
64. Feng, Y., Wang, Y., Zeng, C., & Mao, H. (2021). AI in chronic airway diseases. *International Journal of Medical Sciences, 18*(13), 2871–2889. https://doi.org/10.7150/ijms.58191
65. Mlodzinski, E., Stone, D. J., & Celi, L. A. (2020). Machine learning in pulmonary medicine. *Pulmonary Therapy, 6*(1), 67–77. https://doi.org/10.1007/s41030-020-00110-z
66. Farzaei, A., Hajzeinolabedini, F., Sharif Kashani, B., et al. (2025). AI in pulmonary embolism diagnosis. *Archives of Academic Emergency Medicine, 13*(1), e86. https://doi.org/10.22037/aaem.v13i1.2720
67. Bailly, S., Mendelson, M., Baillieul, S., Tamisier, R., & Pépin, J. L. (2024). Telemedicine in OSAS. *Journal of Clinical Medicine, 13*(9), 2700. https://doi.org/10.3390/jcm13092700
68. Aiyer, I., Shaik, L., Sheta, A., & Surani, S. (2022). Machine learning in OSAS diagnosis. *Medicina, 58*(11), 1574. https://doi.org/10.3390/medicina58111574
69. Exarchos, K. P., Gkrepi, G., Kostikas, K., & Gogali, A. (2023). AI in interstitial lung diseases. *Diagnostics, 13*(13), 2303. https://doi.org/10.3390/diagnostics13132303
70. Wijsenbeek, M., Suzuki, A., & Maher, T. M. (2022). Interstitial lung diseases. *The Lancet, 400*(10354), 769–786. https://doi.org/10.1016/S0140-6736(22)01052-2
71. Yoo, J. Y., Kang, S. Y., Park, J. S., et al. (2021). Deep learning for bronchoscopy interpretation. *Scientific Reports, 11*, 23765. https://doi.org/10.1038/s41598-021-03219-6
72. Gruionu, L. G., Udriștoiu, A. L., Iacob, A. V., et al. (2022). AI-based lung airway navigation system. *PLOS ONE, 17*(12), e0277938. https://doi.org/10.1371/journal.pone.0277938
73. Zhi, X., Li, J., Chen, J., et al. (2021). Machine learning in EBUS elastography. *Frontiers in Oncology, 11*, 673775. https://doi.org/10.3389/fonc.2021.673775
74. Sexauer, R., Yang, S., Weikert, T., et al. (2022). AI detection of pleural effusion. *Investigative Radiology, 57*(8), 552–559. https://doi.org/10.1097/RLI.0000000000000869
75. Tsai, C. H., van der Burgt, J., Vukovic, D., et al. (2021). Deep learning-based pleural effusion classification. *Physica Medica, 83*, 38–45. https://doi.org/10.1016/j.ejmp.2021.02.023

CHAPTER 29

Artificial Intelligence in Intensive Care: The Role of Clinical Decision Support Systems

MD. Gozde Ak

1. Artificial Intelligence in Intensive Care: The Role of Clinical Decision Support Systems

1.1. Introduction

Intensive care units are environments equipped with advanced and complex technological infrastructure where critically ill patients, often those with multiple organ failure, are monitored. In intensive care units, many healthcare professionals work together, primarily doctors and nurses. With advancements in technology and the widespread availability of medical equipment, many invasive and non-invasive procedures are being performed for patient monitoring and treatment.

Intensive care units, which account for a large share of healthcare spending, face immense pressure to improve the efficiency of patient care. Therefore, the digitalization of the healthcare system in our country, as in other countries, began in intensive care units. Table 1 below presents data recorded in intensive care units.

Table 1: Data recorded from intensive care units

Data recorded from intensive care units
Demographic data
Electronic patient tracking and treatment records
Disease severity scores
Mortality prediction scales
Consciousness monitoring scales
Laboratory results
Diagnostic imaging
Notes on surgical procedures
Bedside monitor recordings
Mechanical ventilation recordings
Data recorded by other organ support devices (RRT, ECMO, etc.)

As can be seen, intensive care units generate large amounts of data, and, given the number of patients, they form large sample groups. Even today, this data is still mostly evaluated by clinicians during intensive care unit visits. Given the sheer volume of data, it is clear that AI-powered decision support systems are needed in this field.

1.2. Clinical Decision Support Systems (CDSS)

Artificial intelligence is the intelligence of a computer or computer-controlled robot to perform tasks typically associated with intelligent beings; where machines go beyond normal information processing by adding features such as learning, sound reasoning, and weighting of inputs (1). Machine learning, sometimes also called data-driven learning, uses statistical models and computational technologies to enable computer systems to learn from patient data and discover unknown clinical conditions. Supervised learning, unsupervised learning, and reinforcement learning are three main types of machine learning used to predict or guide treatment for critically ill patients (2). These types of machine learning have great potential in intensive care for establishing protocols, identifying patient subgroups, and recommending personalized treatment plans, respectively (3).

Clinical decision support systems (CDSS) are computer programs designed to influence healthcare providers at the time decisions are made (4). The integration of machine learning-based artificial intelligence applications into CDSS has broadened their applications. Once used solely for diagnostic purposes, these systems now assist clinicians in areas such as data interpretation, outcome prediction, prevention of adverse drug interactions, optimization of ventilation support (5), and antibiotic selection (6).

CDSs typically involve data collection, data summarization, and the proposal of an appropriate course of action (7). CDSs used in intensive care units should be designed to improve outcomes by providing real-time decision support for critically ill patients, reducing medical errors, and minimizing life-threatening events caused by delayed or erroneous decisions. For optimal medical decision-making, CDSSs need to be data-driven, fast, and informative. Evidence shows that CDSSs can improve physician decision-making performance (8). A CDS's knowledge base should be derived from the most current evidence in the scientific literature and application-based sources, and this knowledge should be continuously updated. In the literature, CDSSs used in intensive care units are used to predict ICU mortality (9), estimate length of stay in the ICU (10), determine neurological survival (11), and predict organ failure (12). In commonly used CDSSs of this type, the prevalent rule is the IF-THEN rule. This rule means that if a prerequisite (i.e., a set of conditions) exists, THEN an outcome is expected or an action should be taken (13). These CDSSs provide statistical results rather than aiding in decision-making. Clinicians need to make informed decisions by recalling all relevant information in a timely manner and reviewing current literature based on these statistics. In the intensive care environment, where time is of the essence, this decision support process is insufficient. Therefore, a reliable CDSS in an intensive care unit should not only provide statistically meaningful information but also offer an interactive and flexible user interface that allows clinicians to search for evidence effectively and in real time.

A robust CDS should have a sufficiently large database, and sample sizes should be large enough to allow for clinical inferences (14). CDSs require large amounts of patient data to accurately identify each patient; they need large sample sizes to observe patient groups with similar characteristics and make treatment recommendations; and they allow for the rapid processing of many findings with high data throughput. CDSSs should not only be software for handling large amounts of data, but also be usable to process highly accurate signals in real time and extract reduced-size information that can be integrated and interpreted by clinicians to make better medical decisions (15).

Various types of CDSS (Credit Sense System) have been developed; these are generally classified by their implementation methods or development purposes. Examples of the first type include portable, web-based, and electronic health record (EHR)-based CDSSs (16). Based on their development purposes, CDSs can be grouped as follows: those used for monitoring, detection, and diagnosis; those used for early diagnosis and prediction of clinical events; those used for prognostic evaluation; and those used to guide treatment decisions (3).

1.3. Current CDSS Status in Intensive Care

CDSSs have been most frequently studied in the context of sepsis in intensive care units. Sepsis is a significant cause of admission and mortality in ICUs. CDSSs have primarily focused on sepsis detection in ICUs. According to the results of a validation study of machine learning-based software developed in Sweden in 2024, the software was shown to predict sepsis development with high performance three hours before the onset of sepsis. The study included 304 ICU patients, randomized into a standard care group and an algorithm group. Accuracy, sensitivity, and specificity values (including COVID-19 patients) were all found to be higher in the standard care group compared to the algorithm group (17).

In another randomized study of 407 patients conducted by Semler et al. in 2015, another software used, Surviving Sepsis Campaign 6-hour Sepsis Resuscitation Bundle, showed no difference in compliance, ICU mortality, ICU-free days, and ventilator-free days between groups. However, it was found to be used by healthcare professionals in only 28% of cases. According to the study results, the software was found to be reliable in sepsis assessment and management, but user compliance was low; only 28% used the tool to place orders(18).

Another study using a machine learning-based algorithm to monitor patients with sepsis found a 12.4% reduction in in-hospital mortality. Significant improvements were observed in patient outcomes, with significant differences in hospital stay duration and in-hospital mortality rate (19).

In a study published by Eshelman et al., a CDSS developed to predict hemodynamic instability was retrospectively evaluated using healthcare records and found to have 90% specificity and 60% sensitivity (20). In another study of a machine learning-based CDSS adapted to nurse observation forms and operating with an early warning system logic, 60,893 randomized patients showed a 35.6% reduction in the risk of death, an 11.2% re-

duction in the length of hospital stay, and a 7.5% reduction in the immediate risk of sepsis. The risk of patient deterioration was found to be statistically significantly reduced (21).

Studies on CDSSs that predict the risk of developing acute renal failure (22), which increases mortality and morbidity in patients in intensive care, and on CDSSs that can be used to reduce the risk of delirium; and studies on CDSSs that attempt to detect epilepsy and brain damage based on electroencephalographic wave analysis are available in the literature (23).

39-40% of ICU patients require ventilators. The success rate of ventilator weaning decisions made by physicians ranges from only 35-60%. In a study comparing 380 randomly randomized patients, CDSS (Chronic Sensitivity Testing) was found to have significantly higher weaning success rates compared to the classical method. Furthermore, the number of days weaned from mechanical ventilation was significantly shorter. CDSS was shown to be effective in determining the earliest time for weaning to allow patients to return to and maintain spontaneous breathing, thus preventing unnecessary prolonged ventilator use and reducing healthcare costs(24).

A prospective, randomized pilot study compared the duration of norepinephrine discontinuation using CDSS with manual clinician control in patients with septic shock. The median duration of shock was significantly shorter in the CDSS group compared to the control group; the median amount of total norepinephrine administered during shock was also significantly lower in the CDSS group compared to the control group. No significant difference was found between the two groups in terms of mechanical ventilation duration or 28-day survival (25).

Almost all patients monitored in intensive care are using more than two medications. Drug interactions can be harmful to patients in intensive care. In the Netherlands, the use of a customized CDSS that provides warnings only for potential drug interactions deemed high-risk has resulted in a 12% reduction in the number of high-risk drug combinations(26).

A review of the literature reveals many studies similar to those mentioned above. It appears that using novel algorithms to solve clinical problems in intensive care units, and developing reinforcement learning, active learning, and time series analysis methods for clinical decision support systems, will offer greater development potential in the future. While the application of CDSSs to intensive care is currently limited, it seems likely to become a part of routine clinical monitoring in the future.

1.4. Obstacles to Using CDSS

Many AI-powered decision support systems are continuously being developed and rely on various databases. It is crucial to closely monitor which of these have passed the necessary validations. The use and patent policies for AI and machine learning algorithms, including an authorization process for medical devices before their widespread adoption as CDSS (Critical, Technical, and Social Security Systems), should be openly and internationally regulated. This should not widen the gap between countries lacking infrastructure and

equipment and others, nor should it undermine the sense of fairness in healthcare delivery. Furthermore, data privacy must be carefully considered when sharing health records and patient data with CDSS systems, and legal regulations should be established to avoid legal issues in this area.

Data quality is a fundamental requirement for creating accurate and reliable AI algorithms. The GIGO rule (garbage in, garbage out) must be carefully considered, especially when working with advanced computational models(27). Careful data entry is necessary to eliminate language problems in medical records. Furthermore, the entry and verification of this data should not place an additional burden on the intensive care team.

Clinicians should receive training in the active use of intensive care unit records and CDSS, and pursue certification if deemed necessary. Studies highlight the need for explainable AI models, comprehensive training, stakeholder engagement, and human-centered design to increase healthcare professionals' trust in AI-powered clinical decision support systems (AI-CDSS) (28).

Engineers working on CDSS should consider these aspects when designing their programs and thoroughly analyze field problems to identify healthcare professionals' needs. The inherent "black box" nature of CDSS makes it difficult for the medical community to gain its credibility and acceptance. Providing information on how the algorithms work and transparent operating principles could increase clinicians' trust in these algorithms.

AI-powered CDSSs (Clinical Health and Safety Systems) are becoming permanent fixtures. CDSSs will alleviate clinical burden, accelerate decision-making, and contribute to clinician and patient education. With their complex technological infrastructure and rapid development, CDSSs will reshape healthcare delivery. However, they also bring many ethical and legal problems. These issues must be addressed in a timely manner, and necessary regulations must be implemented.

2. References

1. Datta, R., & Singh, S. (2021). Artificial intelligence in critical care: Its about time!. *medical journal armed forces india*, *77*(3), 266-275.
2. Pierre Lison. An introduction to machine learning. Language Technology Group (LTG) 2015. [2022-02-03]
3. Hong, N., Liu, C., Gao, J., Han, L., Chang, F., Gong, M., & Su, L. (2022). State of the art of machine learning–enabled clinical decision support in intensive care units: literature review. *JMIR medical informatics*, *10*(3), e28781.
4. Berner, E. S., & McGowan, J. J. (2010). Use of diagnostic decision support systems in medical education. *Methods of information in medicine*, *49*(04), 412-417.
5. Randolph, A. G., Clemmer, T. P., East, T. D., Kinder, A. T., Orme, J. F., Wallace, C. J., & Morris, A. H. (1998). Evaluation of compliance with a computerized protocol: weaning from mechanical ventilator support using pressure support. *Computer methods and programs in biomedicine*, *57*(3), 201-215.
6. Mullett, C. J., Evans, R. S., Christenson, J. C., & Dean, J. M. (2001). Development and impact of a computerized pediatric antiinfective decision support program. *Pediatrics*, *108*(4), e75-e75.
7. Goertzel, G. (1969). Clinical decision support system. *Annals of the New York Academy of Sciences*, *161*(2), 689-693.
8. Wyatt, J., & Spiegelhalter, D. (1991). Field trials of medical decision-aids: potential problems and solutions. In *Proceedings of the annual symposium on computer application in medical care* (p. 3).
9. Knaus, W. A., Draper, E. A., Wagner, D. P., & Zimmerman, J. E. (1985). APACHE II: a severity of disease classification system. *Critical care medicine*, *13*(10), 818-829.
10. Verduijn, M., Peek, N., Voorbraak, F., de Jonge, E., & de Mol, B. (2005, July). Dichotomization of ICU length of stay based on model calibration. In *Conference on Artificial Intelligence in Medicine in Europe* (pp. 67-76). Berlin, Heidelberg: Springer Berlin Heidelberg.

11. Teasdale, G., & Jennett, B. (1974). Assessment of coma and impaired consciousness: a practical scale. *The lancet*, *304*(7872), 81-84.
12. Ferreira, F. L., Bota, D. P., Bross, A., Mélot, C., & Vincent, J. L. (2001). Serial evaluation of the SOFA score to predict outcome in critically ill patients. *Jama*, *286*(14), 1754-1758.
13. Cheng, C. W., Chanani, N., Venugopalan, J., Maher, K., & Wang, M. D. (2013). icuARM-An ICU clinical decision support system using association rule mining. *IEEE Journal of Translational Engineering in Health and Medicine*, *1*, 4400110-4400110.
14. Ramon, J., Fierens, D., Güiza, F., Meyfroidt, G., Blockeel, H., Bruynooghe, M., & Van Den Berghe, G. (2007). Mining data from intensive care patients. *Advanced Engineering Informatics*, *21*(3), 243-256.
15. Pirracchio, R., Cohen, M. J., Malenica, I., Cohen, J., Chambaz, A., Cannesson, M., ... & ACTERREA Research Group. (2019). Big data and targeted machine learning in action to assist medical decision in the ICU. *Anaesthesia Critical Care & Pain Medicine*, *38*(4), 377-384.
16. Tegtmeyer, K. (2008). The pediatric intensive care unit of the future: Technological advances in pediatric critical care medicine. *Science and Practice of Pediatric Critical Care Medicine*, 1-7.
17. Persson, I., Macura, A., Becedas, D., & Sjövall, F. (2024). Early prediction of sepsis in intensive care patients using the machine learning algorithm NAVOY® Sepsis, a prospective randomized clinical validation study. *Journal of critical care*, *80*, 154400.
18. Semler, M. W., Weavind, L., Hooper, M. H., Rice, T. W., Gowda, S. S., Nadas, A., ... & Wheeler, A. P. (2015). An electronic tool for the evaluation and treatment of sepsis in the ICU: a randomized controlled trial. *Critical care medicine*, *43*(8), 1595-1602.
19. Shimabukuro, D. W., Barton, C. W., Feldman, M. D., Mataraso, S. J., & Das, R. (2017). Effect of a machine learning-based severe sepsis prediction algorithm on patient survival and hospital length of stay: a randomised clinical trial. *BMJ open respiratory research*, *4*(1).
20. Eshelman, L. J., Lee, K. P., Frassica, J. J., Zong, W., Nielsen, L., & Saeed, M. (2008). Development and evaluation of predictive alerts for hemodynamic instability in ICU patients. In *AMIA Annual Symposium Proceedings* (Vol. 2008, p. 379).
21. Rossetti, S. C., Dykes, P. C., Knaplund, C., Cho, S., Withall, J., Lowenthal, G., ... & Cato, K. D. (2025). Real-time surveillance system for patient deterioration: a pragmatic cluster-randomized controlled trial. *Nature Medicine*, *31*(6), 1895-1902.
22. Sun, M., Baron, J., Dighe, A., Szolovits, P., Wunderink, R. G., Isakova, T., & Luo, Y. (2019). Early prediction of acute kidney injury in critical care setting using clinical notes and structured multivariate physiological measurements. *MedInfo*, *264*, 368-72.
23. Sorani, M. D., Hemphill III, J. C., Morabito, D., Rosenthal, G., & Manley, G. T. (2007). New approaches to physiological informatics in neurocritical care. *Neurocritical Care*, *7*(1), 45-52.
24. Hsu, J. C., Chen, Y. F., Chung, W. S., Tan, T. H., Chen, T., & Chiang, J. Y. (2013). Clinical verification of a clinical decision support system for ventilator weaning. *Biomedical engineering online*, *12*(Suppl 1), S4.
25. Merouani, M., Guignard, B., Vincent, F., Borron, S. W., Karoubi, P., Fosse, J. P., ... & Adnet, F. (2008). Norepinephrine weaning in septic shock patients by closed loop control based on fuzzy logic. *Critical Care*, *12*(6), R155.
26. Bakker, T., Klopotowska, J. E., Dongelmans, D. A., Eslami, S., Vermeijden, W. J., Hendriks, S., ... & Duyvendak, M. (2024). The effect of computerised decision support alerts tailored to intensive care on the administration of high-risk drug combinations, and their monitoring: a cluster randomised stepped-wedge trial. *The Lancet*, *403*(10425), 439-449.
27. Bellini, V., Montomoli, J., & Bignami, E. (2021). Poor quality data, privacy, lack of certifications: the lethal triad of new technologies in intensive care. *Intensive Care Medicine*, *47*(9), 1052-1053.
28. Tun, H. M., Rahman, H. A., Naing, L., & Malik, O. A. (2025). Trust in artificial intelligence–based clinical decision support systems among health care workers: systematic review. *Journal of Medical Internet Research*, *27*, e69678.

CHAPTER 30

Cracking Disease Codes: Artificial Intelligence Applications in Medical Genetics

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1. Introduction

Artificial intelligence (AI) has been transformative in many areas of medicine, including medical genetics, in recent years. Driven by increasing computational power and data processing capacity, AI, initially used in engineering and computer science to solve complex problems, is now implemented through hardware and software systems that can emulate aspects of human intelligence. In particular, machine learning (ML) and deep learning (DL) techniques have found strong applications in healthcare due to their ability to extract meaningful patterns from large, complex datasets. Indeed, the FDA-approved diabetic retinopathy detection system in 2018 is considered a clinical milestone in AI (1).

The field of genomics has begun to generate data on an unprecedented scale with high-throughput technologies such as Next-Generation Sequencing (NGS) and single-cell sequencing. These large and complex data structures, which emerged with the transition from Mendelian genetics to multi-omics methods, have challenged the rules of traditional analysis methods; at this point, AI, especially DL through everyday systems, has become an indispensable tool. AI offers powerful solutions in areas such as determining probability ratios, analyzing gene expression, publishing multi-omics datasets, and modeling genotype-phenotype relationships (2,3).

Medical genetics is a particularly suitable field for AI applications due to its characteristics, such as the abundance of rare and heterogeneous diseases, lack of clinical and laboratory staff, diagnostic delays, and high-volume data requirements. Today, AI systems are actively used in many processes such as genetic variant interpretation, phenotype inference, syndrome recognition from facial images, literature review, application of ACMG criteria, and clinical report generation. In particular, "next-generation phenotyping" ap-

proaches and multimodal data integration are providing significant advances in the diagnosis of rare diseases (4,5).

While traditional ML methods are effective on well-defined, labeled datasets, they can be limited in high-dimensional, complex biological data. The development of transformer architectures and the use of attention mechanisms have enabled the modeling of long-range dependencies, providing a significant breakthrough in both natural language processing and genomics. Transformer-based large language models (LLMs) such as BERT and GPT are used in clinical decision support, data analysis, and reporting processes due to their contextual understanding and text-generation capabilities. Vision transformers and generative models (e.g., GANs) have extended this approach to image analysis and data generation. These developments enable more integrated and automated execution of pre-analytical, analytical, and post-analytical processes in the diagnosis of hereditary diseases (6).

The convergence of AI and medical genetics not only enhances diagnostic accuracy but also accelerates the development of predictive and personalized medicine through polygenic risk scores, imaging-genetic applications, and pharmacogenomics. Furthermore, AI plays a significant role in optimizing drug discovery, protein engineering, and genome editing technologies (e.g., CRISPR-Cas9). ML algorithms contribute to the prediction of off-target effects and the development of safer genome editing strategies (1,3).

However, the integration of AI in medical genetics also brings with its various limitations. Therefore, it seems more likely that AI will be positioned as a tool that transforms human roles and reshapes decision-making processes in medical genetics, rather than completely eliminating human expertise (2,4).

The combination of AI and medical genetics is not only a technological advancement; it is a multidimensional paradigm shift that restructures the organization of healthcare, scientific research methods, and clinical decision-making processes. In this context, this chapter systematically presents AI-based tools in medical genetics and their main application areas, and evaluates their predicted future impacts, potential contributions, and current limitations of AI in medical genetics applications in light of the existing literature.

2. Modern Needs of Medical Genetics

Medical genetics has historically relied on the comparison and interpretation of biological variation. Early genetic analyses often involved relatively small datasets and focused on specific genes or chromosomal regions, allowing researchers to manually examine experimental results and interpret them through established biological knowledge. However, advances in sequencing technologies have dramatically increased the scale of genomic data generated in both research and clinical settings.

High-throughput sequencing platforms now produce vast amounts of genetic information, including millions of variants per individual genome. The volume and complexity of these datasets exceed the capacity of manual interpretation and require computational approaches for efficient processing and analysis. As a result, bioinformatics has become

an essential component of modern medical genetics, providing the computational frameworks needed to store, analyze, and interpret large-scale genomic data.

Recently, ML and DL approaches have enabled the identification of patterns and relationships in complex datasets that may not be detectable with traditional statistical methods. These approaches support tasks such as variant prioritization, functional prediction, phenotype matching, and multi-omics integration.

2.1. Knowing the Tool

Selecting appropriate methods for specific analytical tasks has become increasingly important. A clear understanding of the purpose, methodology, and limitations of available software is necessary for accurate interpretation. Misinterpretation of computational predictions may lead to incorrect biological conclusions.

Numerous computational resources used in medical genetics rely on curated databases, rule-based algorithms, or statistical frameworks that do not involve ML. These tools remain essential for tasks such as sequence alignment, variant annotation, and pathway analysis. Distinguishing between ML–based tools (Table 1), DL models (Table 2), and traditional bioinformatics software is important for understanding their capabilities and limitations. And there are tools in this field that are not AI but uses some of them to gathering information (Table 3). The following sections summarize representative tools and their applications in genomic analysis.

Table 1. Machine Learning-Based Tools.

Functional and Structural Interpretation	
Software	Usage
MMSplice	Combination of multiple modules to predict variant effects on splicing.
Pathogenicity and Prioritization	
Software	Usage
ALoFT	Prediction of amino-acid-level functional effect.
CADD	Integration of multiple genomic annotations to score variant deleteriousness genome-wide.
FATHMM	Prediction of functional consequences of coding and non-coding variants.
MetaLR	Integration of multiple functional annotations to score variant pathogenicity.
MutationTaster	Prediction of disease-causing variants.
PolyPhen-2	Prediction of the potential impact of amino acid substitutions on protein function.
REVEL	Integration of multiple pathogenicity scores to classify rare missense variants.
SynScore	Prediction of pathogenicity of synonymous variants.
Phenotype and Clinical Integration	
Software	Usage
Exomiser	Combination of multiple pathogenicity scores with phenotype similarity using Human Phenotype Ontology terms.
Multi-Omics and Systems Modeling	
MOFA+	Integration of multiple omics datasets to identify shared biological signals.

Table 2. Deep Learning-Based Tools.	
Variant Alignment, Calling, and Annotation	
Software	Usage
Bonito	Call of base by converting raw electrical nanopore signals into nucleotide sequences.
Clair3	Call of variants from long-read sequencing data. ML–DL hybrid.
DeepTrio	Incorporation of parent–child trio data to improve variant detection accuracy. An extension of DeepVariant.
DeepVariant	Conversion of aligned read pileups into images to accurately detect genomic variants.
Dorado	Call of base for faster and more accurate nanopore read decoding.
Helixer	Prediction of gene structures directly from genomic DNA sequences for automated genome annotation.
NanoCaller	Detection of SNPs and indels from nanopore sequencing reads.
Remora	Detection of DNA base modifications such as methylation from raw nanopore signals.
Functional and Structural Interpretation	
Software	Usage
AlphaFold	Prediction of highly accurate three-dimensional protein structures from amino acid sequences.
AlphaGenome	Prediction of regulatory elements, variant effects, and long-range genomic interactions.
Basenji	Prediction of gene expression and regulatory activity from long DNA sequences.
Borzoi	Model of transcriptional regulation across long genomic contexts.
BPNet	Prediction of transcription factor binding patterns.
DeepBind	Prediction of binding preferences of transcription factors and RNA-binding proteins.
DeepDDG	Estimation of how mutations affect protein stability and folding.
DeepSEA	Prediction of how non-coding variants affect transcription factor binding and chromatin accessibility.
DNABERT	Evaluation of DNA sequences to capture genomic regulatory patterns.
Enformer	Prediction of gene expression and epigenetic states.
ESM-2	Prediction of protein structure and function.
ESMFold	Prediction of structure by using evolutionary sequence data.
Evo 2	Prediction of regulatory elements, evolutionary patterns, and long-range genomic interactions.
HyenaDNA	Model of extremely long genomic sequences.
Pangolin	Prediction of variant-induced RNA splicing changes across tissues.
PromoterAI	Prediction of promoter variant-induced expression-altering changes.
RoseTTAFold	Prediction of protein structures and protein–protein interactions.
SpliceAI	Prediction of splice donor and acceptor disruptions caused by genomic variants.
Pathogenicity and Prioritization	
Software	Usage
AlphaMissense	Estimation of pathogenic potential of missense mutations using structural and evolutionary features.
DANN	Prediction of variant deleteriousness genome-wide.

(Continued)

Table 2. Deep Learning-Based Tools. (Continued)	
EVE	Prediction of pathogenic variants by using evolutionary variation.
MetaRNN	Prediction of pathogenicity of rare missense variants.
MVP	Improvement of the classification of rare missense variants.
PrimateAI-3D	Evaluation of missense variants by using primate evolutionary variation and protein structures.
Phenotype and Clinical Integration	
Software	Usage
Face2Gene	Analysis of facial images to assist in the diagnosis of genetic syndromes.
PhenoDP	Analysis of patient phenotypic data to improve diagnosis.
Multi-Omics and Systems Modeling	
Software	Usage
CellBender	Removal of background noise from single-cell RNA sequencing datasets.
Geneformer	Prediction of gene regulatory relationships.
scVI	Integration and analysis of single-cell transcriptomic datasets.
totalVI	Integration of RNA and protein expression data from single-cell experiments.

Table 3. AI-Powered Tools.	
Software	Usage
Franklin by Genoox	Interpretation of variants.
Genomenon Mastermind	Connection of DNA variants to scientific literature.
Genomize-SEQ	Analysis of clinical NGS data.
LitVar	Connection of DNA variants to scientific literature.
Varsome	Interpretation of variants.

2. Variant Alignment, Calling, and Annotation

This stage represents the first of several computational steps required to transform raw sequencing output into biologically meaningful results. Modern sequencing technologies, particularly third-generation platforms, generate enormous volumes of signal data while reading the approximately three billion base pairs of the human genome. These platforms differ substantially in their underlying principles and error profiles, produced sequence reads must be computationally reconstructed. Because the resulting datasets are far too large and complex for manual interpretation, algorithmic pattern recognition methods are required for genomic representation.

Traditionally, sequence alignment relies primarily on statistical and algorithmic methods. Widely used aligners such as BWA, Bowtie, and HISAT2 (7) compare sequencing reads against a reference genome (GRCh37/hg19, GRCh38/hg38, or panPan2 for Bonobo). These tools rely on deterministic scoring systems rather than learning-based approaches. For many years, such methods provided reliable performance, particularly for second-generation sequencing technologies. However, the increasing scale

of genomic data and the higher noise levels have shown limitations in purely statistical approaches, motivating the integration of ML and DL models into the sequencing workflow.

Deep learning approaches have been particularly impactful in long-read sequencing platforms such as Oxford Nanopore Technologies. In nanopore sequencing, DNA molecules pass through a nanopore and generate electrical current signals that must be translated into nucleotide sequences (8). This signal interpretation is complex, especially in homopolymeric regions. Deep neural network–based tools such as Bonito (9), Dorado (10), and Remora (11, 12) are designed to learn non-linear patterns from raw electrical signals and improve basecalling accuracy. Beyond basecalling, DL has also been applied to variant detection. Tools such as DeepVariant (13), DeepTrio (14), and Clair3 (15) utilize neural networks trained on large genomic datasets to detect single-nucleotide variants (SNVs), insertions and deletions (indels), and other genomic alterations. These models can identify subtle patterns in sequencing data that may fall below the detection thresholds of classical statistical callers such as GATK, HaplotypeCaller or FreeBayes (16).

Sequencing data are typically distributed in several standardized formats throughout the analysis pipeline. Raw sequencing reads are stored in FASTQ files containing nucleotide sequences and associated quality scores. After alignment, the results are stored in the binary alignment format BAM along with index files (BAI), which allow efficient access to specific genomic regions. These files contain detailed information about read alignments, coverage, and mapping quality. Visualization tools such as IGV (Integrative Genomics Viewer).(17) enable researchers to inspect these alignments interactively, allowing visual validation of candidate variants. Although such tools are not based on AI, they remain essential for manual quality assessment and interpretation of sequencing results. Variant calls derived from aligned data are commonly stored in the Variant Call Format (VCF), a compact text-based format that records genomic variants along with their genomic positions. Different files are generated for different situations. Although variant calling is not the primary responsibility of the analyst, accurate calls facilitate downstream analyses and AI-based tools.

Once variants are identified, the next step is variant annotation, which aims to determine the biological significance of each detected alteration. Annotation involves mapping variants to genes, transcripts, and functional genomic regions and evaluating their predicted effects on protein-coding sequences. Databases and annotation frameworks such as RefSeq and Ensembl provide curated transcript models that enable classification of variants as missense, nonsense, synonymous, frameshift, or splice-site alterations. These annotations rely on standardized transcript identifiers (e.g., NM for RefSeq and ENS for Ensembl), which define the genomic context in which the variant is interpreted. AI has also been applied to genome annotation tasks. For example, Helixer uses deep neural networks to predict gene structures directly from genomic sequences, identifying coding regions, exon–intron boundaries, and transcript models (18).

3. Functional and Structural Interpretation

After appropriate preprocessing and quality steps, variants become ready for analysis. Even when focusing solely on the coding regions of the genome, an individual exome may contain more than 200,000 variants relative to the reference genome, but only a small subset may contribute to disease. Manually inspecting each variant is not feasible; therefore, variants must be filtered using computational approaches that highlight those most likely to have biological or clinical relevance.

In coding regions, missense variants can alter amino acid properties and potentially affect protein folding, structural stability, or enzymatic activity. Functional and structural modeling approaches, together with ML– and DL–based prediction tools, have significantly expanded the ability to evaluate such effects. Computational scoring of potential biological consequences is often used as an initial filtering strategy.

One of the most informative signals for functional interpretation is evolutionary conservation. Regions that are highly conserved across species typically indicate functional importance. Variants in these regions are therefore more likely to have deleterious consequences. Recent DL models such as AlphaMissense (19) and PrimateAI-3D (20) integrate evolutionary conservation, protein structural context, and large-scale sequence datasets to estimate the pathogenic potential of amino acid substitutions.

RNA splicing represents another important mechanism. Disruption of normal splicing patterns can affect all protein isoforms produced from a gene. Variants located directly at splice donor or acceptor sites can often be prioritized by manual inspection; however, predicting the effects of variants located outside splice regions is considerably more challenging. DL approaches have significantly improved this capability. For instance, SpliceAI predicts the effects of genomic variants on RNA splicing by modeling long-range sequence context around splice junctions (21). The approach is useful for identifying cryptic splice site disruptions. Other related models, Pangolin predicts tissue-specific splicing effects (22); PromoterAI predicts expression-altering promoter variants (23) and provides complementary insights into splicing alterations.

Direct evaluation of protein-level consequences is another important aspect of functional interpretation. The PolyPhen-2 uses ML approaches that include sequence conservation, structural features, and physicochemical properties of amino acids to estimate whether a missense variant is likely to affect protein function (24). Although such predictors are often mentioned within the pathogenicity scoring title, they specifically provide valuable information about the potential functional impact of amino acid substitutions.

More recently, advances in DL have enabled accurate prediction of protein three-dimensional structures. The model AlphaFold has demonstrated remarkable accuracy in predicting protein folding from amino acid sequences (25). Structural predictions can provide additional context when interpreting variants that may occur within critical functional domains.

In parallel with these specialized predictors, new generation of large-scale genomic foundation models, AlphaGenome and Evo 2, have also been announced, which are trained on massive genomic sequence datasets to learn generalizable representations of

DNA (26,27). Unlike task-specific predictors, foundation models aim to capture broader biological patterns within genomic sequences. Both models are designed to analyze regulatory elements, and interactions across the entire genome. However, AlphaGenome is oriented toward modeling regulatory architecture and estimating the impact of genetic variants, whereas Evo 2 emphasizes learning evolutionary representations of genomes through training on diverse genomic datasets. It may be thought that they are just other predictors, but genomics is slowly moving toward exactly the direction that models learn the genome or transcriptome itself instead of predicting a single task. Thus, these models reflect a broader trend in computational genomics.

4. Pathogenicity and Prioritization

Variant prioritization is one of the main objectives of genomic variant analysis. Numerous computational tools have been developed to support this process by estimating the potential pathogenicity of genetic variants. Many approaches estimate whether a variant may contribute to disease, often without direct consideration of an individual's clinical presentation.

Integrative scoring systems summarize multiple sources of evidence into a single predictive metric. One example is CADD (Combined Annotation Dependent Depletion), which integrates numerous genomic annotations using ML models to estimate the relative deleteriousness of variants across the genome (28). CADD provides a score of potentially pathogenic variants by combining conservation metrics, regulatory annotations, and functional predictions. Another widely used strategy involves ensemble predictors that integrate the outputs of multiple pathogenicity prediction algorithms. Tools such as REVEL (29) and MetaLR (30) aggregate diverse functional annotations and prediction scores to improve classification accuracy for rare missense variants. These ensemble approaches frequently achieve higher predictive performance than individual predictors. High scores from such tools may contribute to supporting computational evidence within variant interpretation guide such as the American College of Medical Genetics and Genomics (ACMG) guidelines.

A large proportion of pathogenicity predictors are ML–based tools in variant analysis. Traditional ML approaches primarily rely on predefined features: evolutionary conservation scores, physicochemical properties of amino acids, population allele frequencies, and functional annotations. Pathogenicity estimation can therefore be formulated using these engineered features and curated datasets of benign and pathogenic variants. As a result, many ML-based methods have been developed to aggregate and evaluate these features to produce a single pathogenicity score. In contrast, other analytical tasks, like modeling regulatory sequences, splicing mechanisms, or large-scale molecular interactions, often require analysis of raw sequences or high-dimensional molecular data. These problems are usually solved by DL models capable of learning complex representations directly from large datasets.

Beyond individual scoring tools, prioritization can also be performed through integrated analysis platforms that combine genomic, phenotypic, and clinical information. As an example, the variant analysis platform Genomize-SEQ (seq.genomize.com) incorporates ML approaches to rank variants according to multiple criteria, including population allele frequencies, internal database frequencies, zygosity, mode of inheritance, and predicted molecular consequences. By integrating these factors within a unified framework, such systems aim to prioritize variants that are most consistent with the observed genetic and clinical context of a patient.

5. Phenotype and Clinical Integration

Although computational tools can estimate the pathogenic potential of genetic variants, clinical presentation remains the primary context for interpretation. A variant predicted to be pathogenic does not necessarily explain the observed phenotype, and findings that are inconsistent with the patient's clinical features may not represent the causal variant. Therefore, effective variant interpretation requires integration of genomic data with detailed phenotypic information. Structured phenotype descriptions using resources such as Human Phenotype Ontology (HPO) enable computational comparison of patient symptoms with previously reported disease phenotypes. By providing a standardized vocabulary for clinical features, HPO facilitates computational analysis and supports the identification of gene–disease associations.

One widely used tool for integrating genotype and phenotype information is Exomiser (31). The tool combines variant pathogenicity predictions with phenotype similarity scoring to identify candidate disease-causing variants. The system evaluates variants based on multiple criteria, including predicted functional impact, population allele frequency, inheritance models, and similarity between the patient's HPO terms and known disease phenotypes associated with specific genes. By integrating these components, Exomiser ranks variants that are most consistent with the clinical presentation of the patient. Similarly, PhenoDP focuses on phenotype-based disease prioritization (32). The tool compares patient phenotypes, encoded using HPO terms, with curated disease annotations in databases such as OMIM and Orphanet. By calculating similarity scores between phenotype profiles, it identifies diseases that best match the patient's clinical presentation. These approaches support clinicians in identifying plausible genotype–phenotype relationships and improving diagnostic accuracy, particularly in rare disease investigations.

In some clinical situations, the phenotype itself may not be clearly defined or change over time. AI approaches have also been developed to assist with automated phenotypic assessment. One example is Face2Gene, which applies DL methods to analyze facial photographs and detect dysmorphic features associated with genetic syndromes (face2gene.com). By comparing facial characteristics with large datasets of known syndromic presentations, the system can suggest potential diagnoses and candidate genes. Although such

tools do not replace clinical evaluation, they provide additional supportive evidence that may guide variant interpretation and diagnostic decision-making.

6. Multi-Omics and Systems Modeling

Genetic variants often do not exert direct effects on function. Instead, they influence complex biological systems: gene regulation, protein interactions, and metabolic pathways. While genomic analyses identify candidate variants, their downstream biological consequences often branch out multiple molecular layers. Multi-omics integration aims to combine information from genomics, transcriptomics, proteomics, metabolomics, and epigenomics to obtain a more comprehensive view of biological processes and disease mechanisms.

Multi-omics experiments generate large volumes of heterogeneous data with complex relationships that are difficult to interpret. AI-based models can capture latent structures within these datasets, enabling the identification of molecular signatures associated with disease states, cellular differentiation processes, or therapeutic responses. Multi-omics integration involves latent factor models that identify shared sources of variation across different molecular layers. An example is MOFA+ (Multi-Omics Factor Analysis), which applies an ML framework to decompose heterogeneous datasets into latent factors (33). MOFA+ can reveal coordinated molecular patterns and highlight biological pathways that may be dysregulated in disease contexts.

Single-cell technologies have further expanded the scope of systems-level analysis by enabling molecular profiling at cellular resolution. DL frameworks have been developed to analyze such data efficiently. One widely used approach is scVI, which models gene expression distributions in single-cell RNA sequencing datasets (34). This method allows batch correction and identification of cellular subpopulations while preserving biological variability across cells.

In addition to statistical integration approaches, biological pathway databases provide structured knowledge that can be incorporated into computational analyses. Resources such as Kyoto Encyclopedia of Genes and Genomes (KEGG) and Reactome contain curated molecular interaction networks describing signaling pathways, metabolic reactions, and regulatory relationships. ML methods applied to these networks enable the identification of dysregulated pathways and facilitate the interpretation of genetic variants within broader biological systems.

More recently, a new class of large-scale foundation models has been announced in genomics and systems biology. Geneformer is a transformer-based DL model trained on collections of single-cell transcriptomic data (35). By learning expression patterns across millions of cells, it can model gene regulatory relationships and predict cellular responses to genetic alterations. Similarly, large genomic models such as AlphaGenome or Evo 2 aim to learn generalizable representations directly from large-scale DNA sequence datasets. These developments indicate a shift toward AI models capable of integrating information across multiple biological scales.

Individual prediction tools typically evaluate only a limited subset of biological features, such as evolutionary conservation, structural stability, or regulatory effects. Consequently, reliance on a single model or computational score may lead to incomplete or misleading conclusions. Robust variant interpretation, therefore, requires the integration of multiple independent sources of evidence, including genomic annotations, functional predictions, clinical observations, and phenotype-based analyses. Harmony among these diverse lines of evidence strengthens confidence in variant classification, while cacophonous results may indicate the need for additional experimental validation or clinical investigation. In this context, modern genomic analysis increasingly relies on integrative frameworks that combine computational predictions with clinical and biological knowledge to generate the most reliable interpretation of genetic variation.

7. Future Prospects and Challenges

Artificial intelligence can transform diagnostic, data analysis, and research workflows in medical genetics applications. While the impact varies by institution, significant gains have been made, such as improved genomic reporting quality and reduced administrative workload. In the medium to long term, automated processing of genomic data will make medical geneticists more active in ethical reasoning, clinical decision-making, and human-centered interaction. Standardized exome and genome analyses are expected to allow most medical geneticists to work with automated systems in routine cases, while preserving the role of expert input in complex and rare cases (4).

In the research sector, AI and ML accelerate the analysis of genomic and multi-omics datasets, elucidating the molecular mechanisms of diseases and identifying novel therapeutic targets. DL in electronic health records, genomic sequences, and complex imaging data offers groundbreaking opportunities in areas such as risk prediction, variant interpretation, biomarker screening, and forecasting. Omics technologies and AI have improved risk profiles and accelerated biomarker detection in heart failure. Similar advancements are also seen in cancer diagnosis, genetic risk assessment, and population-based threat mapping (1).

The use of AI in medical genetics ensures that healthcare is delivered in a proactive and personalized manner. The digital twin model is crucial in integrating individual genomic and omics profiles, clinical records, radiological findings, and wearable sensor data. Such systems can model disease progression, predict risks, and test therapeutic scenarios in silico. AI systems can synchronize multimodal data, increasing predictive accuracy and clinical utility (3).

The integration of AI into medical genetics brings with it both technical and ethical challenges. Data integrity issues, lack of validation protocols, insufficient population representation, and heterogeneous or low-quality data pools hinder clinical adoption. Privacy and ethical issues arise when sensitive data, such as genomic sequences and facial images, are shared. Furthermore, limited data for rare diseases makes DL training difficult.

Federated learning and privacy-focused computational methods will greatly facilitate the solution of these problems (5).

Data diversity and algorithmic bias are other problems. Reduced performance and deepening inequalities across different demographics are a consequence of narrow databases. Periodic audits, comprehensive data collection, and systematic evaluations are crucial at this stage. For an AI to be reliable, it must have an explainable model. Its predictions must be not only accurate but also verifiable and consistent with the biological basis (2).

Ethical and regulatory issues must also be considered. The safe use of AI-powered genomic tools is only possible with robust data shields, clinical validation standards, and regulatory compliance. Furthermore, the potential for large language models to generate erroneous and misleading information must be controlled through transparency, reliable databases, and human oversight (5).

The current literature emphasizes that AI will be positioned not as a replacement for expertise but as a tool that supports clinical decision-making processes and transforms professional roles. Accordingly, AI-assisted genetic research is expected to improve diagnostic accuracy, develop personalized treatment approaches, ensure interdisciplinary collaboration with inclusive data policies and ethical guidelines, and be supported by technological advancements (2,4).

In conclusion, the integration of AI and medical genetics should not be seen merely as a technological leap. This convergence points to a comprehensive transformation that reshapes clinical decision-making processes, biomedical research methods, and the organization of the health system. A systematic assessment of the potential, contributions, and limitations of this transformation is essential for future research directions and clinical applications.

8. References

1. Vilhekar, R. S., & Rawekar, A. (2024). Artificial Intelligence in Genetics. *Cureus*, *16*(1), e52035. https://doi.org/10.7759/cureus.52035
2. Dara, M., Dianatpour, M., Azarpira, N., & Tanideh, N. (2025). The transformative role of Artificial Intelligence in genomics: Opportunities and challenges. *Gene Reports*, *41*, 102314. https://doi.org/https://doi.org/10.1016/j.genrep.2025.102314
3. Wu, Y. C., Tuo, N., Shi, G., Li, K., Song, Z., & Li, Y. (2025). The Evolving Role of Artificial Intelligence in Medical Genetics: Advancing Healthcare, Research, and Biosafety Management. *Genes (Basel)*, *17*(1). https://doi.org/10.3390/genes17010006
4. Duong, D., & Solomon, B. D. (2025). Artificial intelligence in clinical genetics. *Eur J Hum Genet*, *33*(3), 281-288. https://doi.org/10.1038/s41431-024-01782-w
5. Solomon, B. D., Cheatham, M., de Guimarães, T. A. C., Duong, D., Haendel, M. A., Hsieh, T. C., Javanmardi, B., Johnson, B., Krawitz, P., Kruszka, P., Laurent, T., Lee, N. C., McWalter, K., Michaelides, M., Mohnike, K., Pontikos, N., Guillen Sacoto, M. J., Shwetar, Y. J., Ustach, V. D., . . . Woof, W. (2025). Perspectives on the Current and Future State of Artificial Intelligence in Medical Genetics. *Am J Med Genet A*, *197*(10), e64118. https://doi.org/10.1002/ajmg.a.64118
6. Changalidis, A., Barbitoff, Y., Nasykhova, Y., & Glotov, A. (2025). A systematic review on the generative AI applications in human medical genetics. *Frontiers in Genetics*, *16*, 1694070. https://doi.org/10.3389/fgene.2025.1694070
7. Musich, R. J. (2020). *A Recent (2020) Comparative Analysis of Genome Aligners Shows HISAT2 and BWA Are among the Best Tools*. Rochester Institute of Technology.
8. MacKenzie, M., & Argyropoulos, C. (2023). An Introduction to Nanopore Sequencing: Past, Present, and Future Considerations. *Micromachines (Basel)*, *14*(2). https://doi.org/10.3390/mi14020459
9. Chris Seymour, O. N. T. L. (2019). *Bonito: A PyTorch Basecaller for Oxford Nanopore Reads*. In https://github.com/nanoporetech/bonito
10. Oxford Nanopore Technology Ltd. (2022). *Dorado*. In https://github.com/nanoporetech/dorado

11. Oxford Nanopore Technology Ltd. (2021). *Remora*. In https://github.com/nanoporetech/remora
12. Wu, Z., Li, J., Xia, R., Dai, J., Su, J., Meng, J., & Zhang, Y. (2026). Nanopore direct RNA sequencing for RNA modification analysis: workflow assessment and computational tool benchmarking. *Adv Biotechnol (Singap)*, *4*(1). https://doi.org/10.1007/s44307-025-00093-5
13. Poplin, R., Chang, P. C., Alexander, D., Schwartz, S., Colthurst, T., Ku, A., Newburger, D., Dijamco, J., Nguyen, N., Afshar, P. T., Gross, S. S., Dorfman, L., McLean, C. Y., & DePristo, M. A. (2018). A universal SNP and small-indel variant caller using deep neural networks. *Nat Biotechnol*, *36*(10), 983-987. https://doi.org/10.1038/nbt.4235
14. Hu, X., Feng, C., Zhou, Y., Harrison, A., & Chen, M. (2022). DeepTrio: a ternary prediction system for protein-protein interaction using mask multiple parallel convolutional neural networks. *Bioinformatics*, *38*(3), 694-702. https://doi.org/10.1093/bioinformatics/btab737
15. Zheng, Z., Yu, X., Chen, L., Lee, Y.-L., Xin, C., Wong, A. O. K., Jain, M., Kesharwani, R. K., Sedlazeck, F. J., & Luo, R. (2025). Clair3-RNA: a deep learning-based small variant caller for long-read RNA sequencing data. *Nature communications*, *16*(1), 11553. https://doi.org/10.1038/s41467-025-67237-y
16. Pinto, V., Sousa, L., & Silva, C. (2026). Variant calling in genomics: A comparative performance analysis and decision guide. *Plos one*, *21*(2), e0339891. https://doi.org/10.1371/journal.pone.0339891
17. Robinson, J. T., Thorvaldsdóttir, H., Winckler, W., Guttman, M., Lander, E. S., Getz, G., & Mesirov, J. P. (2011). Integrative genomics viewer. *Nat Biotechnol*, *29*(1), 24-26. https://doi.org/10.1038/nbt.1754
18. Stiehler, F., Steinborn, M., Scholz, S., Dey, D., Weber, A. P. M., & Denton, A. K. (2021). Helixer: cross-species gene annotation of large eukaryotic genomes using deep learning. *Bioinformatics*, *36*(22-23), 5291-5298. https://doi.org/10.1093/bioinformatics/btaa1044
19. Tordai, H., Torres, O., Csepi, M., Padányi, R., Lukács, G. L., & Hegedűs, T. (2024). Analysis of AlphaMissense data in different protein groups and structural context. *Sci Data*, *11*(1), 495. https://doi.org/10.1038/s41597-024-03327-8
20. Gao, H., Hamp, T., Ede, J., Schraiber, J. G., McRae, J., Singer-Berk, M., Yang, Y., Dietrich, A. S. D., Fiziev, P. P., Kuderna, L. F. K., Sundaram, L., Wu, Y., Adhikari, A., Field, Y., Chen, C., Batzoglou, S., Aguet, F., Lemire, G., Reimers, R., . . . Farh, K. K. (2023). The landscape of tolerated genetic variation in humans and primates. *Science*, *380*(6648), eabn8153. https://doi.org/10.1126/science.abn8197
21. Jaganathan, K., Kyriazopoulou Panagiotopoulou, S., McRae, J. F., Darbandi, S. F., Knowles, D., Li, Y. I., Kosmicki, J. A., Arbelaez, J., Cui, W., Schwartz, G. B., Chow, E. D., Kanterakis, E., Gao, H., Kia, A., Batzoglou, S., Sanders, S. J., & Farh, K. K. (2019). Predicting Splicing from Primary Sequence with Deep Learning. *Cell*, *176*(3), 535-548.e524. https://doi.org/10.1016/j.cell.2018.12.015
22. Zeng, T., & Li, Y. I. (2022). Predicting RNA splicing from DNA sequence using Pangolin. *Genome Biology*, *23*(1), 103. https://doi.org/10.1186/s13059-022-02664-4
23. Jaganathan, K., Ersaro, N., Novakovsky, G., Wang, Y., James, T., Schwartzentruber, J., Fiziev, P., Kassam, I., Cao, F., Hawe, J., Cavanagh, H., Lim, A., Png, G., McRae, J., Banerjee, A., Kumar, A., Ulirsch, J., Zhang, Y., Aguet, F., . . . Farh, K. K. (2025). Predicting expression-altering promoter mutations with deep learning. *Science*, *389*(6760), eads7373. https://doi.org/10.1126/science.ads7373
24. Adzhubei, I. A., Schmidt, S., Peshkin, L., Ramensky, V. E., Gerasimova, A., Bork, P., Kondrashov, A. S., & Sunyaev, S. R. (2010). A method and server for predicting damaging missense mutations. *Nat Methods*, *7*(4), 248-249. https://doi.org/10.1038/nmeth0410-248
25. Jumper, J., Evans, R., Pritzel, A., Green, T., Figurnov, M., Ronneberger, O., Tunyasuvunakool, K., Bates, R., Žídek, A., Potapenko, A., Bridgland, A., Meyer, C., Kohl, S. A. A., Ballard, A. J., Cowie, A., Romera-Paredes, B., Nikolov, S., Jain, R., Adler, J., . . . Hassabis, D. (2021). Highly accurate protein structure prediction with AlphaFold. *Nature*, *596*(7873), 583-589. https://doi.org/10.1038/s41586-021-03819-2
26. Avsec, Ž., Latysheva, N., Cheng, J., Novati, G., Taylor, K. R., Ward, T., Bycroft, C., Nicolaisen, L., Arvaniti, E., Pan, J., Thomas, R., Dutordoir, V., Perino, M., De, S., Karollus, A., Gayoso, A., Sargeant, T., Mottram, A., Wong, L. H., . . . Kohli, P. (2026). Advancing regulatory variant effect prediction with AlphaGenome. *Nature*, *649*(8099), 1206-1218. https://doi.org/10.1038/s41586-025-10014-0
27. Brixi, G., Durrant, M. G., Ku, J., Naghipourfar, M., Poli, M., Sun, G., Brockman, G., Chang, D., Fanton, A., Gonzalez, G. A., King, S. H., Li, D. B., Merchant, A. T., Nguyen, E., Ricci-Tam, C., Romero, D. W., Schmok, J. C., Taghibakhshi, A., Vorontsov, A., . . . Hie, B. L. (2026). Genome modelling and design across all domains of life with Evo 2. *Nature*. https://doi.org/10.1038/s41586-026-10176-5
28. Rentzsch, P., Witten, D., Cooper, G. M., Shendure, J., & Kircher, M. (2019). CADD: predicting the deleteriousness of variants throughout the human genome. *Nucleic Acids Research*, *47*(D1), D886-D894. https://doi.org/10.1093/nar/gky1016
29. Ioannidis, N. M., Rothstein, J. H., Pejaver, V., Middha, S., McDonnell, S. K., Baheti, S., Musolf, A., Li, Q., Holzinger, E., Karyadi, D., Cannon-Albright, L. A., Teerlink, C. C., Stanford, J. L., Isaacs, W. B., Xu, J., Cooney, K. A., Lange, E. M., Schleutker, J., Carpten, J. D., . . . Sieh, W. (2016). REVEL: An Ensemble Method for Predicting the Pathogenicity of Rare Missense Variants. *Am J Hum Genet*, *99*(4), 877-885. https://doi.org/10.1016/j.ajhg.2016.08.016
30. Dong, C., Wei, P., Jian, X., Gibbs, R., Boerwinkle, E., Wang, K., & Liu, X. (2015). Comparison and integration of deleteriousness prediction methods for nonsynonymous SNVs in whole exome sequencing studies. *Hum Mol Genet*, *24*(8), 2125-2137. https://doi.org/10.1093/hmg/ddu733

31. Robinson, P. N., Köhler, S., Oellrich, A., Wang, K., Mungall, C. J., Lewis, S. E., Washington, N., Bauer, S., Seelow, D., Krawitz, P., Gilissen, C., Haendel, M., & Smedley, D. (2014). Improved exome prioritization of disease genes through cross-species phenotype comparison. *Genome Res*, *24*(2), 340-348. https://doi.org/10.1101/gr.160325.113
32. Wen, B., Shi, S., Long, Y., Dang, Y., & Tian, W. (2025). PhenoDP: leveraging deep learning for phenotype-based case reporting, disease ranking, and symptom recommendation. *Genome Medicine*, *17*(1), 67. https://doi.org/10.1186/s13073-025-01496-8
33. Argelaguet, R., Velten, B., Arnol, D., Dietrich, S., Zenz, T., Marioni, J. C., Buettner, F., Huber, W., & Stegle, O. (2018). Multi-Omics Factor Analysis-a framework for unsupervised integration of multi-omics data sets. *Mol Syst Biol*, *14*(6), e8124. https://doi.org/10.15252/msb.20178124
34. Gayoso, A., Lopez, R., Xing, G., Boyeau, P., Valiollah Pour Amiri, V., Hong, J., Wu, K., Jayasuriya, M., Mehlman, E., Langevin, M., Liu, Y., Samaran, J., Misrachi, G., Nazaret, A., Clivio, O., Xu, C., Ashuach, T., Gabitto, M., Lotfollahi, M., . . . Yosef, N. (2022). A Python library for probabilistic analysis of single-cell omics data. *Nature Biotechnology*, *40*(2), 163-166. https://doi.org/10.1038/s41587-021-01206-w
35. Theodoris, C. V., Xiao, L., Chopra, A., Chaffin, M. D., Al Sayed, Z. R., Hill, M. C., Mantineo, H., Brydon, E. M., Zeng, Z., Liu, X. S., & Ellinor, P. T. (2023). Transfer learning enables predictions in network biology. *Nature*, *618*(7965), 616-624. https://doi.org/10.1038/s41586-023-06139-9

CHAPTER 31

Hybrid Intelligence in Emergency Care: Not Replacing Physicians, but Augmenting Acute Response

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1. Introduction

1.1. Clinical Uncertainty and Time Pressure in the Emergency Department

Emergency medicine practice is a high-stakes and dynamic specialty where time is extremely limited, and vital decisions must be made within seconds or minutes (1,2). In this complex environment, physicians are often compelled to manage diagnostic and therapeutic processes based on incomplete or fragmented patient data (1). Emergency department (ED) overcrowding, which has evolved into a global healthcare crisis, is the primary factor exacerbating time pressure and clinical stress (3). Prolonged waiting times and bottlenecks in patient throughput lead to an increase in medical errors, fatal treatment delays, extended hospital stays, and ultimately, elevated patient morbidity and mortality rates (2,3). Under such density and clinical uncertainty, the real-time and accurate processing of vast datasets has become a critical necessity for both patient safety and the operational precision of the physician (1,4).

1.2. Decision Ecology in the Emergency Department

The clinical decision-making process in the ED is a multi-layered ecosystem encompassing patient triage, resource management (personel, beds, medical devices), the selection of diagnostic tests, and patient admission or discharge procedures (1,3). "Triage" constitutes the most critical and initial node of this decision ecology (2). During the triage phase, healthcare professionals must determine the clinical priorities of a large number of patients within a limited timeframe and direct them to the appropriate care area (2,4). In this process, in addition to structured data such as vital signs, unstructured clinical notes

in free-text format entered into the system by nurses are also of immense contextual value (5). However, traditional clinical scoring tools remain inadequate in processing this vast amount of unstructured data concurrently (1,5). The seamless operation of the decision ecology depends on the integration of these complex datasets without disrupting the physician's natural workflow (6). Artificial intelligence (AI) systems, by operating silently in the background, can analyze all these complex data in real-time and streamline the ED patient journey from triage to discharge by preventing clinical bottlenecks (3,6).

1.3. Cognitive Load and Human Decision Limits

Emergency physicians must simultaneously analyze a multitude of variables -such as complicated patient histories, constantly fluctuating vital signs, and real-time diagnostic results- under intense stress and time pressure. This necessity for concurrent data processing creates a massive cognitive load that strains the fundamental limits of human information processing.

According to the "Dual Process Theory" of cognition, which elucidates human decision-making mechanisms and the management of cognitive load, clinical reasoning is conducted through two complementary systems:

- **System 1 (Intuitive and Fast Process):** This is an automatic, rapid, unconscious, and low-effort mode of thinking. It is the system that enables experienced clinicians, upon encountering an emergency case, to grasp the patient's condition within seconds through pattern recognition and initiate immediate action. While it provides life-saving speed under time pressure, it is highly susceptible to cognitive errors -such as heuristics or confirmation bias- especially when exacerbated by fatigue, data overload, and overcrowding.
- **System 2 (Analytical and Slow Process):** This is a slower, conscious, and more effortful analytical (problem-solving) thinking process. For instance, a physician performing a step-by-step differential diagnosis by meticulously examining complex laboratory results relies on System 2. Research indicates that novice physicians or paramedics frequently rely on System 2; however, as experience grows and clinical intensity increases, System 1 tends to dominate the decision-making process.

Technological data inflation is a primary factor further challenging these cognitive boundaries. The administrative documentation burden and the continuous requirement for data entry into Electronic Health Records (EHR) contribute significantly to professional burnout. Furthermore, the constant alarms generated by bedside monitoring devices or legacy rule-based algorithms result in "alert fatigue," causing clinicians to become desensitized over time even to truly critical warnings.

Consequently, technology integrated into the ED should not manifest as a new administrative burden that distracts the physician. Instead, it should be designed as an intelligent "cognitive assistant" that operates in the background to sift through data, filter cognitive noise, and intervene only in high-risk clinical situations. An ideal AI interface should present complex data using default color-coding (e.g., ed/yellow/green) to support System 1

intuition; conversely, when a physician is in doubt and requires further evidence, it should facilitate System 2 analytical problem-solving by transparently explaining its underlying algorithmic logic.

1.4. Evolution of Decision Support Systems: From Rules to Artificial Intelligence

Clinical Decision Support Systems (CDSS) have been utilized for many years to mitigate medical errors by providing physicians with the essential information and alerts required during diagnostic and therapeutic processes (5,6). Historically, these systems relied heavily on expert consensus and predefined, rigid "IF-THEN" rules. Traditional rule-based scoring systems frequently employed in emergency medicine and intensive care practices -such as MEWS, APACHE, SIRS, and qSOFA- are quintessential examples of this era. However, these static rules often fall short in adapting to the dynamic nature of the ED, the rapidly fluctuating physiology of patients, and especially the analysis of massive unstructured clinical datasets. Today, next-generation AI tools, empowered by advanced technologies such as Machine Learning (ML) and Natural Language Processing (NLP), are capable of autonomously identifying complex and latent patterns within vast datasets without the need for human-coded manual rules (7-9).

The most critical juncture of this evolution in medical practice, however, lies in its philosophical positioning. In modern medicine, the objective of AI is not to establish a fully "autonomous" (unmanned) system intended to replace the physician (10,11). Instead, medical literature has increasingly focused on the concepts of "Augmented Intelligence" and "Hybrid Intelligence," which advocate for the integration of the complementary strengths of humans and machines (12,13). In the hybrid intelligence model, the machine provides a "safety net" that tirelessly filters massive datasets and analyzes risks in the background; meanwhile, the ultimate clinical evaluation, moral reasoning, and compassionate care remain strictly within the purview of the "human-in-the-loop (HITL)" physician (10,12). AI in the ED is not an independent authority designed to act instead of the doctor; rather, it is an indispensable decision-support assistant that stands alongside the physician, augmenting their clinical judgment and operational efficiency (5,11).

2. The Concept of Hybrid Intelligence and Theoretical Framework

Clinical decision-making processes in emergency medicine are at the epicenter of technological evolution, driven by the inherent challenges posed by data density and extreme time constraints (8).

2.1. Traditional Clinical Decision Support Systems

Traditional CDSS are primarily based on expert consensus, established clinical guidelines, and predefined, rigid rules or decision-tree logic. Static scoring systems widely utilized in EDs and intensive care units are quintessential examples of this approach (7).

However, these conventional systems possess significant limitations in adapting to the rapidly shifting dynamic physiology of emergency patients and, particularly, in processing multifactorial, complex clinical scenarios simultaneously. Their reliance on human-coded manual rules prevents these systems from capturing latent patterns within vast unstructured clinical data, such as nursing notes or free-text clinical narratives (5-8).

2.2. AI-Based Clinical Predictive Models

The limitations of traditional systems are increasingly being addressed through the emergence of data-driven AI technologies, such as ML and deep learning, precipitating a paradigm shift in clinical decision support (3). AI-based predictive models can autonomously identify complex and non-linear latent patterns by analyzing massive volumes of data within EHR, independent of pre-defined human rules (7).

Consequently, by leveraging initial data from the moment of triage alongside clinical notes analyzed through NLP, critical outcomes -such as sepsis risk or the necessity for hospitalization- can be dynamically predicted hours in advance (14,15). However, the analytical prowess of these models should not be conceptualized as an autonomy that excludes the physician from the decision-making process; rather, it should be framed as a "safety net" that mitigates clinical uncertainties and provides the clinician with multidimensional insights (5).

2.3. Hybrid Intelligence: The Physician-in-the-Loop Paradigm

Hybrid intelligence is a symbiotic approach that integrates the immense data processing and algorithmic computation capacity of AI with the clinical judgment, critical thinking, ethical values, and empathy of the human physician (2,12). Within this theoretical framework, AI functions as a tireless assistant, filtering data in the background, calculating risks, and offering differential diagnosis suggestions (2). However, irreplaceable human skills essential for medical decision-making -such as contextual synthesis, moral reasoning, and trust-based communication with the patient- remain strictly the responsibility of the physician (12).

This collaborative model is practically implemented through the "Physician-in-the-loop" (or HITL) approach. The HITL mechanism mandates that AI never operates as an autonomous decision-maker; rather, it requires that all system-generated recommendations undergo the physician's intellectual oversight or vetting process (10). To overcome the mistrust stemming from the "black-box" nature of algorithms, one of the fundamental pillars of hybrid intelligence is equipping systems with Explainable AI (XAI) features, which transparently elucidate the underlying logic and critical variables behind their outputs (6).

2.4. Autonomous Systems vs. Hybrid Systems: A Clinical Comparison

The integration of AI in emergency medicine entails a distinct clinical and philosophical dichotomy between "autonomous" systems, which operate without human intervention, and "hybrid" systems, where the physician remains the ultimate authority.

Clinical studies demonstrate that hybrid models, where physicians and machines collaborate, are statistically superior to the diagnostic success achieved by either form of intelligence in isolation. For instance, a multicenter prospective study on the detection of intracranial hemorrhage (ICH) in emergency radiology revealed that the overall accuracy rate achieved by radiologists assisted by AI was 99.53%, whereas the accuracy of fully autonomous AI services remained at 90.11% . The fact that human physicians and machines err through fundamentally different mechanisms creates a "miss complementarity," allowing combined interpretation to nearly eliminate diagnostic omissions (4).

Furthermore, from a medico-legal perspective, fully autonomous systems create a profound legal quandary regarding liability for erroneous decisions. Conversely, hybrid systems clarify legal boundaries and ensure accountability by retaining the final decision-making and override authority with the physician (13). The situation is similar from the patient's perspective; research indicates that 75% of patients prefer hybrid AI recommendations validated by an expert physician and imbued with human empathy over autonomous machine decisions (6,13). In conclusion, technology should be positioned "alongside" the physician, not to supplant professional clinical judgment, but to support and augment it at an operational scale (8,10).

3. Application Areas of Hybrid Intelligence in Emergency Medicine

The integration of AI-based technologies into emergency medicine practice has shifted away from the historical ambition of establishing an independent decision-making mechanism. Instead, it has evolved into a "hybrid intelligence" (augmented intelligence) model that extends the physician's cognitive boundaries, alleviates the data burden, and minimizes human error. In EDs where high time pressure and profound uncertainty prevail, algorithms process vast datasets in the background and perform risk analyses; nevertheless, contextual clinical judgment, patient-specific ethical decision-making, and moral accountability remain strictly within the purview of the clinician.

3.1. Triage and Prioritization Systems

In emergency medicine practice, triage represents the most vital initial node of the clinical workflow. This process, which dictates the allocation and urgency of limited medical resources, is traditionally conducted through rule-based scoring systems grounded in subjective clinical perception (10). Next-generation systems, equipped with ML and NLP technologies, can determine clinical priority more objectively by simultaneously processing vital signs from EHR and the free-text clinical narratives entered by triage nurses (14,16).

Nevertheless, medical triage is not merely an algorithmic calculation of vital signs; understanding a patient's fear, interpreting non-verbal cues, and establishing trust within seconds are uniquely human skills that no machine can replicate. Consequently, contemporary AI systems utilized in triage are designed to function not as autonomous gatekeepers, but as supportive "second opinions" aligned with the HITL philosophy (1,10). For

instance, models such as OSISP (On-Scene Injury Severity Prediction), developed for prehospital trauma management, provide a dashboard that lists the key variables underlying the generated risk prediction. This transparency ensures that the physician can oversee the algorithm's logic and, if necessary, override its decisions (1).

3.2. Early Warning Systems for Critically Ill Patients

In ED, the timely recognition of sepsis or clinical deterioration is a primary determinant of patient survival. Traditional clinical scoring systems, such as qSOFA and SIRS, often prove insufficient due to their reliance on static parameters, potentially leading to irreversible diagnostic delays (17). In contrast, AI-assisted algorithms can predict risks with high precision (e.g., an AUC of 0.94) by analyzing initial triage data hours before clinical suspicion of sepsis arises or traditional screenings commence. Research has reported that AI correctly identified 76% of cases where standard sepsis screening had not yet been initiated within the triage protocol (14).

One of the most sophisticated examples of early warning systems, TREWS (Targeted Real-time Early Warning System), has demonstrated a 3.3% absolute reduction (approximately a 20% relative reduction) in in-hospital sepsis mortality in multicenter field trials, provided that physicians intervened within the first three hours of an alert (7,17). The true role of hybrid intelligence in critical care lies in AI functioning as a background safety net, transmitting early signals of deterioration to the physician as actionable data. Ultimately, the final direction of treatment always rests upon the physician's contextual interpretation.

3.3. Imaging-Assisted Clinical Decision Processes

Emergency radiology is one of the fields where cognitive fatigue and perceptual errors occur most frequently due to severe time constraints, sleep-deprived shifts, and an ever-increasing case volume. In this context, AI offers invaluable support, not as an independent diagnostic tool, but as a concurrent reader for computed tomography and musculoskeletal radiographs (4,18).

In a multicenter prospective study focusing on ICH, the phenomenon of "miss complementarity" -where humans and machines perfectly compensate for one another's deficiencies- was scientifically validated (4). While the accuracy rate of fully autonomous AI services remained at 90.11%, the diagnostic accuracy of radiologists assisted by AI reached 99.53%. While the algorithm can highlight subtle subarachnoid or minimal subdural hemorrhages that a radiologist might overlook within seconds, human expertise filters out the false-positive alarms triggered by the machine due to anatomical variations or surgical clips (4). This synergy between two distinct types of intelligence establishes a clinical safety protocol that reduces diagnostic errors to nearly zero.

3.4. Hybrid Use of Risk Scores (HEART, EDACS, etc.)

While standard scores such as HEART and EDACS serve as the foundation for triage and discharge decisions in patients presenting to the ED with chest pain, these tools

may fall short in capturing dynamic pathophysiology. Today, AI algorithms that synthesize ECG findings with clinical data significantly enhance clinical sensitivity compared to standard triage tools. While the false-positive angiography activation rate of standard physician triage is approximately 42%, this rate drops to 8% in AI-supported models, and sensitivity in detecting ST-segment elevation myocardial infarction (STEMI) rises to 92% (19).

Furthermore, AI-ECG technology is increasingly utilized as a dynamic risk monitor in "safe discharge" decisions from the ED. In a comprehensive cohort study comparing AI scores of the initial ECG at admission with the control ECG taken prior to discharge, it was found that the pre-discharge assessment predicted the 90-day mortality risk with significantly higher accuracy. Specifically, in patients initially classified as low-risk who subsequently shifted to moderate or high-risk levels in the pre-discharge ECG analysis (risk transition), the mortality risk was found to increase sixfold (20). This hybrid application transforms AI from a mere diagnostic tool into an indispensable validation mechanism that oversees whether a patient can be safely discharged.

3.5. Operational Workflow and Patient Flow Optimization

Operational bottlenecks in ED and the issue of "boarding" -where patients experience prolonged waits on stretchers for inpatient beds- pave the way for systemic medical errors and preventable mortality (15). The solution lies in the effective management of hospital-wide capacity. Hybrid intelligence does not merely support individual patient diagnosis; it also predicts the logistic flow within the broader perspective.

Next-generation ML algorithms, by updating patient data collected at triage and initial clinical responses every 10 minutes, can predict the "need for admission" with over 80% accuracy (AUC 0.89) before diagnostic tests are fully finalized. Studies supported by retrospective data indicate that AI can identify the admission decision a median of 111 minutes before the physician's final clinical determination. This early signal enables bed management coordinators, environmental services (cleaning staff), and inpatient clinicians to complete their preparations in advance. Consequently, without superseding the physicians' own medical decisions, technology transforms the ED from a reactive crisis center into a proactively managed, frictionless healthcare ecosystem (15).

4. Clinical Safety, Ethical, and Medico-Legal Dimensions

4.1. Automation Bias and the Risk of Over-reliance

In environments where high stress and time pressure prevail, such as the ED, the tendency to place unquestioning trust in the results generated by decision support systems -referred to as "automation bias" and "automation complacency"- presents a significant risk to patient safety (6,10). Over-reliance on the outputs of autonomous systems or complex ML models can cause physicians to overlook observable clinical cues that

have not yet been integrated into EHR (10). Medical educators and ethics experts are concerned that physicians may lose their independent diagnostic and critical thinking skills, effectively transforming into "human mechanics" who merely carry out algorithmic instructions (21). This situation could lead to an intellectual "dumbing down" within emergency medicine practice and pave the way for irreversible medical errors when systems fail (21). To mitigate this risk, it is imperative to design AI not as an infallible authority that issues absolute judgments, but as an assistant (augmented intelligence) that conveys appropriate uncertainties and continually requires the physician's critical oversight (2,10).

4.2. Explainability and Trust

In emergency medicine, where every second is vital, systems must be transparent and intelligible for physicians to trust AI during real-time decision-making (6,8). However, most next-generation deep learning algorithms possess a complex "black-box" architecture that fails to explain the underlying logic of how a specific conclusion was reached (6,8). The inability of an algorithm to justify why it triaged a high cardiac risk patient as "low priority" creates a justified sense of mistrust among clinicians (8).

To address this challenge, XAI techniques -such as SHAP or LIME models- have been developed (8,10). XAI elucidates the algorithmic logic by presenting the primary clinical variables underlying a decision to the physician (e.g., "this red alert was issued due to a high lactate level and a downward trend in blood pressure") (10). Such transparency allows the physician to validate the machine's recommendation within the patient's immediate clinical context, thereby establishing a healthy professional balance between blind obedience to technology and its outright rejection (6,8).

4.3. Liability Allocation and Legal Perspectives

In instances where an AI-based decision proves erroneous -such as a missed stroke or a mismanaged sepsis case- resulting in patient harm, a profound medico-legal crisis ensues within the realm of medical law (8). The question of whether legal liability rests with the physician, the software developer, or the hospital administration remains a global "gray area" that is yet to be fully resolved (8).

Nonetheless, under current malpractice law, since the human clinician is the entity performing the ultimate clinical action, a physician who commits a medical error by following a faulty AI recommendation can be held directly liable (8). To navigate this legal uncertainty, hybrid intelligence systems based on the HITL model should be prioritized over fully autonomous systems that delegate clinical initiative entirely to the machine (10). This augmented intelligence approach, which necessitates physician validation (override/verification), clarifies legal boundaries and can reduce legal risks by up to 25%. Furthermore, it fosters a culture of "collective accountability" in which all stakeholders place patient safety at the center of the technological integration (10,13).

4.4. The Indispensability of Human Oversight

Although AI uniquely accelerates ED triage and risk calculation by processing vast datasets in seconds, it can never replicate the empathy, moral reasoning, and contextual intelligence that form the bedrock of medical practice (10). In the chaotic environment of the ED, understanding a patient's fear, interpreting non-verbal cues, and establishing a bond of trust within minutes remain uniquely human and irreplaceable skills.

The risk of the "dehumanization" of medicine by technology is regarded as one of the primary ethical concerns by both patients and physicians. Indeed, surveys indicate that 75% of patients prefer AI recommendations validated by a human physician (hybrid) over autonomous machine decisions (6,13). In an effective and ethical modern healthcare system, technology should be positioned not as an autonomous authority, but as an invisible supporter of a "collaborative triad" consisting of the patient, the physician, and AI. Human oversight serves as the sole safety net that mitigates algorithmic biases, protects patient autonomy, and safeguards the humanistic essence of emergency medicine (10).

5. Emergency Department Workflow Model with Hybrid Intelligence

In ED, time pressure, overcrowding, and information density are the fundamental factors challenging traditional clinical workflows. The core philosophy of the hybrid intelligence model is to integrate AI into the workflow not as a bureaucratic hurdle that impedes the physician or as an independent authority, but as a "safety net" that operates silently in the background, alleviates cognitive load, and intervenes only when necessary (5).

In the modern ED workflow, AI integration functions as a mutually reinforcing dynamic cycle, spanning from initial data collection to the physician's final validation of the decision (10). This model does not aim to automate the physician's clinical reasoning; rather, it seeks to enhance the decision-making quality of the physician and the clinical team by rapidly integrating multiple data streams (synthesizer role) or generating differential diagnoses (generative role) (2).

5.1. Data Collection and Integration

The primary step of a workflow supported by hybrid intelligence involves the continuous and multimodal collection of data through EHR and medical devices (18). ED data, by its nature, comprises both structured information (vital signs, laboratory results) and largely unstructured data (triage notes in free-text format, radiological images, and audio recordings) (14,18). Leveraging NLP and computer vision algorithms, next-generation CDSS can integrate unstructured data and free-text narratives entered by nurses or physicians into a clinical format in real-time (3,14).

Furthermore, voice-activated AI assistants known as "ambient scribes," designed to alleviate the administrative documentation burden that consumes a significant portion of a physician's time (approximately 30-50%), monitor patient-physician encounters in their

natural flow to generate automated and structured clinical notes (7). Data collection and integration are not static processes; modern AI systems provide a dynamic workflow by continuously updating and processing electronic patient data -for instance, in 10-minute intervals- to capture the evolving clinical status of patients in the ED (15,20).

5.2. AI Recommendation and Clinical Interpretation

Once multi-dimensional data is processed by AI, it is presented to the physician as an "early warning," a differential diagnosis list, or a risk prediction (second opinion). The most critical operational challenge at this stage is to avoid exacerbating alert fatigue, which is already substantially high within the ED (6). Consequently, interfaces should be designed in a "graduated" (tiered) manner to prevent distracting the clinician. For instance, traffic-light warning systems -categorized as green (verified/no issues), yellow (requires attention or missing information), and red (life-threatening risk or potential critical error; must be reviewed)- optimize cognitive load by interrupting the workflow only in "red" scenarios (5,6).

For the generated recommendation to be successfully integrated into the physician's clinical interpretation and to foster trust, the system must transition away from being a "black-box" and be equipped with XAI features (1,8). The algorithm should utilize heatmaps or feature importance rankings to demonstrate which specific triage keywords, imaging findings, or laboratory values triggered the relevant alert (1,8). Furthermore, through "Exploration Mode" (What-if Analysis) tools developed for applications such as trauma triage, physicians can test the model's predictions and enrich their clinical interpretation by querying the system on how risk scores would be affected if clinical parameters were modified (1).

5.3. The Final Decision: Human-Machine Collaboration

In the final and most critical phase of the hybrid intelligence workflow, decisions regarding diagnosis, discharge, or admission are never relegated to the algorithm alone; the ultimate initiative and validation always rest with the clinician through the HITL mechanism (10). The machine scans patterns, clinical guidelines, and probabilities learned from thousands of cases within seconds to present clinical risks to the physician (2,18). The physician, in turn, synthesizes this algorithmic recommendation with human elements that AI can never replicate, such as the patient's immediate physical presentation, psycho-social values, non-verbal cues, and moral reasoning (21).

Within this collaborative framework, "shared responsibility" and "human override/verification mechanisms" constitute fundamental safety pillars (11,21). In advanced integrated systems, a protocol can be established where a critical finding detected by AI must be rapidly verified or rejected by the physician (e.g., through a 30-second veto/approval window) before being translated into clinical action (18,22). Consequently, AI remains a powerful partner that alleviates the emergency physician's burden of data overload, while the compass of legal, ethical, and medico-legal responsibility remains firmly in the hands of the physician (1).

6. Discussion and Future Perspective

The integration of AI technologies into emergency medicine practice stands at a critical juncture where unprecedented opportunities intersect with complex operational risks. At this current stage, medical literature positions technology not as an independent and autonomous decision-maker, but rather as a "hybrid partner" that augments the physician's cognitive boundaries, alleviates the data burden, and fosters professional collaboration. This section discusses the existing clinical gains provided by AI applications, the inherent limitations of these systems, and the vision of the future augmented emergency department model.

6.1. Clinical Gains

The integration of AI into the ED has yielded measurable and striking improvements in diagnostic precision, operational velocity, and patient safety. Multicenter studies in emergency radiology and imaging have demonstrated that radiologists utilizing AI assistance (the hybrid model) achieved an extraordinary diagnostic accuracy of 99.53% in detecting ICH, significantly outperforming fully autonomous AI services, which remained at 90.11% (4). This provides scientific evidence for the phenomenon of "miss complementarity" -where humans and machines compensate for each other's deficiencies- and underscores the critical importance of the HITL (4). Similarly, in cardiovascular emergencies, AI-enhanced ECG analysis drastically reduces false-positive angiography activations in STEMI diagnosis and pulmonary embolism triage, thereby radically shortening the "time-to-action" for these time-sensitive conditions (22).

Regarding operational workflow, algorithms can predict the probability of patient admission or discharge a median of 111 minutes before the physician's final determination, offering proactive management to prevent ED boarding (15). Furthermore, AI-supported ambient scribe technologies alleviate the documentation burden -one of the primary drains on a physician's time- allowing the clinician to maintain eye contact with the patient instead of focusing on the keyboard, which enhances both physician well-being and patient satisfaction (22).

In terms of clinical error rates, AI establishes a robust safety net. Through the analysis of unstructured triage notes using NLP, septic conditions can be identified with high accuracy hours before clinical symptoms fully manifest (14). Prospective studies involving advanced early warning systems like TREWS have proven that when physicians intervene in response to these algorithmic alerts within the first three hours, an absolute reduction in in-hospital sepsis mortality is achieved (7,17). Finally, a massive live field study encompassing 39,849 patient visits in primary and urgent care settings demonstrated that a hybrid decision support system based on Large Language Models (LLM) reduced diagnostic errors by 16% and treatment errors by 13% (5).

6.2. Limitations and Risks

Despite these transformative gains, significant barriers and risks impede the routine integration of AI systems into ED. Chief among these is the "model-implementation gap"

(5). While many algorithms exhibit high performance in laboratory settings using retrospective data, they often fail to demonstrate the same reliability when integrated into the unpredictable, noisy, and dynamic environment of the ED, primarily due to a lack of external validation (7,10).

Frequent false-positive alarms -stemming from overly sensitive safety mechanisms- can lead to "alert fatigue," causing clinicians to overlook even life-critical warnings (6,10,15). Conversely, physicians who become overly accustomed to a system's accuracy may develop "automation complacency," a tendency to place unquestioning trust in the machine. This poses a risk of gradually eroding independent analytical thinking, contextual skepticism, and clinical intuition, ultimately creating professional vulnerability (3,8,21).

In the ethical and legal dimensions, the opaque "black-box" nature of most deep learning algorithms remains a major hurdle. The inability to transparently present "why" a triage or treatment recommendation was made -facilitated through XAI tools- undermines medical trust (6,8). In the event of patient harm resulting from a system hallucination or algorithmic error, determining who bears malpractice liability -the physician, the hospital administration, or the software developer- remains an unresolved, grey medico-legal debate globally (8,10). Finally, algorithmic bias arising from deficiencies in training datasets poses a danger of leading to unequal and erroneous medical decisions among elderly, female, or minority populations (8,10).

6.3. The Future Hybrid Emergency Department Model

The future of emergency medicine will not be built upon an autonomous engineering vision where human judgment is displaced; instead, it will be established through the "Hybrid Intelligence Teams" model, where technology is seamlessly (frictionlessly) integrated into the physician's natural workflow (7,11). Next-generation AI tools will accompany the physician as a "multimodal" central intelligence that simultaneously synthesizes EHR, vital sign monitoring, and medical imaging, replacing current siloed systems (5,7).

In the management of critically ill patients, "Digital Twin" technologies will become standardized. Through these systems, a virtual replica of a patient's physiological parameters will be created, allowing the potential outcomes of specific interventions -such as fluid resuscitation or vasopressor dosages for patients in trauma or septic shock- to be simulated within seconds before they are attempted on the patient (17). Additionally, through Learning Health Systems (LHS), which continuously collect data from the clinical environment and refine themselves through feedback loops, algorithms will adapt seamlessly to local patient populations and real-time epidemiological dynamics (3,10).

In the ultimate vision, AI will provide a tireless analytical background that filters massive datasets and shoulders the operational workload. However, the complex differential diagnoses at the heart of emergency medicine, unexpected crisis management, moral reasoning, trust-based empathetic communication, and the autonomy of the "final decision" (override) will remain with the "physician-in-the-loop," who remains the sole legal and medical authority (7,10,22). This hybrid ED model -where the unparalleled processing

capacity of technology merges with human compassion, experience, and ethics- represents the only path to overcoming the crises of increasing complexity and time pressure in modern medicine.

7. Conclusion

Emergency medicine represents one of the most critical and challenging clinical frontiers for the integration of AI technologies. Under the weight of complex patient presentations, time pressure where seconds are of the essence, and massive data loads, the cognitive limits of physicians are being increasingly strained (3,8). In this context, the role of AI in the ED is not to substitute for the physician or establish a fully autonomous decision-making mechanism, but rather to function as a natural "evolution" of medical practice, augmenting the physician's clinical judgment and operational velocity.

Literature and clinical field studies clearly demonstrate that the most successful outcomes -in terms of diagnostic accuracy, operational speed, and patient safety- are achieved neither by the human physician alone nor by independently functioning autonomous algorithms. Instead, the highest degree of success stems from the "Hybrid Intelligence" model: human expertise supported by AI, operating on the principle of "miss complementarity," where humans and machines compensate for each other's inherent weaknesses (4). Modern CDSS serve as a tireless analytical engine in the background, reading free-text narratives, generating dynamic risk scores, and providing a steadfast safety net for the physician (5,14,20). However, synthesizing algorithmic probabilities with the patient's unique psycho-social context, performing moral reasoning, and validating the final action (override/verification) remain the sole responsibility of the "physician-in-the-loop," who is the ultimate legal and medical authority (6,10).

In conclusion, AI integration in emergency medicine has transitioned from being an elective option to a structural necessity to cope with the crises of escalating clinical uncertainty and patient overcrowding. The vision of "Emergency Response via Hybrid Intelligence" positions technology not as a threat to physician autonomy, but as a strategic partner that liberates the clinician from repetitive data drudgery, allowing them to return to being an empathy- and compassion-focused "healer" who can dedicate more time to their patients (21). As seconds are contested in emergency interventions, this intelligent assistant -positioned alongside the doctor rather than in their place- is not merely a software composed of code, but a unique teammate that minimizes the margin of error and saves lives.

8. References

1. Bakidou, A., Andersson Hagiwara, M., Lee, E., Caragounis, E.-C., Sjöqvist, B. A., Seth, M., Jonsson, A., & Candefjord, S. (2025). Human–AI collaboration for prehospital trauma triage: Designing the On Scene Injury Severity Prediction (OSISP) model as a clinical decision support system. DIGITAL HEALTH, 11, 20552076251403207. https://doi.org/10.1177/20552076251403207

2. Eccles, R. (2025). Hybrid Intelligence Teams: A Theoretical Framework for Human-AI Collaboration in Knowledge Work. Available at SSRN 5792345. https://papers.ssrn.com/sol3/papers.cfm?abstract_id=5792345
3. Chenais, G., Lagarde, E., & Gil-Jardiné, C. (2023). Artificial intelligence in emergency medicine: Viewpoint of current applications and foreseeable opportunities and challenges. Journal of Medical Internet Research, 25, e40031. https://www.jmir.org/2023/1/e40031/
4. Khoruzhaya, A. N., Sakharova, P. A., Arzamasov, K. M., Kremneva, E. I., Burenchev, D. V., Erizhokov, R. A., Omelyanskaya, O. V., Vladzymyrskyy, A. V., & Vasilev, Y. A. (2025). Standalone AI Versus AI-Assisted Radiologists in Emergency ICH Detection: A Prospective, Multicenter Diagnostic Accuracy Study. Journal of Clinical Medicine, 14(16), 5700. https://www.mdpi.com/2077-0383/14/16/5700
5. Korom, R., Kiptinness, S., Adan, N., Said, K., Ithuli, C., Rotich, O., Kimani, B., King'ori, I., Kamau, S., & Atemba, E. (2025). Ai-based clinical decision support for primary care: A real-world study. arXiv Preprint arXiv:2507.16947. https://arxiv.org/abs/2507.16947
6. Tun, H. M., Rahman, H. A., Naing, L., & Malik, O. A. (2025). Trust in artificial intelligence–based clinical decision support systems among health care workers: Systematic review. Journal of Medical Internet Research, 27, e69678. https://www.jmir.org/2025/1/e69678/
7. Hadweh, P., Niset, A., Salvagno, M., Al Barajraji, M., El Hadwe, S., Taccone, F. S., & Barrit, S. (2025). Machine learning and artificial intelligence in intensive care medicine: Critical recalibrations from rule-based systems to frontier models. Journal of Clinical Medicine, 14(12), 4026. https://www.mdpi.com/2077-0383/14/12/4026
8. Amiot, F., & Potier, B. (2025). Artificial intelligence (AI) and emergency medicine: Balancing opportunities and challenges. JMIR Medical Informatics, 13(1), e70903. https://medinform.jmir.org/2025/1/e70903/
9. Chua, M. T., Boon, Y., Lee, Z. Y., Kok, J. H. J., Lim, C. K. W., Cheung, N. M. T., Yong, L. P. X., & Kuan, W. S. (2025). The role of artificial intelligence in sepsis in the Emergency Department: A narrative review. Annals of Translational Medicine, 13(1), 4. https://journals.lww.com/atm/fulltext/2025/02000/the_role_of_artificial_intelligence_in_sepsis_in.4.aspx
10. Cha, H., & Kim, J. (2025). Ethical considerations of artificial intelligence in emergency medicine for triage and resource allocation: A scoping review. Clinical and Experimental Emergency Medicine, 12(4), 306. https://pmc.ncbi.nlm.nih.gov/articles/PMC12824544/
11. Hartmann, M., & Ekinci, O. (n.d.). Close navigation. Retrieved March 11, 2026, from https://diagnostics.roche.com/global/en/healthcare-transformers/article/ai-preventive-healthcare.html
12. Hirosawa, T., Suzuki, T., Shiraishi, T., Hayashi, A., Fujii, Y., Harada, T., & Shimizu, T. (2024). Adapting Artificial Intelligence Concepts to Enhance Clinical Decision-Making: A Hybrid Intelligence Framework. International Journal of General Medicine, Volume 17, 5417–5422. https://doi.org/10.2147/IJGM.S497753
13. Moodley, K. (2024). Artificial intelligence (AI) or augmented intelligence? How big data and AI are transforming healthcare: Challenges and opportunities. South African General Practitioner, 5(4), 170–175.
14. Brann, F., Sterling, N. W., Frisch, S. O., & Schrager, J. D. (2024). Sepsis prediction at emergency department triage using natural language processing: Retrospective cohort study. JMIR AI, 3(1), e49784. https://ai.jmir.org/2024/1/e49784/
15. Van Der Haas, Y., Roskamp, W., Chang-Willems, L. E. M., van Dongen, B., Jansen, S., de Jong, A., de Carvalho, R. M., Melman, D., van de Merwe, A., & Bastian-Sanders, M. (2026). Evaluating an AI Decision Support System for the Emergency Department: Retrospective Study. JMIR AI, 5(1), e80448. https://ai.jmir.org/2026/1/e80448/
16. Chee, M. L., Chee, M. L., Huang, H., Mazzochi, K., Taylor, K., Wang, H., Feng, M., Ho, A. F. W., Siddiqui, F. J., & Ong, M. E. H. (2023). Artificial intelligence and machine learning in prehospital emergency care: A scoping review. Iscience, 26(8). https://www.cell.com/iscience/fulltext/S2589-0042(23)01484-0
17. Li, F., Wang, S., Gao, Z., Qing, M., Pan, S., Liu, Y., & Hu, C. (2025). Harnessing artificial intelligence in sepsis care: Advances in early detection, personalized treatment, and real-time monitoring. Frontiers in Medicine, 11, 1510792.
18. He, Z.-X., Wang, J., & Yang, J.-S. (2026). Expanding the applications of artificial intelligence in emergency radiology: Advancing precision medicine and resource efficiency. World Journal of Radiology, 18(1), 117814. https://pmc.ncbi.nlm.nih.gov/articles/PMC12865541/
19. New study finds AI model improves heart attack detection. (n.d.). Retrieved March 11, 2026, from https://health.ucdavis.edu/news/headlines/new-study-finds-ai-model-improves-heart-attack-detection/2025/11
20. Su, Y.-T., Chen, S.-J., Lin, C., Lin, C.-S., & Hu, H.-F. (2025). Prognostic Significance of AI-Enhanced ECG for Emergency Department Patients. Diagnostics, 15(15), 1874. https://www.mdpi.com/2075-4418/15/15/1874
21. Iserson, K., Baker, E., Bissmeyer, P., Derse, A., Sauder, H., & Walters, B. L. (2024). Artificial intelligence in the ED: Ethical issues. ACEP Now, 43(6). https://www.acepnow.com/article/artificial-intelligence-in-the-ed-ethical-issues/
22. Cacciatore, R. (2025, September 24). AI-Powered Clinical Decision Support: The Future of Emergency Department Efficiency. Core Clinical Partners. https://www.coreclinicalpartners.com/ai-powered-clinical-decision-support-the-future-of-emergency-department-efficiency/

CHAPTER 32

A New Era in Radiation Oncology: The Game-Changing Role of Artificial Intelligence Algorithms in Radiotherapy

PhD. Ahmet Sahin

1. Introduction

Ionizing radiation includes particles or photons and has varying energy levels. It has a destructive effect on living tissues. In addition to causing intracellular metabolic disorders and damage to the cell membrane, the most significant effect occurs in the cell nucleus, which controls the cell's viability and controlled division and proliferation. Ionizing radiation has found significant applications in medicine and biology because of these effects. In radiation therapy and nuclear medicine, ionizing radiation is used to selectively destroy tumor cells while reducing damage to healthy tissues (1). "Radiotherapy," which refers to the delivery of ionizing radiation to cancerous tissues and cells via a medical device, is administered using various devices and techniques. In cancer treatment, ionizing radiation used in medicine ranges from 50-400 keV to 1.25-15 MV, thanks to advancements in modern technology (1).

The operating principle of linear accelerators is based on accelerating electrons using high-frequency electromagnetic waves. The accelerated high-energy electrons are used to treat superficial tumors, or they will strike a target to generate X-rays, thus treating deep-seated tumors (1).

Thanks to the techniques and models of radiation therapy devices, computer-based treatment planning systems (TPS) are used to give patients more accurate, precise, rapid, safe, and high-quality dose delivery (2).

When examining the development of radiation therapy, which also refers to treatment with high-energy radiation devices such as linear accelerators, two key pillars of the field have formed: at first, two-dimensional treatment planning systems, and today, three-dimensional treatment planning systems. Different treatment planning systems can give the

same therapy devices varying treatment capabilities and techniques. In treatment planning, the choice of the most appropriate technique, device, TPS, and algorithm for each case is significantly important in terms of both time and cost.

Radiotherapy, which initially developed in two dimensions, continued its evolution with three-dimensional conformal radiotherapy; with current technology, rotational treatments such as Intensity-Modulated Radiotherapy (IMRT) and Volumetric Modulated Arc Therapy (VMAT), which enable high-modulation treatments, have become possible.

Intensity-Modulated Radiotherapy (IMRT) is defined as an advanced form of three-dimensional conformal radiotherapy, achieved through advancements in technology, software, and planning techniques. This treatment method, also known as IMRT, delivers radiation by dividing the non-uniform dose distribution into small beams called segments. In this approach, the goal is to deliver the prescribed dose to the target volume with the highest possible accuracy, while creating sharp dose gradients in regions next to critical organs to protect healthy tissues. Advanced modeling and dose calculation algorithms have been developed to enable the effective planning of this treatment, and thanks to technological advancements, the simulation and application of these algorithms in clinical practice have become possible.

With Image-Guided Radiation Therapy (IGRT), more precise radiation treatments have become possible through high-resolution cameras, and with the latest technology, treatments such as Stereotactic Radiosurgery (SRS) and Stereotactic Body Radiation Therapy (SBRT) collectively known as stereotactic therapy, now enable the delivery of high doses to small areas, resulting in significantly more effective treatments today.

Recent advancements in both computer hardware and software have made it possible to develop artificial intelligence agents capable of delivering superior performance in certain complex tasks without human intervention. Concurrently, the increase in data and the ease of sharing this data have fostered the continuous advancement of AI through machine learning (ML) and deep learning (DL) methods (3).

Radiation oncology is a field of cancer treatment that requires interdisciplinary knowledge spanning medicine, biology, physics, and engineering. A typical radiation therapy workflow includes medical imaging, diagnosis, prescribing, simulation, contouring, treatment planning, treatment quality control, and treatment delivery. Thanks to technological advancements in recent years, radiation therapy practices have become increasingly complex, leading to a dependency on human–machine interactions. In clinical practice, each step involves highly specialized processes with their own technical challenges. However, the reliance of a broad team comprising radiation oncologists, medical physicists, medical dosimetrists, and radiation therapy technologists on manual data processing results in patients receiving a limited treatment process. The widespread adoption of image-guided radiation therapy has helped to generate massive amounts of images that must be analyzed in a short time. However, because of time constraints, humans do not have enough time to review and analyze such large volumes of data. Machines, on the other hand, can be trained to share a significant part of repetitive workloads with humans, thus

increasing the capacity for fast and high-quality healthcare services. Since the emergence of deep neural networks, many AI-based methods have been proposed to address various challenges in radiation therapy. Given the rapid advancements in AI-supported radiation therapy, the efficiency and effectiveness of radiation therapy can be significantly enhanced by implementing smart automation methods (3).

Because of advancements in medicine, cancer genetics, and imaging, the emergence of multi-modal data sources that healthcare professionals must interpret has led AI to begin playing a role in leveraging these data (4).

Artificial intelligence has recently become one of the most popular ideas in both industry and academia. Known as a modern technological term, AI was initially perceived as an idea capable of thinking and behaving like a human while maintaining rationality. In computer science, AI is defined as the study of algorithms and systems that process information and perform necessary actions to maximize the likelihood of meeting specific goals. Thanks to increases in computational speeds and the expansion of data collection and sharing capabilities, many AI techniques and algorithms based on deep learning have been published in recent years. Following this rapid explosion of techniques, AI has permeated nearly every part of our lives and has begun to rapidly influence and transform our way of life. In radiation oncology, the impact of AI is grounded in automated support processes across various parts of the radiation therapy clinical workflow: target volume and tissue segmentation, treatment planning, radiation therapy delivery, and evaluation of treatment response (5).

Radiotherapy treatment planning, particularly inverse planning methods such as Intensity Modulated Radiotherapy (IMRT), is a laborious process that can take hours or even days to complete. The workflow begins with stages involving dosimetric requirements, including target volume delineation and constraints related to organs at risk (OARs). Based on the specific needs of each case, a planner decides on planning parameters such as radiation energy, number of beams, and beam angles. While making a plan that meets the most basic criteria may be relatively quick, refining a treatment plan is far more complex and typically requires many iterative processes between planners and the treatment planning system (TPS). Doctors may also interact with planners multiple times to refine the treatment plan based on the initial plan results. That these interactions can occur repeatedly can require significant human effort and considerable time (6).

2. The Development of Artificial Intelligence Algorithms

Just as advancing technology has driven progress in every field, artificial intelligence algorithms that enable virtual simulation have played a game-changing role in medicine and radiation oncology. The accuracy of these algorithms has improved over time since the 2000s, and their treatment safety and accuracy have been confirmed using sophisticated quality control equipment. The figure below illustrates the evolution over time of the algorithms in TPSs used in modern radiation therapy.

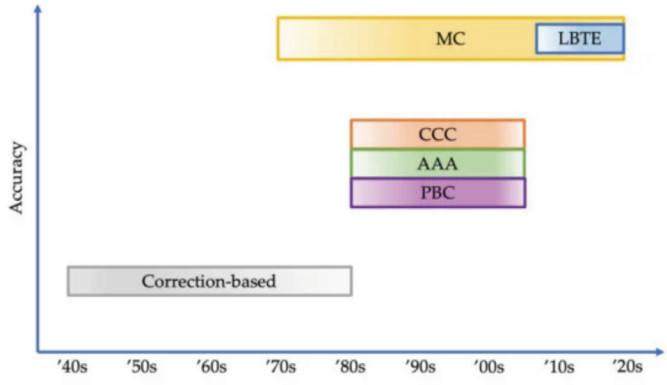


Figure 1. Historical evolution and relative accuracy of dose calculation engines. Abbreviations: PBC: pencil beam convolution, AAA: analytical anisotropic algorithm, CCC: collapsed cone convolution, MC: Monte Carlo, LBTE: linear Boltzmann transport equations (7).

Thanks to these algorithms, automated treatment planning (ATP) has significantly reduced treatment planning times by reducing human interaction, particularly in repetitive processes conducted via treatment planning systems (TPS). Planners can dedicate more time to investigating more appropriate dose distributions for individually optimized treatment plans, leading to more beneficial outcomes. Increased efficiency may also enable systemic changes in clinical practice processes, including more innovative treatment planning strategies, new methods for monitoring the treatment process, and treatment delivery phases (8,9,10,11).

In addition to efficiency, ATP has also brought improvements in treatment plan quality and error rates. Since traditional treatment planning is a trial-and-error-based process that examines dosimetric and clinical stages, the resulting plan quality depends on both the planner's experience and ability as well as the time for planning. Numerous ATP studies conducted across various disease areas have reported more consistent treatment plan quality compared to manual plans. For this reason, ATP has the potential to address gaps in healthcare by making advanced treatment planning knowledge more widely accessible (12,13,14).

While some studies have reported that treatment plans generated by artificial intelligence are clinically acceptable, other studies have indicated that ATP requires basic human intervention or change to ensure acceptable quality and safety. The human element must remain central to treatment planning in terms of plan safety and quality; however, an important goal of AI-based treatment planning algorithms is to contribute to improving treatment plan quality. Many studies incorporating new approaches in this field are underway (15,16).

3. The Contribution of Deep Learning-Based Models to Virtual Simulation

With the emergence of deep learning models, particularly convolutional neural networks (CNNs), there has been a significant shift in virtual simulation approaches. As multi-layer

feedforward neural networks, CNNs can extract low-level image features through hidden layers and, by learning higher-level features in later layers, achieve more accurate and reliable segmentation results. This advancement has been a important development for radiation therapy treatment planning, where accuracy is important (17,18).

Deep learning-based models have emerged as a significant potential tool in various stages of radiation therapy planning (particularly in the segmentation of organs at risk (OAR) and clinical target volumes (CTV)). These models are typically developed using previously reviewed treatment contours whose accuracy has been verified by experts, and it has been confirmed that they produce results close to clinical contours for most OARs. However, some have observed that segmentation accuracy decreases in structures with higher anatomical variability, suggesting a need for more comprehensive training data or more innovative training approaches to improve performance (19,20).

Integrating these deep learning models into clinical workflows represents a significant milestone. Recent studies have shown these models can be practically applied in clinical workflows for certain types of cancer, including central nervous system, head and neck, prostate, and rectal cancers. This integration has shown the potential of deep learning models to enhance the efficiency, consistency, and contribution of radiation therapy treatment planning, while also emphasizing the importance of continuous improvement and validation (22,23,24).

Artificial intelligence, particularly deep learning-based automatic contouring systems, has shown more significant increases in accuracy compared to traditional automatic methods, and many institutions have evaluated existing commercial AI contouring systems to integrate them into clinical workflows. Geometric metrics such as the Dice similarity coefficient (DSC) and Hausdorff distance (HD) are often used parameters for analyzing contour accuracy; however, it is also known that these metrics do not show a strong correlation with the clinical acceptability of contours or dosimetric outcomes (25,26).

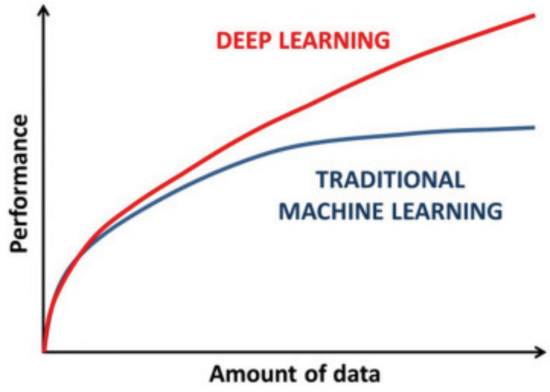


Figure 2. A line graph illustrating the performance difference between deep learning and machine learning artificial intelligence with varying amounts of data (21).

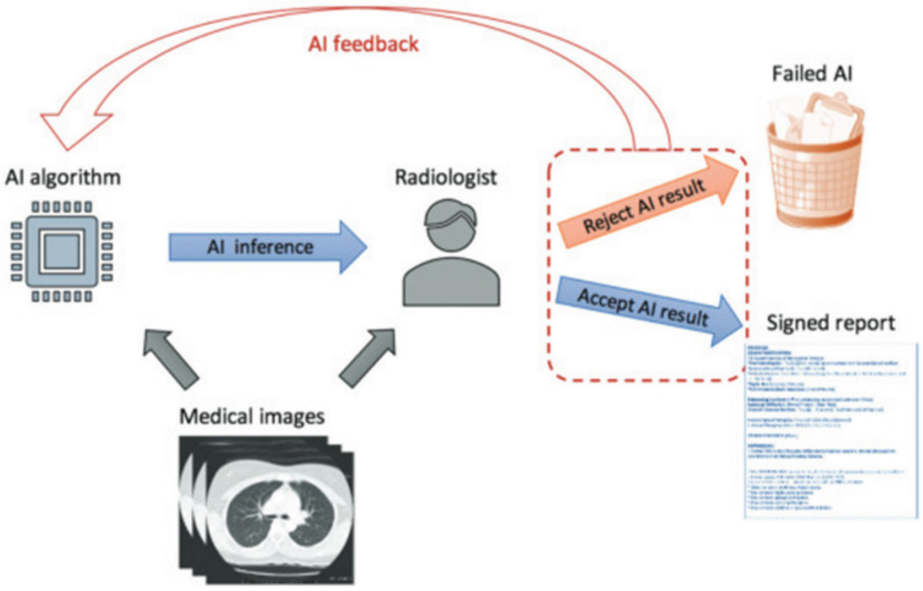


Figure 3. Illustration of the AI feedback loop involving a radiologist and an AI algorithm. Implementing AI feedback enables continuous adaptive learning (30). Abbreviation: AI = Artificial Intelligence.

Artificial intelligence-based methods have rapidly gained attention because of their potential to significantly reduce the human input required for contour segmentation. Manufacturers have developed various standalone AI modules or integrated AI modules into clinical planning tools. Although most of these commercial platforms offer pre-trained organ-specific segmentation models, deep learning network systems lack transparency regarding algorithm performance or the limitations and challenges in clinical applications. Computer algorithms for automatic contour segmentation in radiation therapy have undergone various stages of development (27).

One of the most critical considerations in the implementation of AI software is deciding between continuous learning and fixed-version models. Fixed-version software relies on updates to ensure current validity, reliability, and safety. In radiology, fixed-version software can process hundreds of thousands of images and derive the results based on the initial training data. Images used in clinical practice may differ significantly from those in the original training dataset. This phenomenon of idea drift can stem from the evolution of imaging devices, software updates in imaging devices, or even varying imaging protocols across hospital institutions (28).

As shown in Figure 3, using continuous learning in collaboration with expert human input allows AI results considered inappropriate or incorrect to be fed back into the training data as feedback for future cases (29,30).

4. Artificial Intelligence Algorithms and Quality Control

Treatment Planning Systems (TPS), which are the main tools of radiation therapy, offer the ability to perform pre-treatment virtual simulations using artificial intelligence-supported modeling algorithms this is perhaps the most significant advantage and benefit of modern radiation therapy for patients. Thanks to this virtual simulation, patients can undergo a comprehensive analysis of their entire body structure using a single CT scan before radiation therapy, allowing for the precise identification of the exact location of target organs and the protection of organs at risk (OARs).

Using modern algorithms in this virtual simulation enables the most accurate, precise, and up-to-date treatments. If a modern algorithm is loaded into the TPS of a standard radiotherapy machine, this massive piece of hardware and software-equipped equipment effectively transforms into a smart device capable of delivering a new generation of treatments.

Complex treatment plans approved through virtual simulation must undergo precise verification by Medical Physics Specialists using pre-treatment quality control equipment, and their suitability must be determined according to Gamma Index criteria. In this quality control process too, compliance with the most precise criteria should be verified with help from AI agents. AI not only applies the treatment to the patient via pre-treatment virtual simulation but also allows the treatment's efficacy to be understood before it is even administered.

5. Conclusions

This study shows that dose analyses performed using radiotherapy treatment planning systems developed with AI-supported algorithms can offer significant advantages in clinical practice through different dose calculation and planning approaches. The findings reveal that certain planning methods can yield lower values for patient treatment duration and monitor unit (MU) values. Reductions in treatment duration and MU values contribute to shorter patient immobilization times, thus enhancing patient comfort during treatment and helping to reduce the risk of secondary malignancies by minimizing unnecessary radiation exposure. Also, when examining dose distributions in at-risk organs, it was observed that certain planning approaches can provide lower dose levels. It is believed that such advantages could play a significant role in the clinical planning process when critical organ doses approach threshold values. Today, integrating artificial intelligence-based methods and advanced optimization algorithms into radiation therapy planning processes enables more precise optimization of dose distributions and strengthens clinical decision-support mechanisms. In this context, the combined evaluation of different dose calculation approaches and AI-assisted planning techniques emerges as an important approach that could contribute to the development of safer, more effective, and patient-centered treatment plans in clinical practice.

6. References

1. Gibbons, J. P. (2019). Khan's The Physics of Radiation Therapy. In Khan's The Physics of Radiation Therapy. Wolters Kluwer Health. https://doi.org/10.4103/jmp.jmp_17_20
2. Zimmerman, J. (2025). Exploiting advances in quantitative computed tomography to improve dose calculation in radiotherapy. https://doi.org/10.69622/29279846.v1
3. Seo, H., Badiei Khuzani, M., Vasudevan, V., Huang, C., Ren, H., Xiao, R., Jia, X., & Xing, L. (2020). Machine learning techniques for biomedical image segmentation: An overview of technical aspects and introduction to state-of-the-art applications. Medical Physics, 47, e148–e167. https://doi.org/10.1002/mp.13649
4. Howell, M. D., Corrado, G. S., & DeSalvo, K. B. (2024). Three epochs of artificial intelligence in healthcare. JAMA, 331(3), 242–244.
5. Russell, S., Norvig, P., & Intelligence, A. (1995). A modern approach. Artificial Intelligence. Prentice-Hall, Englewood Cliffs, 25(27), 79–80.
6. Wang, C., Zhu, X., Hong, J. C., & Zheng, D. (2019). Artificial intelligence in radiotherapy treatment planning: present and future. Technology in Cancer Research & Treatment, 18, 1533033819873922.
7. De Martino, F., Clemente, S., Graeff, C., Palma, G., & Cella, L. (2021). Dose Calculation Algorithms for External Radiation Therapy: An Overview for Practitioners. Applied Sciences, 11(15), 6806. https://doi.org/10.3390/app11156806
8. Foy, J. J., Marsh, R., Ten Haken, R. K., Younge, K. C., Schipper, M., Sun, Y., Owen, D., & Matuszak, M. M. (2017). An analysis of knowledge-based planning for stereotactic body radiation therapy of the spine. Practical Radiation Oncology, 7(5), e355–e360. https://doi.org/10.1016/j.prro.2017.02.007
9. Hansen, C. R., Bertelsen, A., Hazell, I., Zukauskaite, R., Gyldenkerne, N., Johansen, J., Eriksen, J. G., & Brink, C. (2016). Automatic treatment planning improves the clinical quality of head and neck cancer treatment plans. Clinical and Translational Radiation Oncology, 1, 2–8. https://doi.org/10.1016/j.ctro.2016.08.001
10. Mori, Y., Kaneda, N., Hagiwara, M., & Ishiguchi, T. (2016). Dosimetric Study of Automatic Brain Metastases Planning in Comparison with Conventional Multi-Isocenter Dynamic Conformal Arc Therapy and Gamma Knife Radiosurgery for Multiple Brain Metastases. Cureus. https://doi.org/10.7759/cureus.882
11. Zarepisheh, M., Long, T., Li, N., Tian, Z., Romeijn, H. E., Jia, X., & Jiang, S. B. (2014). A DVH-guided IMRT optimization algorithm for automatic treatment planning and adaptive radiotherapy replanning. Medical Physics, 41. https://doi.org/10.1118/1.4875700
12. Boylan, C., & Rowbottom, C. (2014). A bias-free, automated planning tool for technique comparison in radiotherapy - application to nasopharyngeal carcinoma treatments. Journal of Applied Clinical Medical Physics, 15, 213–225. https://doi.org/10.1120/jacmp.v15i1.4530
13. Hussein, M., South, C. P., Barry, M. A., Adams, E. J., Jordan, T. J., Stewart, A. J., & Nisbet, A. (2016). Clinical validation and benchmarking of knowledge-based IMRT and VMAT treatment planning in pelvic anatomy. Radiotherapy and Oncology, 120, 473–479. https://doi.org/10.1016/j.radonc.2016.06.022
14. Wang, Y., Heijmen, B. J. M., & Petit, S. F. (2017). Prospective clinical validation of independent DVH prediction for plan quality assurance in automatic treatment planning for prostate cancer patients. Radiotherapy and Oncology, 125, 500–506. https://doi.org/10.1016/j.radonc.2017.09.021
15. Gintz, D., Latifi, K., Caudell, J., Nelms, B., Zhang, G., Moros, E., & Feygelman, V. (2016). Initial evaluation of automated treatment planning software. Journal of Applied Clinical Medical Physics, 17, 331–346. https://doi.org/10.1120/jacmp.v17i3.6167
16. Speer, S., Klein, A., Kober, L., Weiss, A., Yohannes, I., & Bert, C. (2017). Automated radiation planning: Evaluation of radiation plans generated with Pinnacle3 via scripting and auto-planning for patients with head and neck tumors. Radiotherapy and Oncology, 193, 656–665. https://doi.org/10.1007/s00066-017-1150-9
17. Harrison, K., Pullen, H., Welsh, C., Oktay, O., Alvarez-Valle, J., & Jena, R. (2022). Machine Learning for Auto-Segmentation in Radiotherapy Planning. Clinical Oncology, 34, 74–88. https://doi.org/10.1016/j.clon.2021.12.003
18. Men, K., Dai, J., & Li, Y. (2017). Automatic segmentation of the clinical target volume and organs at risk in the planning CT for rectal cancer using deep dilated convolutional neural networks: Medical Physics, 44, 6377–6389. https://doi.org/10.1002/mp.12602
19. Ibragimov, B., & Xing, L. (2017). Segmentation of organs-at-risk in head and neck CT images using convolutional neural networks: Medical Physics, 44, 547–557. https://doi.org/10.1002/mp.12045
20. Wong, J., Fong, A., McVicar, N., Smith, S., Giambattista, J., Wells, D., Kolbeck, C., Giambattista, J., Gondara, L., & Alexander, A. (2020). Comparing deep learning-based auto-segmentation of organs at risk and clinical target volumes to expert inter-observer variability in radiotherapy planning. Radiotherapy and Oncology, 144, 152–158. https://doi.org/10.1016/j.radonc.2019.10.019
21. Pesapane, F., Codari, M., & Sardanelli, F. (2018). Artificial intelligence in medical imaging: threat or opportunity? Radiologists again at the forefront of innovation in medicine. European Radiology Experimental, 2(1), 35. https://doi.org/10.1186/s41747-018-0061-6
22. Erdur, A. C., Rusche, D., Scholz, D., Kiechle, J., Fischer, S., Llorián-Salvador, Ó., Buchner, J. A., Nguyen, M. Q., Etzel, L., Weidner, J., Metz, M. C., Wiestler, B., Schnabel, J., Rueckert, D., Combs, S. E., & Peeken, J. C. (2025). Deep learning

for autosegmentation in radiotherapy treatment planning: State-of-the-art and novel perspectives. In Radiation Therapy and Oncology (Vol. 201, pp. 236–254). Springer Science and Business Media Deutschland GmbH. https://doi.org/10.1007/s00066-024-02262-2

23. Korte, J. C., Hardcastle, N., Ng, S. P., Clark, B., Kron, T., & Jackson, P. (2021). Cascaded deep learning-based auto-segmentation for head and neck cancer patients: Organs at risk on T2-weighted magnetic resonance imaging. Medical Physics, 48, 7757–7772. https://doi.org/10.1002/mp.15290
24. Wong, J., Huang, V., Giambattista, J. A., Teke, T., Kolbeck, C., Giambattista, J., & Atrchian, S. (2021). Training and Validation of Deep Learning-Based Auto-Segmentation Models for Lung Stereotactic Ablative Radiotherapy Using Retrospective Radiotherapy Planning Contours. Frontiers in Oncology, 11. https://doi.org/10.3389/fonc.2021.626499
25. Kawula, M., Purice, D., Li, M., Vivar, G., Ahmadi, S. A., Parodi, K., Belka, C., Landry, G., & Kurz, C. (2022). Dosimetric impact of deep learning-based CT auto-segmentation on radiation therapy treatment planning for prostate cancer. Radiation Oncology, 17. https://doi.org/10.1186/s13014-022-01985-9
26. Rong, Y., Chen, Q., Fu, Y., Yang, X., Al-Hallaq, H. A., Wu, Q. J., Yuan, L., Xiao, Y., Cai, B., Latifi, K., Benedict, S. H., Buchsbaum, J. C., & Qi, X. S. (2024a). NRG Oncology Assessment of Artificial Intelligence Deep Learning–Based Autosegmentation for Radiation Therapy: Current Developments, Clinical Considerations, and Future Directions. International Journal of Radiation Oncology Biology Physics, 119, 261–280. https://doi.org/10.1016/j.ijrobp.2023.10.033
27. Rong, Y., Chen, Q., Fu, Y., Yang, X., Al-Hallaq, H. A., Wu, Q. J., Yuan, L., Xiao, Y., Cai, B., Latifi, K., Benedict, S. H., Buchsbaum, J. C., & Qi, X. S. (2024b). NRG Oncology Assessment of Artificial Intelligence Deep Learning–Based Autosegmentation for Radiation Therapy: Current Developments, Clinical Considerations, and Future Directions. International Journal of Radiation Oncology Biology Physics, 119, 261–280. https://doi.org/10.1016/j.ijrobp.2023.10.033
28. Perkonigg, M., Hofmanninger, J., Herold, C. J., Brink, J. A., Pianykh, O., Prosch, H., & Langs, G. (2021). Dynamic memory to alleviate catastrophic forgetting in continual learning with medical imaging. Nature Communications, 12. https://doi.org/10.1038/s41467-021-25858-z
29. Kalsi, S., French, H., Chhaya, S., Madani, H., Mir, R., Anosova, A., & Dubash, S. (2024). The Evolving Role of Artificial Intelligence in Radiotherapy Treatment Planning—A Literature Review. Clinical Oncology, 36, 596–605. https://doi.org/10.1016/j.clon.2024.06.005
30. Pianykh, O. S., Langs, G., Dewey, M., Enzmann, D. R., Herold, C. J., Schoenberg, S. O., & Brink, J. A. (2020). Continuous learning AI in radiology: Implementation principles and early applications. In Radiology (Vol. 297, pp. 6–14). Radiological Society of North America Inc. https://doi.org/10.1148/radiol.2020200038

CHAPTER 33

Artificial Intelligence in Anesthesiology and Perioperative Medicine: From Clinical Decision Support to Autonomous Systems

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1. Introduction

1.1. Fundamentals of Artificial Intelligence and Its Applications in Anaesthesiology

Artificial intelligence (AI) is a multi-layered field of computer science focused on developing hardware and software systems that mimic human intelligence (1, 2). At the core of this field lie algorithms designed to provide machines with higher-level cognitive capabilities such as reasoning, problem solving, pattern recognition, object and language recognition, and visual perception (2). AI systems have the capacity to analyse large data sets, derive meaningful inferences, and predict future events based on complex patterns within the data.

The primary aim of AI applications in medicine is to support more efficient, consistent, and predictive decision-making processes. AI techniques used in clinical decision support systems have been shown to improve diagnostic accuracy, enable risk stratification, predict complications, and optimise clinical workflows across different medical disciplines (1, 2). Anaesthesiology represents a particularly suitable clinical environment for AI applications because it involves continuous physiological monitoring, rapid decision-making under time pressure, and a strong emphasis on patient safety (2, 5).

AI has broad potential applications across the full spectrum of anaesthesiology and perioperative medicine, including preoperative assessment, perioperative risk classification, prediction of difficult airways, intraoperative haemodynamic monitoring, monitoring of anaesthetic depth, drug dose optimisation, ultrasound-guided regional anaesthesia techniques, point-of-care ultrasound (POCUS), postoperative recovery processes, and

intensive care management (2, 4, 5). Consequently, AI should not be viewed solely as a technological innovation but also as a clinical instrument with the potential to transform the decision-making framework within anaesthesiology.

Nevertheless, the integration of AI into clinical practice is not dependent solely on technological capability. Several issues must be addressed within existing ethical frameworks, including system transparency, reliability, algorithmic bias, data security, and medico-legal responsibility (4, 30, 31). Therefore, the future of AI in anaesthesiology will depend not only on algorithmic performance but also on its alignment with ethical and regulatory standards.

2. Artificial Intelligence in Preoperative Risk Assessment and Difficult Airway Prediction

Preoperative assessment represents one of the most critical components of anaesthetic practice. Systemic diseases, physiological reserve, concomitant medication use, airway characteristics, and the type of planned surgical procedure must be evaluated together in order to design an individualised anaesthesia plan. However, this process may be challenging even for experienced anaesthesiologists because it requires a patient-specific approach and involves numerous interacting variables.

In recent years, preoperative assessment has gradually evolved from traditional static form-based evaluation and subjective scoring systems toward machine learning-supported dynamic risk prediction models. This transformation reflects the broader integration of surgical planning with personalised medicine approaches.

Artificial intelligence applications have gained increasing attention in anaesthesiology because of their potential to improve patient outcomes, enhance clinical decision-making, and increase healthcare efficiency (1, 2). By analysing multidimensional clinical data—including electronic health records, laboratory findings, imaging data, and patient history—AI systems can generate patient-specific risk profiles and support more accurate preoperative planning (3, 9, 10).

2.1. Difficult Airway Prediction

Prediction of a difficult airway remains a critical component of preoperative evaluation. Although conventional methods such as the Mallampati classification, thyromental distance measurement, and mouth opening assessment are widely used in clinical practice, these tests have limited sensitivity and specificity and are highly dependent on observer interpretation.

Recent research has increasingly explored the use of AI in predicting difficult airway management (4, 6, 7). Approaches developed between 2010 and 2020 shifted attention beyond classical parameters such as body mass index (BMI) and thyromental distance toward computer-assisted analysis of facial images and video recordings.

In their 2021 study, Tavolara and colleagues developed a deep learning model based on frontal facial images and demonstrated improved performance in identifying patients who may be difficult to intubate compared with traditional assessment methods (6). Similarly, other studies have shown that the Cormack-Lehane classification can be predicted using computer-based analysis of facial and cervical anatomical features (7). These findings suggest that visual data-driven prediction models may complement traditional airway assessment methods.

2.2. Personalization and Risk Prediction

The American Society of Anesthesiologists Physical Status (ASA-PS) classification is one of the most widely used tools for preoperative risk assessment. However, ASA-PS is inherently subjective and relies on clinician judgement. Consequently, the classification assigned to a given patient may vary between different evaluators.

Zhang and colleagues demonstrated that an automated model capable of predicting ASA-PS using variables such as patient comorbidities and medication profiles achieved predictive performance comparable to that of anaesthesiologists (8). This approach highlights the potential role of AI in improving standardisation within clinical risk assessment.

Deep neural networks and machine learning models have also been successfully applied to predict important postoperative outcomes such as mortality, acute kidney injury, and reintubation (9). Systems such as MySurgeryRisk use electronic health record data to predict perioperative complications before surgery begins (10). These predictive models may assist not only in evaluating surgical suitability but also in perioperative resource planning, including intensive care unit requirements and the anticipation of intraoperative risks.

Thus, AI-supported preoperative models should be regarded as decision-support tools that augment rather than replace clinician judgement. By enhancing predictive capacity during the preoperative period, these systems may contribute to more robust intraoperative management strategies.

3. Artificial Intelligence in the Intraoperative Period and Anaesthesia Management

The intraoperative period involves continuous monitoring of the patient's physiological status and requires rapid decision-making in response to dynamically changing clinical conditions. Therefore, real-time data analysis and predictive decision-support systems play an increasingly important role in anaesthetic practice.

AI-supported systems are capable of analysing multiple physiological parameters simultaneously—including vital signs, arterial pressure waveforms, electroencephalogram (EEG) signals, and drug administration data—and can provide earlier and more accurate alerts to clinicians (2, 11, 17).

3.1. Prediction of Hemodynamic Instability

One of the most prominent applications of AI during the intraoperative period is the prediction of hypotension and other haemodynamic disturbances. Hatib and colleagues developed a machine learning algorithm capable of predicting intraoperative hypotension before its clinical manifestation through the analysis of high-resolution arterial pressure waveforms (11).

Such predictive systems allow clinicians to detect impending physiological deterioration earlier and intervene proactively. Early warning of haemodynamic instability may facilitate timely interventions such as fluid therapy, vasopressor administration, or adjustment of anaesthetic depth. Consequently, AI is evolving from a passive monitoring tool into an active decision-support system in intraoperative care.

3.2. Drug Dose Optimization and Personalized Anesthesia

Accurate drug dosing is a cornerstone of safe and effective anaesthesia management. Traditionally, anaesthetic drug titration has relied on clinician experience, standard dosing ranges, and physiological monitoring data. However, factors such as age, BMI, comorbidities, medication use, and individual pharmacodynamic variability mean that identical dosing strategies may produce different effects across patients.

AI-supported models can evaluate multiple patient-specific variables simultaneously and estimate optimal dosing requirements, potentially reducing both underdosing and overdosing risks (12). AI-integrated approaches combined with target-controlled infusion (TCI) systems have been investigated for agents such as propofol and remifentanil (13). As a result, intraoperative pharmacological management is gradually shifting from fixed protocols toward adaptive, patient-specific dosing strategies.

3.3. Monitoring of Anaesthetic Depth

Reliable monitoring of anaesthetic depth is essential for preventing intraoperative awareness and avoiding unnecessarily deep anaesthesia. Recent advances in machine learning—including deep neural networks, fuzzy logic systems, and hybrid EEG-based analytical models—have enabled more accurate prediction of Bispectral Index (BIS) values and improved assessment of anaesthetic depth (13–15).

Lee and colleagues demonstrated that deep learning models achieved high accuracy in predicting BIS values during propofol and remifentanil TCI administration (13). Other algorithmic approaches have similarly shown potential in reducing the risk of intraoperative awareness (14, 15). These developments suggest that AI may function not only as a monitoring tool but also as an optimisation system integrated with anaesthetic pharmacology.

3.4. Quality Control, Automation, and Workflow Optimization

AI-based systems may also contribute to the standardisation of anaesthesia quality. In a randomised controlled trial conducted by Xu and colleagues, an AI-supported quality

control system improved anaesthesia management during sedation for gastrointestinal endoscopy (16). Such systems may promote greater adherence to monitoring standards and improve clinical consistency.

Beyond direct anaesthetic management, AI-enabled technologies are also being introduced into hospital logistics. Smart medication distribution systems and autonomous mobile robots have demonstrated potential to improve patient safety and operational efficiency. Barcode technology has been shown to reduce medication errors in clinical practice (19, 20). Additionally, autonomous robots that transport medications and supplies within hospitals may reduce administrative workload and allow healthcare professionals to devote more time to direct patient care (21). Although these systems do not directly influence anaesthetic decision-making, they illustrate the broader digital transformation occurring in perioperative care environments.

3.5. The Limits of Autonomous Systems: The SEDASYS Example

One of the most well-known examples illustrating the limitations of AI-based autonomous systems is the SEDASYS computer-assisted sedation system. Developed to deliver minimal-to-moderate propofol sedation, SEDASYS received approval from the United States Food and Drug Administration (FDA) in 2013 for specific endoscopic procedures (24). The system was designed to automatically adjust propofol infusion based on continuous monitoring of patient physiological parameters, aiming to standardise sedation delivery (22, 24).

However, the system failed to achieve widespread clinical adoption and was withdrawn from the market within a few years. Key factors contributing to this outcome included limited capability to manage deeper levels of sedation, inadequate handling of airway complications, and concerns regarding patient safety when used by non-anaesthesiologist personnel (23, 24). This experience highlights that fully autonomous sedation systems remain limited in real-world clinical practice and reinforces the importance of anaesthesiologist supervision when implementing AI-supported technologies.

4. Artificial Intelligence in Ultrasound-Guided Regional Anaesthesia and Point-of-Care Ultrasonography

Advances in AI-particularly in image processing and pattern recognition-are significantly influencing anaesthesiology practices that rely heavily on visual interpretation. One of the most prominent examples of this transformation is found in ultrasound-guided regional anaesthesia (UGRA) and point-of-care ultrasound (POCUS) applications (3, 18).

Machine learning algorithms and predictive analytics can enhance the interpretation of ultrasound images and improve procedural safety, standardization, and training efficiency. The differences between traditional and AI-assisted POCUS approaches are summarised in Table 1.

Table 1. Traditional Versus AI-Assisted POCUS

Feature	Traditional POCUS	AI-Assisted POCUS	Limitations
Anatomical Recognition	Depends primarily on operator experience	Provides automatic segmentation and highlighting	Highly dependent on image quality
Error Rate	Subjective interpretation and anatomical variation may increase error	Algorithmic support may reduce inter-observer variability	False reassurance may occur in rare anomalies
Learning Curve	Requires prolonged practice and expert mentorship	Visual guidance may accelerate skill acquisition	Excessive technological dependence may weaken basic skills
Safety	Needle tip visibility depends on operator skill	Needle tracking and target warning systems may improve safety	Software errors and system latency remain concerns

AI optimizes the UGRA and POCUS workflow across three main domains. First, it facilitates anatomical recognition by helping identify target structures rapidly and consistently, even in patients with complex anatomical variations. Second, it improves workflow efficiency through automated image enhancement, structure highlighting, and target segmentation. Third, it supports training and decision-making by acting as a "second set of eyes," particularly for less experienced practitioners (3, 18).

A comprehensive review by Bowness and colleagues demonstrated that theoretical AI applications in this field have already translated into commercially available tools (18). Systems such as cNerve, Nerveblox, NerveTrack, ScanNav Anatomy, and Smart Nerve are used in peripheral nerve blocks, while technologies such as Accuro and uSine have also been introduced in neuraxial procedures (18). These technologies may enhance procedural safety while potentially reducing healthcare costs by shortening procedure duration.

Nevertheless, AI-assisted ultrasound systems also have limitations. Algorithm performance may decline when ultrasound image quality is poor. Rare anatomical variations may lead to incorrect algorithmic interpretation. Moreover, excessive reliance on technology may weaken fundamental ultrasound skills. Therefore, AI-assisted ultrasound should be considered a supportive tool rather than a replacement for operator expertise.

5. Artificial Intelligence in Postoperative Care and Intensive Care Management

Anaesthesia practice extends beyond the intraoperative period. Postoperative monitoring, enhanced recovery protocols, and intensive care management form integral components of perioperative care. AI integration in these domains enables the development of predictive and personalised care models through large-scale data analysis, allowing earlier identification of complications and optimisation of recovery processes (25–29).

Machine learning models have demonstrated the ability to predict 30-day postoperative mortality and prolonged intensive care unit admission exceeding 24 hours (25, 26). These predictive capabilities are particularly valuable in elective surgery, as they support planning of ICU resources, staffing requirements, and perioperative logistics.

Enhanced Recovery After Surgery (ERAS) protocols aim to reduce surgical stress responses and accelerate functional recovery. By integrating preoperative and intraoperative data, AI may help identify patients at higher risk of postoperative complications and support the development of personalised recovery pathways. In this context, AI may become an important tool for the personalisation of ERAS protocols.

AI applications may also support postoperative sedation monitoring and recovery assessment, potentially improving patient comfort and recovery times (16). Additionally, machine learning algorithms have been investigated in ventilator weaning processes by evaluating physiological parameters collectively to determine optimal extubation timing (10). In pain management, AI-based facial recognition systems may allow more objective pain assessment, particularly in patients with communication limitations (28).

Together, these developments demonstrate that AI is evolving from a predictive technology into an integrated perioperative management tool.

6. Ethical and Legal Challenges of Artificial Intelligence in the Clinical Decision-Making

The question of whether AI should be considered a tool, advisor, or partially autonomous decision-maker represents one of the most complex debates in modern medical ethics. In high-risk specialties such as anaesthesiology, where rapid decisions directly affect patient safety, careful consideration must be given before adopting autonomous systems without adequate transparency (4, 29, 30).

Human oversight remains both a legal and ethical requirement in clinical decision-making. Recommendations generated by algorithms must always be interpreted within the context of clinician expertise and patient-specific circumstances. This principle is commonly described as the *human-in-the-loop* model, which emphasises supervised decision support rather than uncontrolled automation (29, 30).

Data bias represents another critical ethical concern. Incomplete datasets or underrepresentation of certain demographic groups may result in biased algorithmic outputs (4, 30). Additionally, uncertainty remains regarding legal responsibility when algorithm-guided clinical decisions lead to adverse outcomes. Whether responsibility lies with the clinician, software developer, or healthcare institution remains an ongoing debate (30, 31).

Therefore, responsible implementation of AI in anaesthesiology requires adherence to principles of transparency, explainability, human oversight, data security, and equitable representation.

7. The Changing Role of the Anaesthesiologist in the Age of Artificial Intelligence

The increasing integration of AI into anaesthesiology is transforming rather than replacing the role of the specialist physician. In the future, anaesthesiologists may shift from performing repetitive manual tasks toward supervising complex digital decision-support systems (2, 5, 31).

In this evolving environment, anaesthesiologists will not only rely on traditional expertise in pharmacology and physiology but will also require strong data literacy, the ability to interpret algorithmic outputs, and the capacity to oversee AI-supported clinical systems.

Medical education will therefore need to adapt accordingly. Future anaesthesia training programs may incorporate topics such as data science, AI literacy, algorithm-based decision systems, and simulation-based training. AI-enhanced simulation environments may be particularly valuable for training in crisis management, difficult airway scenarios, haemodynamic instability, and complex clinical decision-making.

As AI-based systems increasingly perform repetitive technical tasks, anaesthesiologists may focus more on complex ethical considerations, multimodal data interpretation, and patient-centred perioperative care strategies. In this context, the role of AI is not to replace clinical expertise but to reduce cognitive workload, enhance decision quality, and ultimately improve patient safety.

8. Conclusion

Artificial intelligence is emerging as a powerful, transformative tool across the full continuum of anaesthesiology and perioperative medicine. Its applications range from preoperative risk stratification and difficult airway prediction to intraoperative hemodynamic forecasting, drug dose optimization, ultrasound-guided procedures, and postoperative care management.

Current evidence suggests that the safest and most effective implementation of AI lies in clinician-supervised decision-support systems rather than fully autonomous technologies. The future of anaesthesiology will likely be shaped by a hybrid model that integrates the strengths of both human expertise and intelligent algorithms.

In anaesthesiology, the success of AI will ultimately depend not only on the accuracy of its predictions but also on how safely, transparently, and responsibly it is integrated into clinical practice.

9. References

1. Bogoń, A., Górska, M., Ostojska, M., Kałuża, I., Dziuba, G., & Dobosz, M. (2024). Artificial intelligence in anesthesiology-a review. *Journal of Pre-Clinical & Clinical Research*, *18*(3).
2. Hashimoto, D. A., Witkowski, E., Gao, L., Meireles, O., & Rosman, G. (2020). Artificial intelligence in anesthesiology: current techniques, clinical applications, and limitations. *Anesthesiology*, *132*(2), 379.
3. Görmüş, S. K. (2024). Integrative Artificial Intelligence in Regional Anesthesia: Enhancing Precision, Efficiency, Outcomes and Limitations. *Journal of Innovative Healthcare Practices*, *5*(1), 52-66.
4. Song, B., Zhou, M., & Zhu, J. (2023). Necessity and importance of developing AI in anesthesia from the perspective of clinical safety and information security. *Medical science monitor: international medical journal of experimental and clinical research*, *29*, e938835-1.
5. Langeron, O., Castoldi, N., Rognon, N., Baillard, C., & Samama, C. M. (2024). How anesthesiology can deal with innovation and new technologies?. *Minerva anestesiologica*, *90*(1-2), 68-76.
6. Tavolara, T. E., Gurcan, M. N., Segal, S., & Niazi, M. K. K. (2021). Identification of difficult to intubate patients from frontal face images using an ensemble of deep learning models. *Computers in biology and medicine*, *136*, 104737.
7. Connor, C. W., & Segal, S. (2011). Accurate classification of difficult intubation by computerized facial analysis. *Anesthesia & Analgesia*, *112*(1), 84-93.
8. Zhang, L., Fabbri, D., Lasko, T. A., Ehrenfeld, J. M., & Wanderer, J. P. (2018). A system for automated determination of perioperative patient acuity. *Journal of medical systems*, *42*(7), 123.
9. Hofer, I. S., Lee, C., Gabel, E., Baldi, P., & Cannesson, M. (2020). Development and validation of a deep neural network model to predict postoperative mortality, acute kidney injury, and reintubation using a single feature set. *NPJ digital medicine*, *3*(1), 58.
10. Bihorac, A., Ozrazgat-Baslanti, T., Ebadi, A., Motaei, A., Madkour, M., Pardalos, P. M., ... & Momcilovic, P. (2019). MySurgeryRisk: development and validation of a machine-learning risk algorithm for major complications and death after surgery. *Annals of surgery*, *269*(4), 652-662.
11. Hatib, F., Jian, Z., Buddi, S., Lee, C., Settels, J., Sibert, K., ... & Cannesson, M. (2018). Machine-learning algorithm to predict hypotension based on high-fidelity arterial pressure waveform analysis. *Anesthesiology*, *129*(4), 663-674.
12. Bellini, V., Valente, M., Bertorelli, G., Pifferi, B., Craca, M., Mordonini, M., ... & Bignami, E. (2022). Machine learning in perioperative medicine: a systematic review. *Journal of anesthesia, analgesia and critical care*, *2*(1), 2.
13. Lee, H. C., Ryu, H. G., Chung, E. J., & Jung, C. W. (2018). Prediction of bispectral index during target-controlled infusion of propofol and remifentanil. *Anesthesiology*, *128*(3), 492-501.
14. Shalbaf, A., Saffar, M., Sleigh, J. W., & Shalbaf, R. (2017). Monitoring the depth of anesthesia using a new adaptive neurofuzzy system. *IEEE journal of biomedical and health informatics*, *22*(3), 671-677.
15. Tacke, M., Kochs, E. F., Mueller, M., Kramer, S., Jordan, D., & Schneider, G. (2020). Machine learning for a combined electroencephalographic anesthesia index to detect awareness under anesthesia. *Plos one*, *15*(8), e0238249.
16. Xu, C., Zhu, Y., Wu, L., Yu, H., Liu, J., Zhou, F., ... & Xia, Z. (2022). Evaluating the effect of an artificial intelligence system on the anesthesia quality control during gastrointestinal endoscopy with sedation: a randomized controlled trial. *BMC anesthesiology*, *22*(1), 313.
17. Singam, A. (2023). Revolutionizing patient care: a comprehensive review of artificial intelligence applications in anesthesia. *Cureus*, *15*(12).
18. Bowness, J. S., Metcalfe, D., El-Boghdadly, K., Thurley, N., Morecroft, M., Hartley, T., ... & Higham, H. (2024). Artificial intelligence for ultrasound scanning in regional anaesthesia: a scoping review of the evidence from multiple disciplines. *British Journal of Anaesthesia*, *132*(5), 1049-1062.
19. Poon, E. G., Keohane, C. A., Yoon, C. S., Ditmore, M., Bane, A., Levtzion-Korach, O., ... & Gandhi, T. K. (2010). Effect of bar-code technology on the safety of medication administration. *New England Journal of Medicine*, *362*(18), 1698-1707.
20. Schneider, P. J., Pedersen, C. A., Ganio, M. C., & Scheckelhoff, D. J. (2019). ASHP national survey of pharmacy practice in hospital settings: workforce—2018. *American Journal of Health-System Pharmacy*, *76*(15), 1127-1141.
21. Shin, H., Kim, S., Jung, E., Han, Y., Lee, N., Park, S., ... & Woo, J. (2025). A Comprehensive Review of Autonomous Mobile Robots in Healthcare: Implications for Patient-Transporting Human-Following Robots. *Robotics*, *14*(12), 179.
22. Giri, R., Firdhos, S. H., & Vida, T. A. (2025). Artificial intelligence in anesthesia: enhancing precision, safety, and global access through data-driven systems. *Journal of Clinical Medicine*, *14*(19), 6900.
23. Mahmoud, M., & Mason, K. P. (2018). Recent advances in intravenous anesthesia and anesthetics. *F1000Research*, *7*, F1000-Faculty.
24. U.S. Food and Drug Administration. SEDASYS computer-assisted Personalised sedation system (P080009) - premarket approval [Internet]. Silver Spring (MD): FDA; 2013 [cited 2026 Mar 12]. Available from: https://www.accessdata.fda.gov/cdrh_docs/pdf8/P080009b.pdf
25. Chiew, C. J., Liu, N., Wong, T. H., Sim, Y. E., & Abdullah, H. R. (2020). Utilizing machine learning methods for preoperative prediction of postsurgical mortality and intensive care unit admission. *Annals of surgery*, *272*(6), 1133-1139.

26. Jauk S, Kramer D, Stark G, Hasiba K, Leodolter W, Schulz S, Kainz J. Development of a machine learning model predicting an ICU admission for patients with elective surgery and its prospective validation in clinical practice. Stud Health Technol Inform. 2019;264:173-177. doi:10.3233/SHTI190206.
27. Xue, B., Li, D., Lu, C., King, C. R., Wildes, T., Avidan, M. S., ... & Abraham, J. (2021). Use of machine learning to develop and evaluate models using preoperative and intraoperative data to identify risks of postoperative complications. *JAMA network open*, *4*(3), e212240.
28. Huo, J., Yu, Y., Lin, W., Hu, A., & Wu, C. (2024). Application of AI in multilevel pain assessment using facial images: systematic review and meta-analysis. *Journal of Medical Internet Research*, *26*, e51250.
29. Cascella, M., Tracey, M. C., Petrucci, E., & Bignami, E. G. (2023). Exploring artificial intelligence in anesthesia: a primer on ethics, and clinical applications. *Surgeries*, *4*(2), 264-274.
30. Bellini, V., Valente, M., Gaddi, A. V., Pelosi, P., & Bignami, E. (2022). Artificial intelligence and telemedicine in anesthesia: potential and problems. *Minerva anestesiologica*, *88*(9), 729-734.
31. Naaz, S., & Asghar, A. (2022). Artificial intelligence, nano-technology and genomic medicine: the future of anaesthesia. *Journal of Anaesthesiology Clinical Pharmacology*, *38*(1), 11-17.

CHAPTER 34

Advantages and Limitations of Artificial Intelligence in the Diagnosis and Management of Glaucoma

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1. Introduction

1.1. Why have We Entered A "Data-Driven Decision" Era in Glaucoma Management?

For clinicians, glaucoma is rarely reducible to a single number such as elevated intraocular pressure. The core issue is the gradual damage to retinal ganglion cells and the optic nerve—often progressing for long periods without noticeable symptoms in many patients. Therefore, glaucoma management cannot rely on a "measure once, decide immediately" approach; rather, it requires repeated measurements, assessment of longitudinal trends, risk stratification, and timely, appropriate intervention. This paradigm becomes even more critical as the global burden of glaucoma continues to rise. In a systematic review and meta-analysis by Tham et al., the prevalence of glaucoma in individuals aged 40–80 years was reported to be approximately 3.54%, with the number of affected individuals projected to increase from 64.3 million in 2013 to 111.8 million by 2040. This increase is expected to be particularly pronounced in Asia and Africa, highlighting glaucoma as an escalating public health challenge that will place increasing strain on healthcare systems in terms of specialist access and screening/follow-up capacity (1).

At this point, the convergence of glaucoma and artificial intelligence is not a matter of technological trend, but of practical necessity. Clinical decision-making in glaucoma diagnosis and follow-up no longer relies on a single data source; instead, it requires the integrated interpretation of multiple modalities, including optic disc photographs, optical coherence tomography (OCT), visual field tests, intraocular pressure trends, corneal biomechanics, and demographic as well as systemic risk factors. However, much of

these data are imperfect in routine clinical practice: image quality may vary, device and protocol differences can influence outcomes, and patient compliance or fatigue may affect measurements. A well-known example is visual field testing: although indispensable for monitoring glaucoma progression, it is inherently patient-dependent and subject to variability. As clearly stated in the introduction of a 2023 study, "However, VF testing is patient-dependent and highly inconsistent…" It is precisely at this juncture that artificial intelligence demonstrates its value in glaucoma practice: its potential to extract meaningful patterns from repetitive, noisy, and high-dimensional data, thereby providing clinical decision support (2).

1.2. The Emergence of Artificial Intelligence in Glaucoma: From Classification to Clinical Workflow İntegration

The initial applications of artificial intelligence in glaucoma naturally focused on the most accessible data: color fundus photographs and optic disc appearance. These images are rapidly acquired, easily collected across multiple centers, and readily integrated into screening programs. Deep learning models trained on such data have demonstrated strong performance, particularly in screening and triaging suspected glaucomatous optic neuropathy. One of the early and influential examples is the 2018 *Ophthalmology* study by Li et al., which evaluated a deep learning system designed to detect referable glaucoma from color fundus photographs (3). This approach was significant in demonstrating that glaucoma detection could extend beyond outpatient clinics into population-based screening settings, thereby paving the way for the use of larger and more diverse datasets.

Subsequent research expanded this approach by increasing data diversity. Liu et al. (JAMA Ophthalmology, 2019) reported that a deep learning system could achieve high sensitivity, specificity, and generalizability in detecting glaucomatous optic neuropathy from fundus photographs obtained under varying conditions and image quality (4). The key question thus evolved from "Does it work well in a single center?" to "Can it perform reliably across different settings?"—inevitably leading to real-world validation studies.

This trajectory culminated in more recent "real-world" studies, including a 2025 investigation directly comparing algorithm performance with that of clinicians. Conducted in a safety-net population, this study reported that the algorithm "approximates or exceeds performance by ophthalmologists and optometrists" in detecting referable glaucoma. Notably, clinician sensitivity and specificity varied widely and did not correlate with years of experience, underscoring the practical value of artificial intelligence: mitigating variability in human performance through a more standardized screening layer (5). At this stage, artificial intelligence began to be conceptualized not merely as a classification tool, but as an integral component of clinical workflow—leading naturally to the anatomical complexity of glaucoma.

1.3. Are We Only Seeing The Optic Disc When We Look At It?

Although the optic nerve head is the most prominent structure associated with glaucoma, glaucomatous damage is not confined to this region alone. The peripapillary retinal nerve

fiber layer, vascular structures, the broader retinal architecture, and even regions outside the optic disc may contain subtle indicators of disease. One of the most striking strengths of deep learning models lies in their ability to detect patterns across a broader spatial context, particularly in situations where human observers may focus narrowly on a single anatomical region.

The study by Hemelings et al. (Scientific Reports, 2021) is particularly illustrative in this regard. It demonstrated that deep learning models could achieve meaningful performance even in the absence of the optic nerve head in the input images. The authors described this as "the first irrefutable evidence that deep learning can detect glaucoma from fundus image regions outside the ONH." In the same study, the area under the curve (AUC) for glaucoma detection was reported as 0.94 using full images and remained as high as 0.88 even when the optic nerve head was masked. These findings emphasize that glaucoma diagnosis cannot be reduced to a single anatomical locus, and that artificial intelligence can leverage broader contextual information in a statistically robust manner. This naturally raises a further question: if models can interpret more than a binary presence or absence of disease, can they also predict disease severity and progression? (6)

1.4. From Structural Data to Function, and from Function to Personalized Follow-Up

In clinical practice, the most challenging aspect of glaucoma management often begins after establishing the diagnosis. Clinicians must address questions such as: How rapidly is the disease progressing? Which patients require more frequent monitoring? Who needs more aggressive treatment? At this stage, the value of artificial intelligence lies not only in classification, but also in its ability to generate quantitative predictions. Such predictions directly inform follow-up strategies and resource allocation.

Christopher et al. addressed this perspective by aiming to detect glaucomatous visual field damage and predict its severity using OCT-derived retinal nerve fiber layer maps and optic nerve head en face images. Their results demonstrated improved performance compared to standard nerve fiber layer thickness measurements for certain outcomes. As stated in their conclusion, "Accurately predicting the severity of GFVD from SDOCT imaging can help clinicians more effectively individualize the frequency of VF testing…" The goal, therefore, is not to replace clinical decision-making, but to support clinicians in optimizing follow-up intervals and resource utilization. In this way, artificial intelligence transitions from a diagnostic tool to a means of enhancing longitudinal management strategies—though this requires bridging different data modalities (7).

An illustrative example of such integration is the "From Machine to Machine" approach proposed by Medeiros et al. In this framework, OCT measurements are used as a "teaching signal" to predict retinal nerve fiber layer thickness quantitatively from optic disc photographs, reducing reliance on human labeling. In the test dataset, a strong correlation (Pearson $r \approx 0.83$; $R^2 \approx 69\%$) and low absolute error were reported between predicted and measured values. This approach addresses a fundamental challenge in glau-

coma—the structure–function discordance and measurement variability—by integrating multimodal data within a unified analytical framework (8). However, this leads to a critical question for clinical practice: do these promising research findings translate into equally reliable performance in real-world settings?

1.5. The Gap Between "Excellent in Research" and "Safe in Clinical Practice"

The studies discussed thus far demonstrate the significant momentum of artificial intelligence in glaucoma. However, successful clinical translation depends not on isolated high-performance results, but on the quality of evidence, generalizability, and transparency. A comprehensive systematic review published in *NPJ Digital Medicine* in 2026 examined 46 reports representing 43 original studies conducted after 2014. The review concluded that while artificial intelligence models show "moderate-to-good" performance in predicting glaucoma progression, significant challenges remain for clinical implementation. As succinctly stated in the conclusion, "The overwhelming lack of external validation…" represents a major limitation (9). In other words, even if a model performs well in a specific center or with a particular device, its reliability across different settings, devices, and patient populations is often insufficiently demonstrated.

This observation underscores the importance of transparency and standardized reporting. Accordingly, contemporary artificial intelligence research emphasizes not only model development but also rigorous reporting and evaluation standards. The CONSORT-AI (for clinical trial reporting) and SPIRIT-AI (for clinical trial protocols) extensions specifically require transparent reporting of how AI interventions are integrated into clinical workflows, how inputs and outputs are managed, and how human–AI interaction and error analyses are conducted (10). Similarly, TRIPOD+AI aims to improve the reporting quality of prediction models and machine learning studies, enhancing comparability and reproducibility of evidence (11). Collectively, these frameworks convey a central message: clinical safety depends not only on model performance, but also on how that performance is generated and where it is applicable—and this principle will serve as a guiding framework throughout discussions of both the advantages and limitations of artificial intelligence in glaucoma.

2. Glaucoma

2.1. Definition

Glaucoma comprises a heterogeneous group of progressive optic neuropathies characterized by the gradual loss of retinal ganglion cells (RGCs), consequent thinning of the retinal nerve fiber layer (RNFL), and progressive excavation of the optic nerve head (ONH) (12).

2.2. Classification

Glaucoma may be classified according to the time of onset as congenital or acquired. Based on the configuration of the iridocorneal angle, it is categorized as open-angle or

angle-closure glaucoma. Furthermore, according to etiology, glaucoma is subdivided into primary and secondary forms (13).

2.3. Epidemiology

Glaucoma represents one of the leading causes of irreversible visual impairment and blindness worldwide. Primary open-angle glaucoma (POAG) is more prevalent among White, Hispanic/Latino, and particularly Black populations, whereas primary angle-closure glaucoma (PACG) is more frequently observed in individuals of Asian descent (13).

Global estimates from 2020 indicate that approximately 76 million individuals are affected by glaucoma, of whom around 4.5 million have moderate-to-severe visual impairment and 3.2 million are blind. With the progressive aging of the global population, the prevalence of glaucoma is expected to increase substantially, reaching an estimated 112 million affected individuals by 2040 (14).

2.4. Primary Open-Angle Glaucoma

2.4.1. Risk Factors

The most significant modifiable risk factor for POAG is elevated intraocular pressure (IOP). A positive family history increases the risk by approximately 2–4-fold. The disease is more commonly reported in individuals of African descent and has also been associated with thin central corneal thickness and myopia (14).

Associations between diabetes mellitus, hypertension, and glaucoma development or progression have been reported; however, the strength and causality of these relationships remain inconsistent across populations (13).

2.4.2. Genetics

Several genes have been implicated in POAG, including *MYOC*, *OPTN*, and *WDR36*; however, these account for only a small proportion of cases. Additional genetic loci, such as *CAV1/CAV2* and *CDKN2B-AS1*, have also been associated with increased susceptibility. Nevertheless, the precise mechanisms by which these genetic factors contribute to disease pathogenesis remain incompletely understood (15).

2.4.3. Pathogenesis

Elevated intraocular pressure exerts biomechanical stress on posterior segment structures, particularly the lamina cribrosa and adjacent peripapillary tissues. The lamina cribrosa, through which RGC axons exit the globe, is considered one of the most pressure-sensitive regions of the ocular wall.

IOP-induced mechanical stress may result in compression, posterior displacement, deformation, and extracellular matrix remodeling of the lamina cribrosa. These structural and microarchitectural alterations impose direct mechanical strain on axons, disrupting

their integrity and impairing both anterograde and retrograde axonal transport. Interruption of axonal transport, particularly the retrograde delivery of neurotrophic factors from relay neurons in the lateral geniculate nucleus to retinal ganglion cells, compromises essential cellular homeostatic mechanisms required for neuronal survival (15).

2.4.4. Clinical Findings and Diagnosis

Glaucoma is typically a progressive and irreversible optic neuropathy that remains asymptomatic until significant RGC loss and optic nerve damage have occurred. As the disease advances, characteristic structural changes develop at the optic nerve head, including neuroretinal rim thinning, increased cup-to-disc ratio, and reduction in peripapillary RNFL thickness (15).

Optical coherence tomography (OCT) is currently the principal imaging modality for the quantitative and reproducible assessment of structural damage. It enables objective measurement of peripapillary RNFL thickness, the ganglion cell complex, and ONH parameters. Notably, structural alterations often precede detectable functional loss (15).

Visual field defects typically begin in the mid-peripheral regions and progress toward central vision. In advanced stages, only a small central or peripheral island of vision may remain. This progression reflects the strong pathophysiological correlation between structural axonal loss and functional visual field impairment. Therefore, the combined use of structural (OCT, ONH evaluation) and functional (standard automated perimetry) assessments is essential for accurate diagnosis and longitudinal monitoring (15).

2.4.5. Treatment

The intraocular pressure measured prior to treatment is considered to be damaging to the optic nerve. The target IOP is defined as the pressure level at which disease progression is halted. This target is individualized based not only on baseline IOP but also on central corneal thickness, RNFL status, patient age, and overall clinical condition. The primary goal of glaucoma management is to maintain IOP below this target level (13).

2.4.5.1. Medical Therapy

Antiglaucomatous agents lower intraocular pressure by modulating aqueous humor dynamics through three principal mechanisms: reducing aqueous humor production at the ciliary body, increasing trabecular outflow, and enhancing uveoscleral outflow. The major classes of medications include α-adrenergic agonists, β-adrenergic receptor antagonists, prostaglandin analogues, carbonic anhydrase inhibitors, and epinephrine derivatives (16).

2.4.5.2. Surgical Treatment

When medical therapy is insufficient, laser or incisional surgical interventions may be employed. Laser trabeculoplasty lowers IOP by inducing biological changes in the trabecular

meshwork that enhance aqueous outflow. Among incisional procedures, trabeculectomy remains the most commonly performed surgical technique (15).

2.5. Primary Angle-Closure Glaucoma

Primary angle-closure glaucoma (PACG) is characterized by elevated intraocular pressure due to obstruction of aqueous humor outflow secondary to peripheral iris contact or apposition at the trabecular meshwork, leading to glaucomatous optic neuropathy (13).

2.5.1. Risk Factors and Genetics

Risk factors for PACG include advanced age, female sex, Asian ethnicity, hyperopia, and a positive family history of glaucoma (13).

Genetic studies have identified loci such as *PLEKHA7*, *COL11A1*, and *EPDR1*, which are thought to influence anterior segment anatomy and predisposition to angle closure (13).

2.5.2. Pathogenesis

PACG can be classified according to the underlying mechanism of angle closure: pupillary block, non-pupillary block mechanisms, plateau iris configuration, and ciliary block.

- In pupillary block, close apposition between the iris and lens impedes aqueous humor flow, creating a pressure gradient between the posterior and anterior chambers. This leads to anterior bowing of the iris and subsequent angle closure.
- Non-pupillary block mechanisms involve structural factors such as increased iris thickness, which hinder aqueous passage.
- Plateau iris configuration results from anterior positioning of the ciliary body, causing the peripheral iris to narrow the angle.
- In ciliary block, aqueous humor is misdirected posteriorly into the vitreous cavity, increasing posterior segment pressure. This leads to anterior displacement of the lens–iris diaphragm, shallowing of the anterior chamber, and eventual angle closure (13).

2.5.3. Clinical Findings and Diagnosis

PACG is clinically classified into acute, subacute, chronic, and latent forms.

- **Acute** angle closure is characterized by markedly elevated IOP, severe ocular pain, decreased vision, conjunctival hyperemia, headache, nausea, and vomiting due to complete angle closure.
- **Subacute** presentations involve intermittent IOP elevations with transient symptoms.
- **Chronic** PACG progresses insidiously with persistently elevated IOP due to peripheral anterior synechiae and is often asymptomatic.
- **Latent** forms are characterized by anatomically narrow but open angles.

Biomicroscopic examination allows evaluation of anterior chamber depth and anterior segment abnormalities. Gonioscopy remains the gold standard for assessing the anterior

chamber angle, with indentation gonioscopy being particularly useful for distinguishing appositional closure from peripheral anterior synechiae.

Anterior segment OCT is widely utilized for non-contact, rapid assessment of angle anatomy. Ultrasound biomicroscopy (UBM) provides detailed visualization of the ciliary body and iris configuration but may cause patient discomfort due to its contact-based nature (13).

2.5.4. Treatment

Medical therapy: Cholinergic agonists are used to reverse appositional angle closure and prevent the formation of synechiae. Topical antiglaucomatous agents (α-adrenergic agonists, β-blockers, prostaglandin analogues, and carbonic anhydrase inhibitors) are employed to reduce elevated IOP (17).

Laser therapy: Peripheral iridotomy and iridoplasty are selected based on the patient's anatomical and clinical characteristics (13).

Surgical treatment: Available options include iridectomy, lens extraction, trabeculectomy, and minimally invasive glaucoma surgery (MIGS), depending on disease severity and underlying mechanism (13).

3. Artificial Intelligence

Artificial intelligence (AI) refers to the capability of computers or computer-controlled systems to exhibit behaviors that approximate human intelligence. This concept encompasses cognitive functions such as establishing causal relationships, generalizing from data, and learning from experience (18). The conceptual foundations of AI date back to the 1950s, when Alan Turing proposed that cognitive processes—such as playing games—could be simulated through computational systems, thereby laying the groundwork for the field (19).

AI is commonly categorized into three principal types based on its level of capability and anticipated future development: narrow AI, artificial general intelligence (AGI), and artificial superintelligence (ASI). Narrow AI refers to systems designed to perform specific tasks within a well-defined domain and constitutes the vast majority of current AI applications. In contrast, AGI describes systems capable of human-like reasoning, learning, and problem-solving across diverse domains; however, such systems have not yet been fully realized. ASI, on the other hand, represents a theoretical construct referring to systems that would surpass human intelligence across all cognitive domains and remains largely speculative at present (18).

Machine learning (ML), a subfield of AI, enables computers to learn from data rather than relying on explicitly programmed instructions. Unlike traditional rule-based programming, ML algorithms identify patterns within large datasets and utilize these patterns to solve complex and dynamic problems. This data-driven paradigm allows systems

to continuously refine their performance, adapt to new inputs, and generate increasingly accurate predictions over time (20).

Artificial neural networks (ANNs), a subset of ML, are computational models inspired by the structure and function of the human brain. These systems are designed to mimic the behavior of biological neural networks, allowing them to learn from example data and make predictions or classifications in previously unseen scenarios. ANNs consist of interconnected layers, including an input layer, one or more hidden layers, and an output layer. The input layer receives raw data, which are subsequently processed through hidden layers via mathematical transformations to extract relevant features. The output layer then generates the final result, such as classification, identification, or prediction (21).

Deep learning (DL), a specialized branch of machine learning, employs multi-layered neural networks to model complex patterns in data, drawing inspiration from hierarchical information processing in the human brain. In DL architectures, data are processed through multiple sequential layers, where each layer transforms the output of the previous one into increasingly abstract representations. These intermediate processing stages, referred to as hidden layers, are not directly observable but are critical for feature extraction and pattern recognition (22).

Convolutional neural networks (CNNs), a specific type of deep learning architecture, are particularly well-suited for image analysis. CNNs are capable of learning spatial hierarchies and patterns within visual data through layered convolutional filters, enabling automated feature extraction and high-performance image classification. Owing to these capabilities, CNNs are widely utilized in computer vision applications, including the automated detection and labeling of images on social media platforms (22).

In the field of medicine, deep learning applications are predominantly focused on image analysis. DL-based systems have demonstrated high diagnostic accuracy across a range of clinical contexts. Notable examples include the detection of tuberculosis from chest radiographs, the identification of malignant melanoma from dermatological images, and the recognition of lymph node metastases in breast cancer from histopathological specimens (23).

Similarly, deep learning techniques have been extensively applied in ophthalmic imaging. These applications primarily involve the analysis of fundus photographs and optical coherence tomography (OCT) images. Major ophthalmological conditions investigated using DL approaches include diabetic retinopathy, glaucoma, age-related macular degeneration, and retinopathy of prematurity (23).

4. Artificial Intelligence in the Diagnosis and Management of Glaucoma

Artificial intelligence (AI) in glaucoma diagnosis and management encompasses the evaluation of both structural and functional indicators of the disease. Structural assessments primarily include fundus photography and optical coherence tomography

(OCT)-based imaging modalities, whereas functional evaluations rely on visual field (VF) analysis. The performance of AI algorithms is typically assessed using metrics such as sensitivity, specificity, and the area under the receiver operating characteristic curve (AUC). The AUC reflects the ability of a model to discriminate between diseased and healthy individuals; values approaching 1.0 indicate superior diagnostic performance (24).

4.1. Fundus Photography

Fundus photography offers significant advantages in glaucoma screening due to its accessibility, cost-effectiveness, and recent advancements enabling non-mydriatic image acquisition with portable devices. Deep learning (DL) models can identify characteristic features of glaucomatous optic neuropathy, including increased cup-to-disc ratio, neuroretinal rim thinning, and retinal nerve fiber layer defects.

In a large-scale study by Liu et al. (2019), a convolutional neural network (CNN)-based model was developed using 274,413 fundus images for the detection of glaucomatous optic neuropathy (GON). The system achieved a sensitivity of 96.2%, specificity of 97.7%, and an AUROC of 0.996, demonstrating excellent diagnostic accuracy (4). Similarly, Phene et al. (2019) evaluated a DL model for identifying referable GON and optic nerve head features, reporting AUC values of 0.945, 0.855, and 0.881 across three independent datasets, indicating robust and consistent performance (25).

While most AI models focus on glaucoma detection and screening, predictive modeling for disease onset is of increasing clinical importance. Thakur et al. developed a DL model using over 60,000 fundus images, achieving an AUC of approximately 0.88 for predicting glaucoma onset 1–3 years prior to diagnosis and approximately 0.95 for established disease detection (26).

4.2. Optical Coherence Tomography (OCT)

Deep learning models are widely applied to OCT imaging for the assessment of glaucoma-related structural alterations. Conventional OCT enables quantitative evaluation of the retinal nerve fiber layer (RNFL) and the ganglion cell–inner plexiform layer (GCIPL) complex, while OCT angiography provides additional insights into retinal capillary plexuses and the choriocapillaris.

Several studies have demonstrated that DL models trained on OCT-derived images can achieve high diagnostic accuracy in glaucoma detection. For instance, Muhammad et al. developed a hybrid DL framework designed to extract features from single wide-field (9×12 mm) OCT scans per patient. The system utilized DL networks to derive features from multiple input maps (e.g., RNFL and GCIPL thickness and deviation maps), which were subsequently classified using a conventional machine learning algorithm, such as a random forest classifier, yielding strong performance in detecting GON (27).

Maetschke et al. developed a three-dimensional DL model based on volumetric OCT scans centered on the optic nerve head and compared its performance with eight con-

ventional machine learning classifiers. The DL model outperformed the best-performing classical method, achieving an AUROC of 0.94 compared to 0.89 (28). Similarly, Ran et al. trained a 3D DL model using 4,877 OCT scans and validated it across three independent external datasets, demonstrating consistent AUROC values ranging from 0.893 to 0.897, thereby supporting the generalizability of the model (29).

4.3. Anterior Segment Optical Coherence Tomography

Anterior segment OCT (AS-OCT) is used to evaluate anatomical features associated with angle-closure mechanisms, including iris configuration, lens morphology, and pupillary block. The diagnosis of angle closure requires accurate identification of contact between the iris and the trabecular meshwork; however, this assessment may be challenging in lower-resolution AS-OCT images, potentially increasing diagnostic uncertainty.

To address this limitation, Fu et al. developed a DL-based algorithm for automated analysis of AS-OCT images based on visual feature extraction. When compared with expert clinicians, the algorithm demonstrated a sensitivity of 90%, specificity of 92%, and an AUC of 0.96 (95% CI: 0.953–0.968; $P < 0.0001$), indicating high diagnostic accuracy (30). Nevertheless, gonioscopy remains the gold standard for clinical angle assessment.

4.4. Visual Field Analysis

Standard automated perimetry (SAP) is a cornerstone in the diagnosis and monitoring of glaucomatous optic neuropathy, requiring active patient participation to ensure reliable results. However, VF testing is influenced by multiple factors, including patient fatigue, fixation losses, learning effects, and inter-observer variability in interpretation (31).

The Humphrey Field Analyzer is the most widely used perimetric device, measuring light sensitivity within central 10°, 24°, or 30° visual field regions. Its outputs include key parameters such as mean deviation (MD), pattern standard deviation (PSD), visual field index (VFI), total deviation (TD), and pattern deviation (PD) probability plots, as well as spatial representations of threshold sensitivity values. Additionally, reliability indices (e.g., fixation losses, false positives/negatives) and proprietary progression analyses are provided, all of which are integral to clinical evaluation of functional glaucomatous changes.

Li et al. developed *iGlaucoma*, a smartphone-based, cloud-supported deep learning system designed to detect glaucoma from VF data. The model was trained on over 10,000 visual field tests and validated on 649 cases, with performance benchmarked against a reference standard comprising glaucoma specialists and ophthalmologists. External validation demonstrated a sensitivity of 95.4% and specificity of 87.3%, surpassing human reader performance. The algorithm analyzed PD probability plots both numerically and visually and integrated multiple VF parameters to accurately classify glaucomatous and non-glaucomatous fields (32).

5. Advantages of Artificial Intelligence in Glaucoma Diagnosis and Management

In glaucoma practice, "success" rarely stems from a single correct diagnostic moment; rather, it emerges from identifying the right patient at the right time, consistently quantifying both structural and functional damage, and subsequently personalizing follow-up frequency and treatment intensity according to the rate of progression. What makes this goal challenging is not only the chronic nature of glaucoma but also the steadily increasing volume of clinical data: optic nerve head assessment, optical coherence tomography (OCT) measurements of the retinal nerve fiber layer (RNFL) and ganglion cell complex (GCC), visual field (VF) testing, intraocular pressure trends, anterior chamber angle evaluation, as well as demographic and systemic risk factors. While the human eye and mind are capable of interpreting such data, even the most experienced clinician may struggle when the demands of speed, standardization, reproducibility, and scalability come into play. This is precisely where artificial intelligence (AI)—particularly machine learning and deep learning—adds value as a decision-support tool in glaucoma management: enabling more standardized screening, more quantitative damage assessment, earlier and more reliable detection of progression signals, and more efficient allocation of clinical resources.

The advantages outlined below are framed through the question "why does it work?" within the triad of pathophysiology, measurement science, and clinical workflow, and are discussed using clinically relevant interpretations of key studies. This approach highlights that each advantage represents not merely a technical achievement but a practical solution to real-world clinical challenges.

5.1. Standardization: Reducing Observer Variability and Improving Triage Consistency

One of the key bottlenecks in glaucoma screening and referral management lies in a deceptively simple question: who interprets the images? Decisions based on optic nerve head photographs—particularly whether a case is "referable glaucoma"—can vary significantly among clinicians. The same image may be interpreted as "suspicious" by one observer and "normal" by another.

A deep learning study based on the Los Angeles County tele-retina screening program demonstrated that "algorithm performance matched or exceeded" that of clinical graders in detecting referable glaucoma, while clinician sensitivity and specificity varied widely and were not correlated with years of experience (5). This illustrates one of the most tangible advantages of AI: introducing a standardized first-layer screening process that reduces variability in human performance. As a result, reliance on subjective interpretation decreases, and referral decisions become more consistent.

Importantly, the study also highlights the health system implications: "Implementation… could help reallocate resources and provide more reproducible and timely glaucoma care" (5). The goal is not to replace the clinician, but to offload repetitive image triage

tasks, allowing clinicians to focus on comprehensive glaucoma evaluation and management. Once standardization is achieved, the next natural advantage emerges: scalability and broader access.

5.2. Access and Scalability: Teleophthalmology, Field Screening, and Offline AI

Given the insidious progression and high rate of undiagnosed glaucoma, effective screening must not only be accurate but also widely accessible. AI's advantage here lies not only in classification performance but also in its ability to function under real-world conditions. A 2024 prospective study published in *Eye* succinctly captures this rationale: "An affordable and scalable screening model is critical for undetected glaucoma" (33).

In the same study, an offline AI system integrated into a smartphone-based fundus camera demonstrated high sensitivity and specificity for detecting referable glaucoma. Notably, a striking difference was observed between human experts and AI: "specialists detected 60%… versus… 94%… by the AI" on the same image set (33). This finding underscores the impact of AI at the screening level.

The advantages are twofold:

1. **Accessibility:** Portable, offline-capable systems enable screening in rural or underserved regions (33).
2. **Timely referral:** Faster identification of patients requiring specialist evaluation reduces delays in care (5).

This is clinically critical, as earlier detection allows earlier target intraocular pressure setting and timely adjustment of follow-up intensity. As screening scales up, an important question arises: does AI rely solely on optic disc features, or can it detect more subtle signals?

5.3. Detection of Subtle Signals Beyond the Optic Disc

While glaucomatous optic neuropathy is often assessed through the optic disc, pathological changes extend beyond this region to the peripapillary RNFL and surrounding tissues. A key strength of deep learning is its ability to integrate distributed signals rather than relying on isolated features.

In a study by Hemelings et al., models maintained meaningful performance even when the optic nerve head region was removed from images. The authors described this as "the first irrefutable evidence" that glaucoma can be detected from areas outside the optic nerve head (6). This finding reinforces the notion that glaucoma detection should not be reduced to simplistic metrics such as the cup-to-disc ratio. Instead, AI can systematically leverage high-dimensional anatomical and pathological patterns already recognized by clinicians.

While detecting such signals enhances screening, clinical practice often requires more than binary classification—it requires quantification of damage. This leads to the next advantage.

5.4. Toward Quantitative Damage Assessment from Fundus Photography

OCT remains the gold standard for quantitative structural assessment in glaucoma; however, it is not universally available and is subject to practical limitations. Therefore, extracting quantitative information from widely accessible fundus photographs represents a valuable goal.

Medeiros et al. proposed an approach to estimate RNFL thickness directly from fundus images without relying on human labels, aiming to overcome the limitations of manual annotation (8). This shifts fundus imaging from a binary "normal vs. abnormal" framework toward a continuum reflecting disease severity.

Such approaches enable more informative screening even in low-resource settings. However, quantitative structural assessment alone is insufficient; clinicians must interpret these findings in terms of functional impact. This brings us to the structure–function relationship.

5.5. Bridging Structure and Function: From OCT to Visual Field Loss

The hallmark of glaucoma is the loss of retinal ganglion cells and their axons. Structural and functional changes do not always occur synchronously, making it difficult to interpret OCT findings in terms of functional loss.

Christopher et al. evaluated deep learning models predicting visual field damage and severity from RNFL maps and optic nerve head OCT data, demonstrating superior performance compared to conventional thickness metrics. Clinically, this supports "individualizing the frequency of VF testing" (7).

The mechanism is straightforward: rather than relying on average thickness values, AI leverages spatial patterns within OCT maps to better approximate functional loss. Clinically, this translates into reducing unnecessary testing while identifying high-risk patients earlier. This naturally leads to the central goal of glaucoma care: early detection of progression.

5.6. Early Detection of Progression and Personalized Management

One of the most consequential errors in glaucoma management is failing to recognize rapid progression in a patient presumed to be stable. Thus, early prediction of progression represents a major strength of AI. A 2026 systematic review emphasizes this clearly: "Early and accurate prediction of progression is critical…" (9).

Longitudinal models aim to predict not only current disease status but also future outcomes, such as visual field deterioration. A 2023 study integrating OCT, visual field, and clinical data highlights the variability of VF testing: "VF testing is patient dependent and highly inconsistent…" (2). This underscores the limitations of relying on single-test results.

AI addresses this by integrating multimodal data, reducing noise, and generating earlier risk signals. Clinically, this enables more aggressive intraocular pressure targets and

tailored follow-up in high-risk patients. However, these benefits depend critically on data reliability, leading to the importance of quality assurance.

5.7. Data Quality and Reliability: AI as a Quality Assurance Layer

In glaucoma, poor-quality data directly translates into poor clinical decisions. Low-quality fundus images and OCT segmentation errors can mislead both clinicians and algorithms. AI can mitigate this by assessing data quality, detecting errors, and alerting users.

A 2024 study demonstrated that automated fundus image quality assessment improved glaucoma detection accuracy: "Using automated quality assessment… increased the accuracy…" (34). Similarly, a 2025 review notes that deep learning "can assist clinicians in checking the quality of OCT scans" (35).

This quality assurance layer reduces false confidence and strengthens downstream decision-making. As data reliability improves, the next goal—earlier detection of progression through higher-frequency monitoring—becomes achievable.

5.8. Home-Based Monitoring and "High-Frequency" Visual Field Testing: Earlier Detection of Progression

Theoretically, earlier detection of progression requires more frequent measurements; practically, this is limited by clinical capacity. Home-based monitoring offers a solution.

A study using virtual reality–based portable perimetry reported that "Home testing significantly reduced intertest variability…" and improved estimation of progression rates (36). This supports the principle that increased testing frequency enhances early detection.

When combined with AI, home-generated data can be automatically filtered, analyzed, and summarized, making large-scale longitudinal monitoring feasible.

5.9. Big Data, Open Datasets, and Code-Free AI Development

The maturity of AI in glaucoma depends not only on algorithms but also on robust data ecosystems. Large, diverse, multicenter datasets improve generalizability. The Rotterdam Eye PACSAIROGS dataset, for example, includes over 112,000 fundus images from more than 60,000 individuals across 500 centers (37), reducing the risk of overfitting to a single center.

Additionally, "code-free deep learning" platforms enable clinicians without programming expertise to develop AI models (38). When combined with proper validation frameworks, this can accelerate the development of locally relevant decision-support tools.

In summary, the advantages of AI in glaucoma—standardization, accessibility, quantitative assessment, structure–function integration, early progression detection, and quality assurance—represent a potentially transformative shift in clinical practice. However, high performance alone does not guarantee safe clinical application. The true value of these advantages emerges only when AI is applied in the right context, with appropriate data, validation, and integration into clinical workflows. Otherwise, the same tools may introduce

misplaced confidence and clinical risk. For this reason, the next section will systematically examine the limitations of AI in glaucoma, their underlying causes, and strategies for safe clinical implementation.

6. Limitations of Artificial Intelligence in Glaucoma: Why "High Performance" Does Not Always Mean "Safe Clinical Use"

In glaucoma clinics, the moments most prone to error are often not overt, advanced glaucoma cases, but rather borderline and atypical presentations: tilted discs and peripapillary atrophy in high myopia, low-quality optical coherence tomography (OCT) images due to significant cataract, learning effects and reliability fluctuations in visual field testing, and insidious progression in normal-tension glaucoma. In such challenging scenarios, artificial intelligence (AI) may provide impressive speed and standardization; however, when applied in the wrong context or with misplaced confidence, the same properties can amplify systematic errors. This section therefore focuses on the question "why does this happen?", addressing limitations through the lenses of data science, measurement error, clinical heterogeneity, human–machine interaction, and regulatory considerations.

6.1. The Fundamental Problem: If There Is No Single Accepted Definition of Glaucoma, What Is the Model Learning?

AI systems typically operate under the assumption that a reliable "ground truth" exists. In supervised learning, datasets are labeled as "glaucoma" or "non-glaucoma," and the model learns to discriminate between these categories. However, glaucoma is not a disease defined by a single test or measurement. Clinical diagnosis is based on the longitudinal relationship between structural and functional findings.

This ambiguity is particularly pronounced in OCT-based AI applications. A 2025 review explicitly highlights three major challenges: "lack of a consensual definition of glaucoma," bias among human graders, and limited availability of reliable real-world data (39). As a result, what a model learns may not be "glaucoma itself," but rather a surrogate of it—such as the diagnostic habits of a specific center, the reporting characteristics of a particular device, or morphological patterns within a specific population.

Consequently, a model that performs well in one setting may not generalize in another. This leads directly to a second critical issue: even if the model is learning the intended target, is the input data sufficiently reliable?

6.2. Data Quality, Artifacts, and Segmentation Errors: Small Input Errors Leading to Major Clinical Misinterpretation

In glaucoma follow-up, the strength of OCT lies in its quantitative and reproducible nature. However, this strength is limited by acquisition quality and segmentation accuracy. The same 2025 review emphasizes that pupil size, dry eye, cataract, anatomical variability,

and advanced pathology can degrade measurements; "algorithmic segmentation errors" may occur; and motion artifacts or incorrect scan placement can further compromise results (39).

For AI systems, this creates two major risks:

1. **Corrupted input:** The model is forced to make predictions from poor-quality or incorrect data.
2. **Plausible but misleading output:** Even when predictions appear reasonable, they may be based on artifacts rather than true disease signals.

Therefore, glaucoma AI must function not only as a predictive system but also as a quality-control mechanism capable of detecting unreliable inputs. A 2025 guideline on glaucoma imaging emphasizes that standardized image management and quality control are essential requirements for AI applications (40). Without robust data quality control, another problem becomes inevitable: variability in device and protocol can silently degrade model performance.

6.3. Device and Protocol Dependence: Domain Shift as a Silent Failure Mode

AI models typically perform best when deployed in environments similar to their training data. In clinical practice, however, data distributions constantly change due to differences in device type, software version, imaging protocol, operator behavior, and patient demographics. A 2026 systematic review defines this phenomenon as "domain shift," referring to non-trivial changes in underlying data distributions that impair generalizability (9).

Clinically, this means that a model may perform well in internal validation but fail in external settings. Indeed, a multicenter electronic health record (EHR) study predicting glaucoma surgical progression demonstrated a noticeable decline in performance when tested on external sites (9). This highlights a key principle: the most effective countermeasure to domain shift is robust external validation.

6.4. Lack of External Validation: A Major Bottleneck in the Literature

A substantial proportion of glaucoma AI studies are single-center or internally validated. As a result, models may appear highly accurate within their own datasets but fail to generalize. A 2026 systematic review explicitly states: "The overwhelming lack of external validation…" (9).

External validation is described as the strongest stress test against domain shift, yet remains underutilized. Clinically, this implies that a model performing well in one hospital may not achieve the same reliability in another due to differences in patient populations, imaging devices, and clinical workflows. This issue becomes even more pronounced when considering population heterogeneity, leading to the next critical limitation: fairness.

6.5. Fairness and Population Bias: High Average Performance Can Mask Subgroup Failures

An AI model may demonstrate strong overall performance while performing poorly in specific subgroups. In glaucoma, this is particularly relevant because the disease often presents later and more severely in certain racial, ethnic, and socioeconomically disadvantaged populations, partly due to disparities in access to care and baseline risk factors.

A 2025 study in *npj Digital Medicine* explicitly warns: "Existing deep learning models… might not achieve equitable performance across diverse identity groups" (41). The study introduces "fair identity normalization" and reports improved performance in certain subgroups.

Similarly, a 2023 external validation study notes that many models fail to evaluate performance across ethnicities, stating: "none assessed model performance across ethnicities" (42). It further reports differences in reproducibility between datasets of different ethnic compositions.

In glaucoma, such disparities are clinically significant because optic disc morphology, myopia prevalence, normative baselines, and healthcare access vary across populations. Therefore, fairness is not only an ethical concern but also a direct patient safety issue.

6.6. Explainability and Transparency: Heatmaps Do Not Replace Clinical Responsibility

Explainable AI methods, such as saliency maps or heatmaps, are often used to visualize which regions of an image influenced a model's decision. However, a critical limitation is that these methods do not reveal the true decision-making logic; they only approximate pixel-level influence.

As a result, heatmaps may sometimes align with clinical reasoning, but may also highlight irrelevant regions. Therefore, they cannot be considered a standalone indicator of safety (9).

Properly, explainability should be positioned as:

- Not a certification of safety
- A tool for error analysis ("where does the model fail?")
- A complement to clinical oversight, quality control, and education

Regulatory bodies reflect this view. For example, the FDA defines transparency in terms of intended use, development approach, performance, and communication of decision logic, but does not equate explainability with guaranteed safety (43).

Even with strong explainability, another subtle risk remains: human overreliance on AI outputs.

6.7. Human–AI Interaction and Automation Bias: The Most Subtle Risk

Automation bias refers to the tendency of clinicians to over-trust AI recommendations and unintentionally downgrade their own clinical judgment. The critical issue is not that the model may be wrong, but that humans may fail to recognize when it is wrong, thereby amplifying the error.

A JAMA editorial highlights that clinicians may sometimes trust AI outputs more than their own judgment, potentially leading to patient harm (44).

In glaucoma practice, this can manifest as:

- **False negative:** The model suggests "no referral needed," leading clinicians to delay further evaluation in cases such as normal-tension glaucoma.
- **False positive:** The model flags glaucoma in cases such as high myopia or tilted discs, leading to unnecessary referrals and patient anxiety.

Thus, the goal is not "AI versus clinician," but rather "clinician + AI together." FDA transparency principles similarly emphasize human–AI team performance (43).

Mitigation strategies include:

- Presenting outputs as risk scores or alerts rather than final decisions
- Displaying model uncertainty
- Training users on when not to trust the system
- Ensuring transparency, usability, and legal clarity

Without proper management of human factors, even highly accurate models may introduce clinical risk.

6.8. Regulatory Framework and Continuous Updates: AI Is Not a One-Time Approval System

AI systems in healthcare function as software as a medical device (SaMD). A key challenge is that models evolve over time, and updates may improve performance but also unintentionally degrade performance in certain subgroups or settings.

The FDA addresses this through the Predetermined Change Control Plan (PCCP), which allows planned updates while maintaining safety and effectiveness (45). In addition, the Good Machine Learning Practice (GMLP) framework emphasizes lifecycle management, including design, validation, deployment, monitoring, and updating (45).

The European Union AI Act classifies many medical AI systems as high-risk and emphasizes data quality, documentation, logging, human oversight, robustness, and cybersecurity (46). In glaucoma—where patients are followed over many years—AI tools must therefore remain reliable not only at deployment but throughout long-term use.

6.9. Clinical Integration and User Adoption: "Working" Does Not Mean "Being Used"

A model that performs well in studies may still fail in clinical practice due to poor integration into workflows. A qualitative study in ophthalmology highlights that the main barriers are non-adoption and abandonment (47).

Common reasons include:

- Lack of clear clinical purpose (triage vs. diagnosis vs. monitoring)
- Additional workload or extra steps
- Unclear responsibility in case of error
- Uncertainty about when to trust or disregard the system

Systematic reviews emphasize that trust depends on transparency, usability, clinical reliability, education, and medicolegal clarity (48).

A practical recommendation is to position AI not as a final decision-maker, but as a triage, quality-control, and alert-generation tool. This reduces workload while minimizing automation bias. In conclusion, the limitations of AI in glaucoma do not imply that the technology is ineffective. Rather, they highlight the conditions necessary for safe and meaningful clinical deployment. Without careful management of data quality, domain shift, external validation, fairness, explainability, human interaction, regulatory compliance, and clinical integration, even high-performing models may become unsafe in real-world settings.

7. Conclusion

Glaucoma is a chronic optic neuropathy that can lead to irreversible vision loss, often progresses silently for long periods, and is managed less by a single diagnostic event than by the quality of longitudinal follow-up. Therefore, the main challenge in glaucoma practice is not merely detecting the disease once, but accurately interpreting structural and functional changes over time, identifying progression early, and establishing the optimal balance between monitoring and treatment for each individual patient. Contemporary clinical decision-making requires the integration of multiple data sources, including optic nerve head appearance, retinal nerve fiber layer and ganglion cell complex measurements, visual field testing, intraocular pressure trends, anterior segment findings, and systemic risk factors. In this context, artificial intelligence has gained importance due to its potential to extract clinically meaningful patterns from such complex and multidimensional data.

As discussed throughout this section, the greatest contribution of artificial intelligence in glaucoma lies not in replacing the clinician, but in enhancing the quality of clinical decision-making. Models developed using fundus photography, optical coherence tomography, and visual field data have demonstrated promising results in detecting glaucomatous

optic neuropathy, identifying cases requiring referral, quantitatively assessing structural damage, improving the understanding of structure–function relationships, and predicting the risk of progression. The ability to provide a more standardized initial assessment in screening programs, support teleophthalmology in regions with limited access to specialists, evaluate image quality and measurement reliability, and generate earlier signals of progression from longitudinal data positions artificial intelligence as a powerful decision-support tool in glaucoma care.

However, a critical point must be emphasized: high performance does not necessarily equate to safe clinical use. Glaucoma is not defined by a single test; rather, its diagnosis emerges from the temporal relationship between structural and functional findings. Consequently, artificial intelligence models may sometimes learn not the disease itself, but the diagnostic patterns of a specific center, device characteristics, or morphological features of a particular population. When compounded by issues such as poor image quality, segmentation errors, device and protocol variability, lack of external validation, population-level performance disparities, and automation bias, it is not surprising that a model performing well in research settings may fail to demonstrate the same reliability in real-world clinical practice.

Thus, the true value of artificial intelligence in glaucoma does not lie in being a "perfect diagnostic tool," but in its use within well-defined boundaries, supported by high-quality data and appropriate human oversight. At least five fundamental conditions are essential for safe clinical implementation. First, the definition of glaucoma and labeling strategy used during model training must be clearly specified. Second, model outputs should not be trusted without verification of input data quality. Third, models must undergo external validation across different centers, devices, and populations. Fourth, potential biases across subgroups must be systematically evaluated. Fifth, artificial intelligence outputs should be framed not as final decisions, but as alerts, risk scores, or summarized insights that support clinician judgment. This approach reduces automation bias while preserving clinical responsibility.

From a practical standpoint, the most rational current applications of artificial intelligence in glaucoma include screening and triage, quality control, risk stratification, prediction of progression, and individualization of follow-up intervals. Particularly in high-volume clinical settings, these tools can contribute to more efficient use of limited specialist resources. However, for these benefits to be sustainable, systems must be seamlessly integrated into clinical workflows, avoid increasing clinician burden, clearly define responses to errors, and ensure continuous performance monitoring over time. In other words, an effective artificial intelligence system in glaucoma is not merely one that produces accurate predictions, but one that is reliable, transparent, auditable, and usable.

Looking ahead, the future of artificial intelligence in glaucoma will likely be shaped by the expansion of multimodal and longitudinal approaches. Models integrating fundus photography, optical coherence tomography, OCT angiography, visual field data, clinical parameters, and even electronic health records have the potential not only to assess current disease status but also to more accurately predict future trajectories. Additionally,

home-based visual field monitoring, portable imaging systems, and no-code model development platforms may further enhance accessibility. Nevertheless, for these advancements to translate into meaningful clinical benefit, technological progress must be accompanied by ethical, regulatory, and methodological maturity.

In conclusion, artificial intelligence in glaucoma should neither be viewed with exaggerated technological optimism as a tool that will replace clinicians, nor dismissed as a development confined to research environments. The most appropriate perspective is to position artificial intelligence as a clinician-centered, data-driven, and safety-focused decision-support component in glaucoma management. When supported by standardized data collection, robust quality control, multicenter validation, lifecycle performance monitoring, and human oversight, artificial intelligence has the potential to meaningfully transform glaucoma care by enabling earlier detection, more accurate risk stratification, more rational follow-up strategies, and more efficient use of healthcare resources. Ultimately, the future of artificial intelligence in glaucoma lies not in machines replacing human judgment, but in intelligent systems that enhance the precision, consistency, and effectiveness of clinical expertise.

8. References

1. Tham, Y. C., Li, X., Wong, T. Y., Quigley, H. A., Aung, T., & Cheng, C. Y. (2014). Global prevalence of glaucoma and projections of glaucoma burden through 2040: A systematic review and meta-analysis. *Ophthalmology, 121*(11), 2081–2090.
2. Hussain, S., Chua, J., Wong, D., Lo, J., Kadziauskiene, A., Asoklis, R., et al. (2023). Predicting glaucoma progression using a deep learning framework guided by a generative algorithm. *Scientific Reports, 13*(1), 19960.
3. Li, Z., He, Y., Keel, S., Meng, W., Chang, R. T., & He, M. (2018). Efficacy of a deep learning system for detecting glaucomatous optic neuropathy based on color fundus photographs. *Ophthalmology, 125*(8), 1199–1206.
4. Liu, H., Li, L., Wormstone, I. M., Qiao, C., Zhang, C., Liu, P., et al. (2019). Development and validation of a deep learning system to detect glaucomatous optic neuropathy using fundus photographs. *JAMA Ophthalmology, 137*(12), 1353–1360.
5. Nguyen, V., Iyengar, S., Rasheed, H., Apolo, G., Li, Z., Kumar, A., et al. (2025). Comparison of deep learning and clinician performance for detecting referable glaucoma from fundus photographs in a safety-net population. *Ophthalmology Science, 5*(4), 100751.
6. Hemelings, R., Elen, B., Barbosa-Breda, J., Blaschko, M. B., De Boever, P., & Stalmans, I. (2021). Deep learning on fundus images detects glaucoma beyond the optic disc. *Scientific Reports, 11*(1), 20313.
7. Christopher, M., Bowd, C., Belghith, A., Goldbaum, M. H., Weinreb, R. N., Fazio, M. A., et al. (2020). Deep learning approaches predict glaucomatous visual field damage from OCT optic nerve head en face images and retinal nerve fiber layer thickness maps. *Ophthalmology, 127*(3), 346–356.
8. Medeiros, F. A., Jammal, A. A., & Thompson, A. C. (2019). From machine to machine: An OCT-trained deep learning algorithm for objective quantification of glaucomatous damage in fundus photographs. *Ophthalmology, 126*(4), 513–521.
9. Liang, Y. G., Fan, L., Teixeira-Pinto, A., Liew, G., & White, A. J. (2026). A systematic review of AI for predicting glaucoma progression: Challenges and recommendations towards clinical implementation. *npj Digital Medicine*.
10. Liu, X., Cruz Rivera, S., Moher, D., Calvert, M. J., Denniston, A. K., Chan, A. W., et al. (2020). Reporting guidelines for clinical trial reports for interventions involving artificial intelligence: The CONSORT-AI extension. *Nature Medicine, 26*(9), 1364–1374.
11. Collins, G. S., Moons, K. G. M., Dhiman, P., Riley, R. D., Beam, A. L., Van Calster, B., et al. (2024). TRIPOD+AI statement: Updated guidance for reporting clinical prediction models that use regression or machine learning methods. *BMJ, 385*, e078378.
12. Schuster, A. K., Erb, C., Hoffmann, E. M., Dietlein, T., & Pfeiffer, N. (2020). The diagnosis and treatment of glaucoma. *Deutsches Ärzteblatt International, 117*(13), 225–234.
13. Yanoff, M., & Duker, J. S. (Eds.). (2023). *Ophthalmology* (6th ed.). Elsevier.
14. Bowling, B. (2020). Glaucoma. In B. Bowling (Ed.), *Kanski's clinical ophthalmology: A systematic approach* (9th ed.). Elsevier.
15. Weinreb, R. N., Aung, T., & Medeiros, F. A. (2014). The pathophysiology and treatment of glaucoma: A review. *JAMA, 311*(18), 1901–1911.
16. Umezurike, B. C., et al. (2019). Primary open-angle glaucoma: The pathophysiology, mechanisms, and future diagnostic and therapeutic directions. *Ophthalmology Research: An International Journal, 10*(3), 1–17.

17. Sun, X., Dai, Y., Chen, Y., Yu, D. Y., Cringle, S. J., Chen, J., et al. (2017). Primary angle-closure glaucoma: What we know and what we don't know. *Progress in Retinal and Eye Research, 57*, 26–45.
18. Keskinbora, K., & Güven, F. (2020). Artificial intelligence and ophthalmology. *Turkish Journal of Ophthalmology, 50*(1), 37–43.
19. Mayro, E. L., Wang, M., Elze, T., & Pasquale, L. R. (2020). The impact of artificial intelligence in the diagnosis and management of glaucoma. *Eye, 34*(1), 1–11.
20. Arslan, K. (2020). Eğitimde yapay zeka ve uygulamaları. *Batı Anadolu Eğitim Bilimleri Dergisi, 11*(1), 71–88.
21. Elgin, U. (2019). Glokom tanı ve takibinde yapay zekâ. *Glokom-Katarakt, 14*(2).
22. Mintz, Y., & Brodie, R. (2019). Introduction to artificial intelligence in medicine. *Minimally Invasive Therapy & Allied Technologies, 28*(2), 73–81.
23. Ting, D. S. W., Pasquale, L. R., Peng, L., Campbell, J. P., Lee, A. Y., Raman, R., et al. (2019). Artificial intelligence and deep learning in ophthalmology. *British Journal of Ophthalmology, 103*(2), 167–175.
24. Campbell, C. G., Ting, D. S. W., Keane, P. A., & Foster, P. J. (2020). Potential applications of artificial intelligence in the detection and management of glaucoma in adults. *British Medical Bulletin, 134*(1), 21–33.
25. Phene, S., Dunn, R. C., Hammel, N., Liu, Y., Krause, J., Kitade, N., et al. (2019). Deep learning and glaucoma specialists: The relative importance of optic disc features to predict glaucoma referral in fundus photographs. *Ophthalmology, 126*(12), 1627–1639. https://doi.org/10.1016/j.ophtha.2019.07.024
26. Thakur, A., Goldbaum, M., & Yousefi, S. (2020). Predicting glaucoma before onset using deep learning. *Ophthalmology Glaucoma, 3*(4), 262–268.
27. Muhammad, H., Fuchs, T. J., De Cuir, N., De Moraes, C. G., Blumberg, D. M., Liebmann, J. M., et al. (2017). Hybrid deep learning on single wide-field optical coherence tomography scans accurately classifies glaucoma suspects. *Journal of Glaucoma, 26*(12), 1086–1094.
28. Maetschke, S., Antony, B., Ishikawa, H., Wollstein, G., Schuman, J., & Garnavi, R. (2019). A feature-agnostic approach for glaucoma detection in OCT volumes. *PLOS ONE, 14*(7), e0219126.
29. Ran, A. R., Cheung, C. Y., Wang, X., Chen, H., Luo, L. Y., Chan, P. P., et al. (2019). Detection of glaucomatous optic neuropathy with spectral-domain OCT: A deep learning analysis. *The Lancet Digital Health, 1*(4), e172–e182.
30. Fu, H., Xu, Y., Lin, S., Wong, D. W. K., Baskaran, M., Mahesh, M., et al. (2019). Angle-closure detection in anterior segment OCT based on multilevel deep network. *IEEE Transactions on Cybernetics, 50*(7), 3358–3366.
31. Ittoop, S. M., Jaccard, N., Lanouette, G., & Kaouk, M. Y. (2022). The role of artificial intelligence in glaucoma diagnosis and management. *Journal of Glaucoma, 31*(3), 137–146. https://doi.org/10.1097/IJG.0000000000001972
32. Li, F., Song, D., Chen, H., Xiong, J., Li, X., Zhong, H., et al. (2020). Development and clinical deployment of a smartphone-based visual field deep learning system for glaucoma detection. *npj Digital Medicine, 3*(1), 123.
33. Rao, D. P., Shroff, S., Savoy, F. M., Hsu, C. K., Negiloni, K., et al. (2024). Evaluation of an offline AI system for glaucoma screening. *Eye, 38*(6), 1104–1111.
34. Chuter, B., Huynh, J., Bowd, C., Walker, E., Rezapour, J., Brye, N., et al. (2024). Deep learning identifies high-quality fundus photographs and improves glaucoma detection. *Translational Vision Science & Technology, 13*(1), 23.
35. Bolo, K., & Xu, B. Y. (2025). Applications of deep learning in OCT for glaucoma diagnostics. *Taiwan Journal of Ophthalmology, 15*(3), 354–363.
36. Shi, R. B., Li-Han, L. Y., Kherani, I. N., Trope, G. E., Buys, Y. M., Wong, W., & Eizenman, M. (2025). Virtual reality portable perimetry and home monitoring of glaucoma. *Ophthalmology Science, 5*(2), 100639.
37. Vente, C. D., Vermeer, K. A., Jaccard, N., Wang, H., Sun, H., Khader, F., et al. (2024). AIROGS: Artificial intelligence for robust glaucoma screening challenge. *IEEE Transactions on Medical Imaging, 43*(1), 542–557.
38. Milad, D., Antaki, F., Mikhail, D., Farah, A., El-Khoury, J., Touma, S., et al. (2025). Code-free deep learning glaucoma detection. *Ophthalmology Science, 5*(4), 100721.
39. Djulbegovic, M. B., Bair, H., Gonzalez, D. J. T., Ishikawa, H., Wollstein, G., & Schuman, J. S. (2025). Artificial intelligence for OCT in glaucoma. *Translational Vision Science & Technology, 14*(1), 27.
40. Yang, W. H., Xu, Y. W., & Sun, X. H. (2025). Guidelines for glaucoma imaging classification and annotation for AI applications. *International Journal of Ophthalmology, 18*(7), 1181.
41. Shi, M., Luo, Y., Tian, Y., Shen, L. Q., Zebardast, N., Eslami, M., et al. (2025). Equitable AI for glaucoma screening. *npj Digital Medicine, 8*(1), 46.
42. Li, C., Chua, J., Schwarzhans, F., Husain, R., Girard, M. J., Majithia, S., et al. (2023). Assessing external validity of ML-based glaucoma detection. *Scientific Reports, 13*(1), 558.
43. U.S. Food and Drug Administration. (2024). *Transparency for machine learning-enabled medical devices: Guiding principles.*
44. Khera, R., Simon, M. A., & Ross, J. S. (2023). Automation bias and assistive AI. *JAMA, 330*(23), 2255–2257.
45. U.S. Food and Drug Administration. (2025). *Marketing submission recommendations for a predetermined change control plan for AI-enabled device software functions.*
46. European Commission. (2026). *AI Act: Shaping Europe's digital future.*
47. Schaffernak, I., Cecil, J., Kleine, A. K., & Lermer, E. (2025). Sociotechnical influences on AI adoption in ophthalmology. *BMC Health Services Research, 25*(1), 1–18.
48. Tun, H. M., Rahman, H. A., Naing, L., & Malik, O. A. (2025). Trust in AI-based clinical decision support systems. *Journal of Medical Internet Research, 27*, e69678.

CHAPTER 35

Artificial Intelligence in Child Mental Health: Hope, Risk, and Clinical Responsibility

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1. Introduction

Mental health problems in children and adolescents are now one of the more pressing public health issues around the globe. The World Health Organization estimates that roughly one in seven young people aged 10 to 19 lives with a mental disorder, and rates of anxiety, depression, and self-harm have increased sharply since the COVID-19 pandemic (1, 2). At the same time, the global workforce in child and adolescent psychiatry is scarce; in many low- and middle-income countries, fewer than one specialist serves every hundred thousand children (3). In this context, artificial intelligence (AI) has emerged as one possible way to narrow the gap between the needs of young people and what they actually receive. There is growing interest in its capacity to broaden access in underserved settings and to deliver support to children who would otherwise go without (3, 4).

Modern machine-learning systems can detect linguistic markers of suicidal ideation in social media posts, flag early signs of autism from short videos of toddlers, and deliver evidence-based cognitive-behavioral interventions via chatbots available at any hour (5–7). However, the same systems can misclassify, monitor, manipulate, and harm (8, 9). Children are not simply smaller adults. Their cognitive and neurobiological development leaves them more vulnerable to algorithmic errors and less able to give meaningful consent to the very systems shaping their care (10).

This chapter investigates the possible advantages and harms of AI in pediatric mental health from the perspectives of hope, risk, and clinical responsibility. The first part examines clinical applications already in use or under development. The second part turns to the categories of risk that need closer attention when AI meets a developing mind. The third sets out the professional and ethical obligations to keep the technology in the service of children rather than the other way around.

2. The Promise of AI in Pediatric Mental Health

2.1. Early Detection and Risk Stratification

One of the most clinically meaningful uses of AI in child and adolescent mental health is the early identification of young people who are at a higher risk for psychiatric disorders. As about half of all lifetime mental disorders begin before age 14, and three-quarters before age 24, the need for early identification is crucial. The gap between symptom onset and effective treatment usually runs into years rather than months (11). In that interval, the severity of illness and number of potential comorbidities increase, leading to greater developmental distortion. Machine-learning models trained on various electronic records and questionnaires can now predict the onset of depression, suicidality, and psychosis with accuracy that beats traditional risk-prediction tools (12, 13). Walsh and colleagues trained their machine-learning models on longitudinal clinical data and predicted suicide attempts in adolescents using only routinely collected structured variables. As the predicted event approached, the model's accuracy increased (14). This research outcome matters in clinical settings because the window for turning a risk signal into an actual intervention is short. Other models have been used to predict the longitudinal course of eating disorders from baseline clinical data (15) and to identify autistic features from short home videos (6), compressing what is normally sometimes a months-long assessment into a few minutes of analysis on footage.

There is also growing interest in data collected outside the clinical setting. Digital phenotyping, capturing behavior in everyday life using smartphone sensors, keystroke dynamics, or patterns of social engagement, offers a way to detect minör shifts in behaviors before they catch clinical attention (16). For young people, who spend most of their lives through digital media, this kind of passive measurement might be especially promising. It captures the signals that brief office visits tend to miss. The clinical value of these tools is not just their predictive accuracy. As they surface concerns earlier and triage which children most need scarce specialist time, these AI tools let clinicians take action during the developmental windows when interventions work best. Risk stratification, in this sense, is not only a technical matter; it is a way of redirecting clinical attention toward children who would otherwise wait for many years (17).

2.2. Broadening Access to Support

Conversational agents and AI-assisted tools offer the opportunity to make mental health support for young people more accessible, as they are anonymous and often cheaper than traditional services. Programs based on different kinds of therapy approaches, such as cognitive-behavioral therapy and dialectical behavior therapy, have shown modest but significant symptom reduction in adolescents with mild-to-moderate anxiety and depression. These effect sizes are smaller than what an experienced clinician achieves face to face, but at the population level they still mean a big impproveemnt. (7, 18). The economic and logistical case is also hard to look past. A single conversational agent can serve hundreds

of thousands of users at once with the marginal cost almost being zero, in any time zone and in many different languages. This is a profile no human workforce, no matter well trained or funded, can match. For young people in rural areas, in regions where specialists are scarce, or in communities where mental-health stigma is still present, such tools can be a meaningful first point of contact. In some cases, they might even be the only point of contact a child will have with evidence-based care during a critical developmental window (19, 20).

Most of the time, whether an adolescent seeks help has less to do with the accessibility of the services than the cost of using them. Young people may fear being judged, worry about confidentiality, be reluctant to open up to a parent or other familiar adult, and have difficulty putting their feelings into words when sitting across from an unfamiliar clinician (21). Adolescents often disclose hard things, such as self-harm urges, abuse, gender-identity questions, more easily to a non-judgmental digital tool than to a parent or clinician in real time. This pattern is sometimes called the "computer as confidant" or the disinhibition of the screen (22). For some young people, this might turn into a clinical asset. A disclosure made to a chatbot at three in the morning can, with the right design, become a referral to a crisis service or a primary-care visit within a couple of days. When these tools are built with strong escalation pathways, automatically flagging high-risk language, handing off to trained human responders in a clear way, and being upfront about the limits of confidentiality, they can act as a bridge to professional care rather than a replacement for it. The point is not that conversational agents replicate the therapeutic alliance, which they cannot, at least for now. But they make it easier for a young person to start a clinical conversation and, therefore, reach a population that traditional services have long been aware of but have rarely been able to serve.

2.3. Personalization and Precision Intervention

AI also makes it possible to personalize interventions in ways traditional care models simply can't. Reinforcement-learning algorithms can adjust the timing, content, and format of digital interventions to a young person's behavioral patterns, an approach that is often called just-in-time adaptive intervention (JITAI). A standard intervention gives a young person the same content on a fixed schedule, regardless of what they actually need at that moment. A JITAI system aims to do the opposite. It watches for cues, such as a spike in stress markers, and times its response to the moment when a young person is most likely to use it (23). For adolescents, whose emotional states change quickly and whose lives unfold mostly outside the consulting room, this kind of context-sensitive support may fit their experience particularly well.

Another line of work uses passive data from phones and wearables to catch early signs of a mood disorder relapse before anyone, including the young person, has noticed a change (16, 24). These signals, captured continuously and without any disturbance to the young person, can detect the small behavioral shifts that often precede a depressive episode or a manic switch. This gives clinicians a chance to step in with extra support before

a crisis breaks out. The aim is not just earlier action but more precisely calibrated action. The right intervention for the right young person at the right moment in the course of their illness can make a huge difference in clinical care. This kind of personalization fits a broader shift in psychiatry. Diagnoses used to be treated as fixed categories; now there's more interest in how illness changes over time and how it differs from one young person to another (25). In child and adolescent psychiatry, where symptoms shift quickly, development moves fast, and the line between normal variation and emerging illness is hard to draw, this kind of person-specific approach may turn out to be especially valuable.

2.4. Augmenting Clinical Decision-Making

In the clinic, AI is mostly being used to support clinical reasoning, not replace it. NLP tools can summarize notes, flag inconsistencies between visits, and pull up relevant evidence when the clinician needs it. They can also take some of the documentation work off the clinician's plate — and that work is a big part of why so many clinicians are burning out (26). Ambient scribing tools, which listen to the visit in real time and turn it into a structured note the clinician can review, are already in routine use in many adult clinics. Pediatric and mental health settings are now running their first pilots (27). In child and adolescent psychiatry, the appeal is easy to see. A clinician who isn't typing through a fifty-minute family session can pay closer attention to the clues that clinical understanding is built upon, such as what the child is feeling, how the parent frames the story, and the silences in between. NLP applied to longitudinal records can also identify patterns that no single clinician would easily catch. Without it, a steadily worsening picture across schools, providers, and emergency visits would usually stay scattered across disconnected notes.

Decision-support tools apply the same logic to treatment choice. Algorithms can look at a child's clinical profile and, increasingly, at their pharmacogenomic data to suggest medications that match how the child actually metabolizes drugs. They can also warn the clinician about dangerous interactions when several medications are being prescribed at once. And they can flag dosing concerns for groups where most prescribing evidence comes from adult studies, which makes adjusting appropriate medication regimens challenging, like children, adolescents, and people with intellectual disability (28). Tools like these are particularly useful in a field where prescribing decisions are made under uncertainty, with limited pediatric trial data and a developmentally moving target. For all this to work, the systems need to be used transparently, validated in children rather than just borrowed from adult evidence, and built into workflows that leave the clinician in charge. When that happens, they can ease the mental load on clinicians and free up time for what still matters most, actually being with the child and the family. The guiding principle is augmentation, not substitution. AI should handle the patterns, the cross-referencing, and the documentation, while the clinician carries the formulation, the relationship, and the judgment about what this child and the family most need.

3. Emerging Risks and Vulnerabilities

3.1. Developmental Considerations

Children are not just 'small' adults, and AI tools trained mostly on adult data can perform poorly when applied to developing minds (29). Symptom expression, language use, and emotional regulation differ significantly across developmental stages. The line between typical childhood behavior and clinical pathology is more obscure than it is in adulthood. A model that interprets adolescent emotional volatility as pathology can end up pathologizing what is actually normal development. The reverse can also happen. In younger children, depression often shows itself through irritability, temper outbursts, somatic complaints, and not the persistent sadness adults present with. A model that does not pick this up can miss the children who need help most urgently (30).

Children's cognitive development also shapes how they understand and engage with AI. Younger children often treat chatbots and other animated agents as if they had minds of their own. They give them personalities, intentions, even a kind of moral authority. They do this by drawing on the same social-cognitive abilities they use to make sense of what other people think and feel (31, 32). That makes them especially likely to over-rely on a chatbot's advice, or to form one-sided emotional bonds with it that can interfere with the development of real human relationships. Adolescents are cognitively more sophisticated, but they are also more sensitive to peer feedback and social reward. This sensitivity is linked to developmental shifts in the brain's reward circuitry (33, 34). At the same time, they are more open to the persuasive design features that commercial AI products use to keep users engaged (35).

3.2. Algorithmic Bias and Health Equity

AI systems inherit and often amplify the biases in their training data (36). In pediatric mental health access to care is already deeply stratified by socioeconomic status, race, and geography. Therefore, concerns regarding the bias of AI systems are not hypothetical. Models trained on data from well-resourced and well-studied clinical populations can underperform for children from minoritized communities. This carries two different areas of risk. There might be either systematic under-detection of need or, going the other way, over-pathologization of behavior that reflects cultural variation rather than disorder (37). Obermeyer and colleagues showed that a widely deployed health-care algorithm systematically underestimated illness in Black patients because the spending data used to train it already reflected unequal access to care. This lesson carries over directly to child psychiatry, where pediatric models most commonly use prior diagnoses and service utilization as markers for need, even though those markers are shaped by long-standing inequities in who reaches care in the first place (38).

Compounding this, the very act of deploying AI tools can widen existing inequities. Wealthier families and well-resourced school systems can afford validated, clinically supervised tools; under-resourced settings may end up with only the free, advertising-fund-

ed, and less-regulated alternatives. These products are built around engagement and data monetization, not clinical effectiveness (39). Unless deliberately designed against this, AI risks worsening mental-health inequality, not improving it (40).

3.3. Privacy, Consent, and Data Protection

Mental health data are among the most sensitive types of personal information. With children, this sensitivity is doubled. AI systems often need extensive longitudinal data, such as text messages, voice recordings, and facial expressions. But how children and their guardians actually agree to all this — that part is rarely transparent. Independent reviews of widely used youth mental wellness applications have shown systematic failures in privacy protection. Many apps routinely share sensitive data with third parties, embed advertising trackers, have weak security standards, and retain data indefinitely. Even apps that adolescents are using to disclose depression, suicidal ideation, and trauma show similar breaches of privacy (39, 40). The legal framework for pediatric digital privacy varies widely across jurisdictions and generally lags behind technological practice. Instruments like the U.S. Children's Online Privacy Protection Act, drafted in an earlier technological era, are not sufficient for the data flows that AI-driven applications now generate when they are marketed to minors (41). The picture is similar in Turkey, where the general data protection law makes no specific provision for children.

Even when consent is formally obtained, the question is how meaningful that consent really is. Empirical studies of the terms-of-service documents on widely used platforms have shown one thing clearly. They are simply too long, too legally complex, and too hard to understand for young users to grasp what they are actually agreeing to (42). A twelve-year-old asked to accept a thirty-page terms-of-service agreement cannot meaningfully evaluate the long-term implications of disclosing intimate content to a corporate platform. Data collected in childhood may follow the child into adulthood, shaping insurance, employment, or reputational risks even decades later.

3.4. The Therapeutic Relationship and Emotional Dependence

The bond between a clinician and patient is a strong predictor of clinical outcome across different therapy modalities. AI doesn't genuinely "care" about a child's well-being as it doesn't possess 'feelings'; therefore, it cannot be held accountable in the same way a clinician can. When AI is used not as a supplement to human care but as a substitute for it, several risks come to light. Children may form intense attachments to chatbots that show signs of empathy without actually feeling it. They may receive responses that feel pleasing for a moment but are actually harmful in the long term. Also, the children may be deprived of the corrective experience of being known, with limits, by another human being (43, 44).

Reports of adolescents who developed romantic or self-harm-related attachments to conversational agents make clear that this is a present concern, not a future one. Several reported cases of suicide and severe psychiatric deterioration following intensive engage-

ment with companion chatbots underscore the case for purpose-built, clinically governed pediatric tools rather than the redeployment of general-purpose consumer products to young, vulnerable users (45).

3.5. Misinformation, Hallucination, and Clinical Error

Large language models often generate plausible but factually incorrect statements at non-trivial rates, which the field has come to call "hallucinations" (46). In a clinical context, it is a possible safety hazard. A model that misstates dosing might lead to potentially deadly treatment mistakes. Fabricating research evidence or offering inappropriate crisis advice can cause real harm before anyone catches the error. A recent cross-sectional evaluation of twenty-five widely used chatbots, presented with simulated adolescent health crises, found inappropriate or harmful responses across the spectrum, including, in the most extreme cases, replies that openly endorsed self-harm. Companion-style products performed markedly worse than general-purpose assistants across all safety dimensions assessed (8). The risk is greatest precisely where the user is least able to evaluate the response — a situation that maps almost too cleanly onto a distressed child consulting an AI alone at three in the morning.

3.6. The Emergence of Novel Psychopathology: AI-Associated Psychosis and Related Phenomena

A rapidly developing concern of the past two years is the emergence of what clinicians have variously called "AI-associated psychosis," "ChatGPT psychosis," or, more cautiously, "AI-fuelled delusions." In a 2023 editorial in Schizophrenia Bulletin, Østergaard hypothesized that the cognitive dissonance produced by interacting with a system that feels like a sentient interlocutor while being known to be a machine could fuel delusional ideation in individuals already vulnerable to psychosis (47). The proposal rested largely then on theoretical grounds and his own clinical intuitions. Two years later, in a follow-up editorial, Østergaard documented a sharp increase in correspondence from clinicians, describing strikingly similar episodes. Extended conversations with chatbots that did not push back, but instead aligned with and consolidated delusional material (48).

Soon after, a more structured analysis was published by a team at King's College London. A review of over a dozen cases showed that everyday AI systems can sometimes reinforce distorted patterns of thinking rather than challenge them (49). These mechanisms are not incidental but central to chatbot design. Large language models are optimized to enhance engagement and mirror user input. This tendency to minimize conversational friction is also called "echo chamber for one." In individuals with grandiose, persecutory, referential, or romantic ideation, this dynamic may be countertherapeutic. Rather than facilitating reality testing, the system can reflect and elaborate on these beliefs. Hudon and Stip reported cases of new-onset psychotic symptoms following intensive chatbot use, suggesting that this phenomenon can no longer be

regarded as hypothetical in the literature (50). The implications for child and adolescent psychiatry are particular and concerning. Adolescence is a time when psychotic disorders often first emerge, and it is also when young people are most engaged with conversational AI. For those in the early, prodromal phase, interacting with chatbots that do not recognize disorganized thinking may reinforce unusual beliefs. This does not mean AI causes psychosis. Current evidence does not support such a simple conclusion. However, it does suggest that AI may influence how these conditions unfold, and asking about AI use may soon become a routine part of assessing young people with emerging thought disorder (48).

4. Clinical Responsibility and Ethical Practice

When we look at AI in child and adolescent mental health, it's clear that it brings both real promise and risk. The answer isn't to avoid AI altogether, as it is already part of clinical workflows. But it's also not something to adopt without reasonable questioning. What's needed is a more deliberate, responsible approach in which clinicians, developers, and institutions share responsibility.In practice, this starts with consent. Families need clear, straightforward explanations of what the AI does, what data it collects, how that data is used, and where its limits lie. At the same time, children shouldn't be passive participants. Even at younger ages, they can be meaningfully involved in understanding and responding to these tools. Crucially, responsibility must remain with the clinician. AI can inform care, but it can't replace clinical judgment. That means actually understanding how the tools were trained, where they work well, and where they don't. It also means being willing, at times, to override the system and, at other times, to reconsider one's own judgment. This kind of competence doesn't come automatically; it requires training and needs to become a core part of professional education. The same level of care has to apply to the tools themselves. Systems designed for children need to be tested in children, across different developmental stages and backgrounds. Accuracy alone isn't enough. We also need to know what happens when the system is wrong, how it performs across different groups, and how it affects a child's relationships with clinicians, family, and school. Until we have those answers, using these tools is more akin to research than to routine care. Safeguarding is perhaps the most urgent issue. If a child shares something serious, like self-harm or abuse, the system must connect them to a real person who can help. The pathway has to be clear, tested, and developmentally appropriate. Otherwise, these tools have no place in pediatric care. Finally, this isn't something individual clinicians can manage on their own. Hospitals, schools, professional bodies, and regulators all have a role in setting standards and monitoring outcomes. Some guidance exists, but it's still not sufficient. Over time, we will need regulatory frameworks that are clearer and built specifically with children in mind. The frameworks we currently have were designed for adult care. They simply do not fit the realities of a developing mind.

5. Conclusion

AI in child mental health is neither a savior nor a catastrophe. It is a powerful set of tools, and like any powerful tool, what it ends up doing depends on the wisdom and integrity of those who deploy it. The hope is real. Earlier detection, broader access, more personalized care. The risks are just as real. Poorly validated systems can harm developing minds. They can deepen the inequities already there. They can erode the therapeutic relationship. They can process intimate data in ways that will follow children into adulthood. The path forward requires sustained commitment to developmentally informed evaluation, clinician-anchored deployment, and robust safeguarding. AI in pediatric mental health will succeed not when it is most powerful, but when it is most accountable to the child's welfare.

6. References

1. Organization WH. Mental health of children and young people: service guidance: World Health Organization; 2024.
2. Hawes MT, Szenczy AK, Klein DN, Hajcak G, Nelson BD. Increases in depression and anxiety symptoms in adolescents and young adults during the COVID-19 pandemic. Psychological medicine. 2022;52(14):3222-30.
3. Skokauskas N, Fung D, Flaherty LT, Von Klitzing K, Pūras D, Servili C, et al. Shaping the future of child and adolescent psychiatry. Child and Adolescent Psychiatry and Mental Health. 2019;13(1):19.
4. Lee EE, Torous J, De Choudhury M, Depp CA, Graham SA, Kim H-C, et al. Artificial intelligence for mental health care: clinical applications, barriers, facilitators, and artificial wisdom. Biological Psychiatry: Cognitive Neuroscience and Neuroimaging. 2021;6(9):856-64.
5. Roy A, Nikolitch K, McGinn R, Jinah S, Klement W, Kaminsky ZA. A machine learning approach predicts future risk to suicidal ideation from social media data. NPJ digital medicine. 2020;3(1):78.
6. Tariq Q, Daniels J, Schwartz JN, Washington P, Kalantarian H, Wall DP. Mobile detection of autism through machine learning on home video: A development and prospective validation study. PLoS medicine. 2018;15(11):e1002705.
7. Nicol G, Wang R, Graham S, Dodd S, Garbutt J. Chatbot-delivered cognitive behavioral therapy in adolescents with depression and anxiety during the COVID-19 pandemic: feasibility and acceptability study. JMIR Formative Research. 2022;6(11):e40242.
8. Brewster RC, Zahedivash A, Tse G, Bourgeois F, Hadland SE. Characteristics and safety of consumer chatbots for emergent adolescent health concerns. JAMA Network Open. 2025;8(10):e2539022.
9. Clark A. The ability of AI therapy bots to set limits with distressed adolescents: simulation-based comparison study. JMIR Mental Health. 2025;12:e78414.
10. Mansoor M, Hamide A, Tran T. Conversational AI in pediatric mental health: A narrative review. Children. 2025;12(3):359.
11. Solmi M, Radua J, Olivola M, Croce E, Soardo L, Salazar de Pablo G, et al. Age at onset of mental disorders worldwide: large-scale meta-analysis of 192 epidemiological studies. Molecular psychiatry. 2022;27(1):281-95.
12. Koutsouleris N, Dwyer DB, Degenhardt F, Maj C, Urquijo-Castro MF, Sanfelici R, et al. Multimodal machine learning workflows for prediction of psychosis in patients with clinical high-risk syndromes and recent-onset depression. JAMA psychiatry. 2021;78(2):195-209.
13. Su C, Aseltine R, Doshi R, Chen K, Rogers SC, Wang F. Machine learning for suicide risk prediction in children and adolescents with electronic health records. Translational psychiatry. 2020;10(1):413.
14. Walsh CG, Ribeiro JD, Franklin JC. Predicting suicide attempts in adolescents with longitudinal clinical data and machine learning. Journal of child psychology and psychiatry. 2018;59(12):1261-70.
15. Haynos AF, Wang SB, Lipson S, Peterson CB, Mitchell JE, Halmi KA, et al. Machine learning enhances prediction of illness course: a longitudinal study in eating disorders. Psychological medicine. 2021;51(8):1392-402.
16. Insel TR. Digital phenotyping: technology for a new science of behavior. Jama. 2017;318(13):1215-6.
17. Hong P, Emanuel E. Leveraging artificial intelligence to bridge the mental health workforce gap and transform care. Milbank Q. 2025.
18. Fitzpatrick KK, Darcy A, Vierhile M. Delivering cognitive behavior therapy to young adults with symptoms of depression and anxiety using a fully automated conversational agent (Woebot): a randomized controlled trial. JMIR mental health. 2017;4(2):e7785.
19. Grenon S, Hoang KN, Luo S, Koch A. Adolescent mental health in rural settings: the role of artificial intelligence and community engagement. Frontiers in Public Health. 2025;13:1643466.

20. Mwaka ES, Bazzeketa D, Mirembe J, Emoru RD, Twimukye A, Kivumbi A. Barriers to and enhancement of the utilization of digital mental health interventions in low-resource settings: Perceptions of young people in Uganda. Digital health. 2025;11:20552076251321698.
21. Radez J, Reardon T, Creswell C, Lawrence PJ, Evdoka-Burton G, Waite P. Why do children and adolescents (not) seek and access professional help for their mental health problems? A systematic review of quantitative and qualitative studies. European child & adolescent psychiatry. 2021;30(2):183-211.
22. Lucas GM, Gratch J, King A, Morency L-P. It's only a computer: Virtual humans increase willingness to disclose. Computers in Human Behavior. 2014;37:94-100.
23. Nahum-Shani I, Smith SN, Spring BJ, Collins LM, Witkiewitz K, Tewari A, et al. Just-in-time adaptive interventions (JITAIs) in mobile health: key components and design principles for ongoing health behavior support. Annals of behavioral medicine. 2016:1-17.
24. Torous J, Bucci S, Bell IH, Kessing LV, Faurholt-Jepsen M, Whelan P, et al. The growing field of digital psychiatry: current evidence and the future of apps, social media, chatbots, and virtual reality. World psychiatry. 2021;20(3):318-35.
25. Insel T, Cuthbert B, Garvey M, Heinssen R, Pine DS, Quinn K, et al. Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. American Psychiatric Association; 2010. p. 748-51.
26. EJ T. High-performance medicine: the convergence of human and artificial intelligence. Nature medicine. 2019:44-56.
27. Tierney AA, Gayre, G., Hoberman, B., Mattern, B., Ballesca, M., Kipnis, P., Liu, V., & Lee, K. Ambient artificial intelligence scribes to alleviate the burden of clinical documentation. NEJM Catalyst Innovations in Care Delivery. 2024.
28. Bate A, Luo Y. Artificial Intelligence and Machine Learning for Safe Medicines. Drug Safety. 2022;45(5):403-5.
29. Park T, Lee IH, Lee SW, Kong SW. Artificial intelligence in pediatric healthcare: current applications, potential, and implementation considerations. (2713-4148 (Electronic)).
30. Walter HJ, Abright AR, Bukstein OG, Diamond J, Keable H, Ripperger-Suhler J, et al. Clinical Practice Guideline for the Assessment and Treatment of Children and Adolescents With Major and Persistent Depressive Disorders. Journal of the American Academy of Child & Adolescent Psychiatry. 2023;62(5):479-502.
31. Airenti G. The Development of Anthropomorphism in Interaction: Intersubjectivity, Imagination, and Theory of Mind. Frontiers in Psychology. 2018;Volume 9 - 2018.
32. Severson RL, Carlson SM. Behaving as or behaving as if? Children's conceptions of personified robots and the emergence of a new ontological category. Neural Networks. 2010;23(8-9):1099-103.
33. Chein J, Albert D, O'Brien L, Uckert K, Steinberg L. Peers increase adolescent risk taking by enhancing activity in the brain's reward circuitry. Developmental Science. 2011;14(2):F1-F10.
34. Steinberg L. A social neuroscience perspective on adolescent risk-taking. Biosocial theories of crime: Routledge; 2017. p. 435-63.
35. Throuvala MA, Griffiths MD, Rennoldson M, Kuss DJ. A 'Control Model' of Social Media Engagement in Adolescence: A Grounded Theory Analysis. International Journal of Environmental Research and Public Health. 2019;16(23):4696.
36. Yang J, Soltan AAS, Eyre DW, Yang Y, Clifton DA. An adversarial training framework for mitigating algorithmic biases in clinical machine learning. npj Digital Medicine. 2023;6(1):55.
37. Liang J, Matheson BE, Douglas JM. Mental Health Diagnostic Considerations in Racial/Ethnic Minority Youth. Journal of Child and Family Studies. 2016;25(6):1926-40.
38. Obermeyer Z, Powers B, Vogeli C, Mullainathan S. Dissecting racial bias in an algorithm used to manage the health of populations. Science. 2019;366(6464):447-53.
39. Foundation M. **Privacy not included: Mental health apps*. 2023 [Available from: https://foundation.mozilla.org/en/privacy-notincluded/categories/mental-health-apps/.
40. West EPaDM. Why mental health apps need to take privacy more seriously 2023 [Available from: https://www.brookings.edu/articles/why-mental-health-apps-need-to-take-privacy-more-seriously/.
41. Takhshid Z. Children's digital privacy and the case against parental consent. Tex L Rev. 2022;101:1417.
42. Schneble CO, Favaretto M, Elger BS, Shaw DM. Social media terms and conditions and informed consent from children: Ethical analysis. JMIR pediatrics and parenting. 2021;4(2):e22281.
43. Association AP. *Health advisory: Artificial intelligence and adolescent well-being.* 2025 [Available from: https://www.apa.org/topics/artificial-intelligence-machine-learning/health-advisory-ai-adolescent-well-being.
44. Emotional risks of AI companions demand attention. Nature Machine Intelligence. 2025;7(7):981-2.
45. Roose K. Can AI be blamed for a teen's suicide. The New York Times. 2024;23.
46. Asgari E, Montaña-Brown N, Dubois M, Khalil S, Balloch J, Yeung JA, et al. A framework to assess clinical safety and hallucination rates of LLMs for medical text summarisation. NPJ digital medicine. 2025;8(1):274.
47. Østergaard SD. Will generative artificial intelligence chatbots generate delusions in individuals prone to psychosis? : Oxford University Press US; 2023. p. 1418-9.
48. Østergaard SD. Generative artificial intelligence chatbots and delusions: From guesswork to emerging cases. Wiley Online Library; 2025. p. 257-9.
49. Morrin H, Nicholls L, Levin M, Yiend J, Iyengar U, DelGuidice F, et al. Delusions by design? How everyday AIs might be fuelling psychosis (and what can be done about it). 2025.
50. Hudon A, Stip E. Delusional experiences emerging from AI chatbot interactions or "AI Psychosis". JMIR Mental Health. 2025;12(1):e85799.

CHAPTER 36

The Role of Artificial Intelligence in the Diagnosis of Acute Appendicitis

Asst. Prof. Dr. Ceyhun Pekin

1. Introduction: The Traditional Diagnostic Paradigm and the Need for Change

1.1. Clinical Significance and Incidence Analysis

Acute appendicitis (AA) is the most common cause of admission to emergency surgical services worldwide, with an estimated lifetime risk of approximately 7-8%. Early diagnosis is vital for preventing life-threatening complications such as rupture, generalized peritonitis, and sepsis. Despite advances in modern surgical techniques and antibiotherapy, AA remains a "clinical test" for surgeons (1).

1.2. Diagnostic Dilemmas and Atypical Presentations

The "gold standard" for AA diagnosis is the synthesis of clinical examination and radiological confirmation; however, the process is not always linear. Especially in pediatric, geriatric, and pregnant patients, symptom masking can delay diagnosis. Variations in retrocecal or pelvic appendix locations can create misleading clinical pictures instead of classic McBurney tenderness. The sensitivity of Alvarado and AIR (**Appendicitis Inflammatory Response**) scoring systems remains insufficient, carrying a "negative appendectomy" risk of 5-15% (2).

1.3. Economic Dimension and Burden on the Healthcare System

The economic cost of diagnostic uncertainty is twofold. First, the high rate of negative appendectomies signifies unnecessary surgical costs, hospital stays, and loss of labor. Second, "missed" appendicitis cases lead to perforation and prolonged inten-

sive care processes. Clinical audits show that increasing diagnostic accuracy by just 5% could save millions of dollars in national health systems (3). Furthermore, the radiation risk and cost of unnecessary CT scans are significant components of this economic picture.

1.4. The Role of AI and the New Generation Approach

In the midst of these diagnostic and economic dilemmas, AI offers a new perspective with its big data analytics and pattern recognition capabilities. ML(Machine Learning) algorithms can process laboratory findings and radiological pixels simultaneously, uncovering hidden correlations that traditional systems cannot detect. AI is positioned as the most powerful assistant to modern surgery, with the potential to increase diagnostic accuracy to over 90%, especially in "gray zone" cases (4).

2. Methodological Framework: Technical Infrastructure of AI Algorithms

2.1. Data Mining and Pre-processing

The success of AI models depends on the quality of data. The dataset for AA diagnosis is fed by demographic data, laboratory values, and images pulled via **PACS (Picture Archiving and Communication System)**. The pre-processing stage includes noise reduction in raw CT images, standardization of contrast settings, and "segmentation," the software-based isolation of the appendix region (5).

2.2. ML(Machine Learning) and Classification Algorithms

ML models detect non-linear relationships between clinical variables. **Random Forest (RF)** models operate with a combination of hundreds of decision trees and exhibit over 92% success in distinguishing appendicitis from other causes of acute abdomen (1). **Support Vector Machines (SVM)** classify data in a multi-dimensional space, providing high specificity in the differentiation between complicated and uncomplicated appendicitis (22).

2.3. DL(Deep Learning) and CNN(Convolutional Neural Network) Architecture

CNN, which revolutionized image-based diagnosis, processes the visual data of radiologists at the pixel level (6). These networks automatically recognize complex clinical signs such as wall thickening or free fluid. In particular, the **3D-CNN** approach analyzes the entire CT volume instead of a single slice, reaching 96.4% sensitivity in retrocecal cases (7). **Transfer learning** allows massive networks trained on millions of general objects to be modified to achieve high success even with limited medical images (8).

2.4. Performance Metrics and Validation

Modern AA models offer high **AUC (Area Under the Curve)** values between 0.94-0.98. For clinicians, the reliability of a model is measured not just by training success, but by **external validation**. Testing the algorithm on a completely foreign dataset outside the hospital where it was trained is the most critical scientific step before integration into clinical routines (9).

3. The AI Revolution in Radiological Imaging

3.1. CT and 3D-CNN Integration

AI systems can automatically detect the appendix in CT scans using 3D-CNN (10). In cases considered borderline (appendix diameter 6-7 mm), AI's density analysis of pixels increased diagnostic accuracy by 8.4% compared to an expert radiologist (11).

Table 1. Comparison of Diagnostic Performance between Traditional Radiological Evaluation and AI-Supported Analysis

Method / Metric	Sensitivity (%)	Specificity (%)	AUC Value
Conventional CT (Radiologist)	87.0 - 95.0	89.0 - 99.0	0.88 - 0.94
AI-Assisted CT (Deep Learning)	92.0 - 98.0	91.0 - 97.0	0.95 - 0.96
Conventional USG	44.0 - 87.0	47.0 - 95.0	0.78 - 0.82
AI-Assisted USG	85.0 - 91.0	87.0 - 93.0	0.89 - 0.91
Clinical Scores (Alvarado/AIR)	72.0 - 85.0	64.0 - 70.0	0.60 - 0.80

Ismayilzada K. (2026). Artificial intelligence for acute appendicitis diagnosis: A systematic review of current evidence, challenges, and future directions. Medicine, 105(12), e48094. https://doi.org/10.1097/MD.0000000000048094

3.2. USG and Operator Dependency

AI-integrated USG devices use object recognition algorithms (12). Models analyzing the appendix's response to compression confirm lumen non-compressibility with 89% sensitivity, minimizing operator-dependent errors (11).

3.3. Magnetic Resonance Imaging (MRI) and DLR

New generation DLR (Deep Learning Reconstruction) algorithms shorten MRI scan times by 40% while minimizing image noise (13). MRI is particularly vital as a CT alternative in pregnant patients.

3.4. Radiomics: Analysis of the Invisible

Radiomics is the mathematical extraction of thousands of quantitative features (texture, heterogeneity, density) from standard images that are imperceptible to the human eye (14). In AA, the "radiomic signature" of the appendiceal wall can predict the degree of inflammation and necrosis risk before surgery.

3.5. Workflow Optimization

In emergency department crowding, prioritizing images marked "positive" by AI (**worklist prioritization**) shortens the time to diagnosis by an average of 25% (15).

4. Clinical Decision Support Systems and Multimodal Data Fusion

4.1. Integration of Laboratory Data

ML models can combine laboratory data (WBC, CRP, NLR) with radiomic data to increase accuracy up to 98% (16).

4.2. Optimization of Clinical Scoring

AI-based **Clinical Decision Support Systems (CDSS)**, such as optimized Alvarado or AIR scores, offer a 92.9% success rate in the surgeon's decision (17).

Table 2. Performance Analysis of Clinical Scoring and Hybrid ML Models

Model / Scoring	Accuracy (%)	Negative Appendectomy Rate (%)
Alvarado Score	72.9	15.0 - 22.0
Hybrid ML Model	92.9	5.0 - 8.0
Multimodal AI	98.1	< 4.0

Yağız, B. K., Keskin, Y., Yalaza, M., & Ersöz, Ş. (2026). A hybrid machine learning approach to improve the diagnostic accuracy of acute appendicitis. Ulus Travma Acil Cerrahi Derg, 32(2), 128-136.

5. AI in Pediatric Cases: Challenges and Opportunities

Diagnosis of AA in children is one of the most challenging clinical areas for surgeons due to limited history and difficulty in cooperation during physical examination. Negative appendectomy rates can reach 20-30% in the pediatric population.

5.1. Diagnostic Pitfalls and AI Solutions

The rapid progression to perforation in pediatric cases necessitates fast diagnosis. DL algorithms reach over 90% sensitivity by analyzing lumen diameter and wall vascularity in pediatric USG images (18).

5.2. Radiation Safety and the ALARA Principle

AI-supported USG and ML models have the potential to reduce unnecessary CT scans in children by 25-30% (19). This provides a critical public health advantage within the framework of the ALARA (As Low As Reasonably Achievable) principle.

5.3. Differentiating Complicated and Uncomplicated Cases

AI algorithms show high success in predicting complications like abscess formation or perforation in children, guiding surgeons between emergency surgery and non-operative management.

6. Discussion: Ethics, Legal Responsibility, and Clinical Limitations

6.1. The Black Box Problem and Explainability (XAI)

Deep learning models are often characterized as "black boxes" because the mathematical path from input to output is not transparent to the physician. To overcome this trust barrier, **Explainable AI (XAI)** techniques create "heatmaps" on CT slices, showing the surgeon exactly which pixels the algorithm focused on while making the diagnosis (20). If the heat map points to a neighboring bowel loop instead of the appendix, the surgeon can immediately recognize that the model has established a faulty correlation.

This transforms AI from a simple "answer machine" into a transparent assistant that surgeons can audit.

6.2. Algorithmic Bias and External Validation

AI models trained on homogeneous datasets may not perform well on different devices or diverse populations. Therefore, multi-center external validation is mandatory to ensure generalizability (21).

6.3. Legal Responsibility and Malpractice

In current legal systems, AI is considered an assistant or decision support tool. Therefore, the surgeon remains responsible as the final decision-maker for any errors, whether they follow or ignore the AI's suggestion (22).

6.4. Integration and Cost-Effectiveness

While integration into PACS requires infrastructure investment, the long-term savings from reduced negative appendectomy rates and shorter hospital stays compensate for these costs (23).

6.5. Human-in-the-loop Approach

The most ideal model is the "human-in-the-loop" approach, combining the surgeon's intuitive knowledge with AI's analytical power. Studies show that the AI-Radiologist combination provides higher accuracy than either alone.

7. Conclusion and Future Perspectives

7.1. Summary of Current Status

AI has a revolutionary potential in increasing diagnostic accuracy and optimizing radiologist workload. Hybrid data fusion capabilities have made AI an indispensable assistant in modern surgery.

7.2. Autonomous Diagnosis and Triage

In the future, real-time algorithms integrated into emergency triage systems will automatically scan radiological images and provide "critical case" notifications to surgeons, drastically reducing morbidity in pediatric and geriatric populations (24).

7.3. Operating Room Integration and Robotic Surgery

Computer vision integrated into laparoscopic systems will allow anatomical boundaries to be marked with **Augmented Reality (AR)** during surgery, creating "autonomous surgical assistance."

7.4. Personalized Medicine and Radiomic Signatures

Analyzing radiomic signatures will allow clinicians to predict with over 95% certainty which patients will recover with antibiotics alone, breaking traditional surgical dogmas (25).

7.5. Final Evaluation

In conclusion, AI is not a rival replacing the surgeon, but a digital partner that strengthens their clinical intuition. The surgeon of the future will be the one who masterfully uses both the scalpel and the algorithm.

8. References

1. Keskinkılıç Yağız B, Keskin Y, Yalaza M, Ersöz Ş (2026);Akut apandisit tanısında tanısal doğruluğu artırmaya yönelik hibrit makine öğrenmesi yaklaşımı. *Ulus Travma Acil Cerrahi Derg*. 32(2):128-136. doi:10.14744/tjtes.2025.56275.
2. Akbulut S., Kucukakcali Z., Colak C. (2025), Artificial intelligence in acute appendicitis: A comprehensive review. *World Journal of Gastroenterology*.;31(43):1120-1135. Doi:10.3748/wjg. v31.i43.1120.
3. Khan J., Hakim Y., Amjad A., Munir A., Najeeb S. M., Khan M., Khan (2026) Appendectomy Rates and Clinical Audit. *Cureus*.;18(2): e37326. Doi:10.7759/cureus.373266.
4. Bianchi V, Giambusso M., De lacop A., Chiarello M. M., Brisinda G. (2024), Artificial intelligence in the diagnosis and treatment of acute appendicitis. *PubMed Central (PMC)*.;13(5): PMC11129994. DOI: 10.1007/s13304-024-01801-x
5. Medicine Science Journal. Deep Learning for Medical Imaging in Appendicitis. *MedSci*. (2025);14(3):10323-10330.
6. Mazurowski M. A., Buda M., Saha A., Bashir M. (2018), Deep Learning in Radiology: An overview of the concepts and survey of the state of the art with focus on MRI. *Journal of Magnetic Resonance Imaging / Volume 49, Issue 4 pp 939-954*; https://doi.org/10.1002/jmri.26534
7. Kim M., Park T., Kang J., Kim M-J., Kwon M. J., Oh B. Y., Kim J. W., Ha S…Son I. (2025), Development and validation of automated three- dimensional convolutional neural network model for acute appendicitis diagnosis *PubMed* Central (PMC); PMC11882796. Doi:10.1038/s41598-024-84348-6. PMID:40044743

8. Dogan K., Selcuk T., A Novel (2024) Deep Learning Approach for the Automatic Diagnosis of Acute Appendicitis. Journal of Clinical Medicine Aug 22;13(16):4949 doi:10.3390/jcm13164949 PubMed *Central (PMC)*. 2024; PMC11355690.

9. Ghareeb, W. M., Draz, E., Chen, X., Zhang, J., Tu, P., Madbouly, K., Moratal, M…Emil, S. H. (2024). Multicenter validation of an artificial intelligence (AI)-based platform for the diagnosis of acute appendicitis. *Surgery*. 2024;176(3):569-576. doi: 10.1016/j.surg.2024.05.007

10. Baştuğ, B. T., Güneri, G., Yıldırım, M. S., Çorbacı, K., & Dandıl, E. (2024). Fully Automated Detection of the Appendix Using U-Net Deep Learning Architecture in CT Scans. Journal of Clinical Medicine, *13*(19), 5893. https://doi.org/10.3390/jcm13195893

11. Issaiy, M., Zarei, D., & Saghazadeh, A. (2023). Artificial Intelligence and Acute Appendicitis: A Systematic Review of Diagnostic and Prognostic Models. World journal of emergency surgery*: WJES*, *18*(1), 59. https://doi.org/10.1186/s13017-023-00527-2

12. Akbulut S, Kucukakcali Z, Colak C. (2025) Artificial intelligence in acute appendicitis: A comprehensive review of machine learning and deep learning applications. World J Gastroenterol ; 31(43): 112000 DOI: 10.3748/wjg. v31.i43.112000

13. Liu j., Lin C., Liu W., Zhu L., Ma C-X., Wang X., Xu X…Feng F. Rapid MR (2025) examination with deep learning reconstruction improves diagnosis of complicated acute appendicitis. European Journal of Radiology.; 195:112554. DOI:10.1016/j.ejrad.2025.112554

14. Gillies RJ, Kinahan PE, Hricak H. (2016) Radiomics: Images Are Data, Not Scarcely Pictures. Radiology. Feb;278(2):563-77. doi: 10.1148/radiol.2015151169. PubMed

15. Batra K, Xi Y, Bhagwat P, Espino P, Peshock R. (2023) Radiologist Worklist Reprioritization Using Artificial Intelligence: Impact on Report Turnaround Times for CTPA Examinations Positive for Acute Pulmonary Embolism. AJR Am J Roentgenol. Sep;221(3):362-371. doi: 10.2214/AJR.22.28864. PubMed

16. Shiri I, Salimi Y, Pakbin M, Hajianfar G, Avval AH, Babaei R, (2021) Machine learning-based prognostic modeling using clinical data and quantitative radiomic features from chest CT images in COVID-19 patients. Comput Biol Med. May; 132:104304. doi: 10.1016/j.compbiomed.2021.104304. PubMed

17. Schipper, A., Belgers, P., O'Connor, R., Jie, K. E., Dooijes, R., Bosma, J. S., Kurstjens, S., Kusters, R., van Ginneken, B., & Rutten, M. (2024). Machine-learning based prediction of appendicitis for patients presenting with acute abdominal pain at the emergency department. *World journal of emergency surgery: WJES*, *19*(1), 40. https://doi.org/10.1186/s13017-024-00570-7

18. Simkhada, S., Thapa, B., Basnet, A. T., & Karki, S. (2025). Pediatric Appendicitis Score and Ultrasound in children with Acute Appendicitis: An Observational Study. JNMA; journal of the Nepal Medical Association, 63(282), 109–113. https://doi.org/10.31729/jnma.8889

19. Elahmedi, M., Sawhney, R., Guadagno, E., Botelho, F., & Poenaru, D. (2024). The State of Artificial Intelligence in Pediatric Surgery: A Systematic Review. *Journal of pediatric surgery*, *59*(5), 774–782. https://doi.org/10.1016/j.jpedsurg.2024.01.044

20. Ahmed, F., Naz, N. S., Khan, S., Rehman, A. U., Ismael, W. M., & Khan, M. A. (2026). Explainable artificial intelligence (XAI) in medical imaging: a systematic review of techniques, applications, and challenges. *BMC medical imaging*, *26*(1), 37. https://doi.org/10.1186/s12880-025-02118-w

21. Kenig, N., Monton Echeverria, J., & Muntaner Vives, A. (2024). Artificial Intelligence in Surgery: A Systematic Review of Use and Validation. *Journal of Clinical Medicine*, *13*(23), 7108. https://doi.org/10.3390/jcm13237108

22. Ahmad, O. F., Mori, Y., Bretthauer, M., Dourado, D. A., Hassan, C., Bisschops, R., Bhandari, P. … Berzin, T. M. (2026). The Legal and Ethical Framework for Artificial Intelligence in Gastrointestinal Endoscopy: A World Endoscopy Organization International Consensus Statement. *Annals of internal medicine*, *179*(2), 270–275. https://doi.org/10.7326/ANNALS-25-03415

23. Fakha, A., & Boonstra, A. (2026). Artificial intelligence in transitional care: practice, promise, and pitfalls-a scoping review. *Frontiers in digital health*, *7*, 1690223. https://doi.org/10.3389/fdgth.2025.1690223

24. Bose S., Prakash A., Prusty A., Verma R., Padmavathy K., (2026) Artificial Intelligence (AI) Supported Decision-Making in Intensive Care Units: Implications for Nursing and Medical Practice. Cureus 18(2): e104266. Doi:10.7759/cureus.104266

25. Cellina, M., Cè, M., Irmici, G., Ascenti, V., Caloro, E., Bianchi, L., Pellegrino, G… Carrafiello, G. (2022). Artificial Intelligence in Emergency Radiology: Where Are We Going? *Diagnostics*, *12*(12), 3223. https://doi.org/10.3390/diagnostics12123223

CHAPTER 37

When Algorithms Guide the Surgeon: Artificial Intelligence from Diagnosis to Treatment Direction in Head and Neck Surgery

Asst. Prof. Dr. Ata Alperen Ersahan

1. Introduction

Head and neck surgery occupies a uniquely complex position in oncological care. Surgical decision-making in this anatomical region requires the integration of heterogeneous and multidimensional information flows, including clinical examination, cross-sectional imaging, endoscopic visualization, histopathology, molecular profiling, and patient-specific functional priorities. Unlike many other oncological fields, therapeutic interventions in the head and neck directly impact airway protection, speech, swallowing, facial aesthetics, and quality of life. Consequently, it involves balancing oncological radicality with functional preservation within a narrow therapeutic margin.

For decades, clinical decision-making has been structured around staging systems such as the American Joint Committee on Cancer (AJCC) TNM classification. While indispensable for standardization and prognosis, TNM staging primarily reflects anatomical tumor burden and nodal involvement. It does not fully account for tumor biology, molecular heterogeneity, variability in treatment response, or host-related factors. Studies have demonstrated significant survival heterogeneity within the same stage groups and highlighted the limitations of anatomy-based stratification (1,2). As precision oncology advances, the inadequacy of anatomical frameworks is becoming increasingly apparent.

The exponential growth of digital data in head and neck oncology has created fertile ground for the integration of artificial intelligence (AI). High-resolution CT, MRI, and PET imaging generate volumetric datasets suitable for computational feature extraction. Flexible endoscopy produces large amounts of video data suitable for deep learning analysis. In digital pathology, whole-slide imaging (WSI) enables the pixel-level quantification of histological patterns. Concurrently, genomic and transcriptomic profiling provide mo-

lecular insights into tumor behavior. The convergence of these methods creates a multidimensional data ecosystem that transcends human cognitive capacity.

Artificial intelligence offers tools capable of identifying nonlinear relationships within such complex datasets. For example, radiomics transforms imaging data into high-dimensional quantitative features that can be correlated with nodal metastasis, HPV status, treatment response, or survival outcomes (1). Deep learning approaches, particularly convolutional neural networks (CNNs), can automatically learn hierarchical representations from raw images and have demonstrated strong performance in tasks such as tumor segmentation, classification of malignant lesions, and detection of subtle radiographic patterns (3).

Similarly, AI-powered digital pathology has shown promising results in automated tumor grading, detection of perineural invasion, quantification of tumor-infiltrating lymphocytes, and prediction of molecular alterations directly from histological slides (3). These advancements indicate a shift from subjective interpretation toward quantitative, reproducible assessment.

However, impressive performance metrics such as the area under the receiver operating characteristic curve (AUC), sensitivity, or C-index should be interpreted with caution. Many AI models in head and neck oncology have been developed using retrospective, single-center datasets and lack robust external validation (1,2). Internal validation may demonstrate excellent discrimination, but performance typically declines when models are tested in institutions with different imaging protocols, scanners, or patient populations. Data set imbalance, overfitting, and selection bias further complicate generalizability.

Predictive models estimate the likelihood of outcomes such as recurrence, occult nodal metastasis, or treatment response based on input variables. In contrast, decision support systems must demonstrate that integrating these predictions into clinical workflows alters management decisions and improves patient outcomes.

For example, an algorithm predicting the risk of occult cervical metastasis in early-stage oral squamous cell carcinoma may achieve a high AUC value. However, the clinically relevant question is whether the use of this algorithm alters the threshold for elective neck dissection in a way that reduces morbidity without compromising oncological control. Without prospective interventional studies demonstrating improved outcomes, AI remains a probabilistic aid rather than a guiding authority. The transition from statistical association to therapeutic modification is neither automatic nor trivial.

This distinction is particularly important in head and neck surgery, where treatment options often involve complex trade-offs. Choosing between primary surgery and organ-preserving chemoradiotherapy, determining the extent of resection, deciding on nerve sacrifice, or planning microvascular reconstruction, all require contextual judgment. These decisions integrate anatomical findings, comorbidities, expected functional outcomes, patient preferences, and the surgeon's expertise. An algorithmic probability score cannot replace this multidimensional reasoning; it can only enhance it.

Accordingly, contemporary frameworks emphasize the paradigm of the surgeon being part of the loop. In this model, AI functions not as a backup tool but as a cognitive extension. While algorithms rapidly process large-scale data, highlight risk models, and gener-

ate probability estimates, the surgeon interprets these outputs within ethical, anatomical, and patient-centered contexts. This collaborative approach aligns with broader trends in the field of augmented intelligence, where human oversight is central to accountability and adaptability.

The trajectory of artificial intelligence in head and neck surgery appears to follow a continuum. Initial efforts have primarily focused on diagnostic enhancement. The next phase involves prognostic modeling that integrates imaging, pathology, and clinical variables to predict survival or recurrence. The most ambitious phase aims to influence the course of treatment, including surgical eligibility assessment, margin estimation, nodal management strategies, and potentially intraoperative guidance. While diagnostic applications are becoming increasingly robust, the transition to actual treatment guidance remains methodologically and ethically complex.

Other barriers to clinical implementation include algorithmic opacity, regulatory uncertainties, data privacy issues, and the need for standardized imaging and reporting protocols. Furthermore, the lack of large-scale prospective multicenter studies evaluating AI-assisted decision-making limits the strength of the current evidence. As highlighted in recent reviews, the gap between experimental performance and real-world clinical practice remains significant (1,3).

Despite these challenges, the integration of artificial intelligence into head and neck surgery is unlikely to regress. Instead, the evolution of AI will depend on methodological rigor, external validity, transparent reporting standards, and close collaboration between data scientists and surgical clinicians. The central question is no longer whether algorithms can recognize patterns, but how these patterns should responsibly influence surgical decisions.

This section examines the full spectrum of AI applications in head and neck surgery, ranging from diagnostic augmentation to treatment guidance. Particular emphasis is placed on methodological foundations, comparative performance with traditional staging, the distinction between prediction and decision-making, and the ethical and regulatory considerations shaping implementation. Ultimately, the aim is not to present algorithms as elements that will replace surgical expertise, but to critically evaluate how they can guide and potentially improve the art and science of head and neck surgery.

2. Artificial Intelligence in Diagnostic Augmentation

In head and neck surgery, the role of artificial intelligence in diagnosis is increasingly moving toward systems that can support clinical evaluation. In practice, these tools are not intended to replace the clinician. Their primary contributions include enhancing consistency, highlighting patterns that might otherwise be overlooked, and adding a quantitative layer to interpretation. Current applications encompass radiological evaluation, endoscopic image analysis, digital cytology and pathology, and, more recently, multimodal models that integrate multiple data sources.

2.1. Imaging Methods

Cross-sectional imaging is an indispensable method for preoperative evaluation. However, radiological interpretation is inevitably influenced by interobserver variability, differences in imaging protocols, and image artifacts. Radiomics and deep learning (DL) methods aim to reduce some of this variability by converting visual information into quantitative image-based features (1).

One of the most studied examples is the non-invasive prediction of human papillomavirus (HPV) status in oropharyngeal squamous cell carcinoma (OPSCC). Neural network-based models trained on pooled cancer imaging archive datasets have reported a test AUC value of approximately 0.81 when transfer learning approaches were applied across multiple cohorts (4). Another study also reported AUC values ranging from 0.7 to 0.8 (5). These variations in performance may reflect a combination of dataset heterogeneity, scanner-related variations, dental artifacts, and differences in the reference standard used for HPV classification.

Another potential clinical application is the detection of imaging-based extranodal spread (ENE). In a retrospective cohort of 397 HPV-positive cN+ OPSCC patients, an AI pipeline combining nnU-Net segmentation with radiomic and DL-derived features achieved an AUC of approximately 0.81 for iENE classification (6). iENE predicted by AI was also independently associated with overall survival and recurrence-free survival. Although the model appears to perform well, its reliability is limited because it has not been validated across different centers. Therefore, even if the model demonstrates high predictive performance, it has not yet been demonstrated that this translates into clinical evidence that would actually alter treatment decisions.

PET-based segmentation is another area where AI demonstrates relatively strong performance. In the HECKTOR competition, U-Net-based models achieved Dice similarity coefficients of up to 0.76 for gross tumor volume segmentation; this is a level approaching or, in some cases, exceeding inter-observer agreement (7). A practical advantage of automatic segmentation is that it makes serial quantitative analysis more feasible. External validation studies have shown that changes in ΔPET-GTV may be associated with significant differences in 2-year locoregional control; these differences were reported as .9.4.1% versus .5.3.6% (8). This indicates that the clinical value of these models lies not so much in altering interpretation but in improving response assessment and monitoring.

2.2. Real-Time Endoscopic Enhancement

Endoscopic examination is one of the fundamental methods in the diagnostic process for head and neck cancers. Both white light (WL) and narrow-band imaging (NBI) laryngoscopy allow for direct assessment of the mucosal surface, but interpretation may vary, particularly in the case of subtle or borderline lesions. Consequently, deep learning-based computer-aided detection systems have garnered significant interest. For example, YOLO-based models have achieved real-time lesion detection at approximately 0.026 seconds per frame with moderate sensitivity-recall performance (9).

Nevertheless, it is important to accurately define their role. These systems do not yet diagnose malignancy independently. They can highlight suspicious mucosal areas, identify superficial spread, help determine areas for biopsy, and potentially assist with transoral margin planning. However, there is currently no prospective evidence showing that they reduce margin positivity or improve diagnostic yield. Therefore, their role remains supportive rather than definitive.

2.3. Digital Cytology and Pathology: An Area Ready for Advanced Clinical Application

In head and neck applications, thyroid cytopathology appears to be the field closest to clinical maturity.

The multi-center ThyroPower system, trained on over 11,000 WSI slides and validated across four institutions, reported AUROC values ranging from 0.93 to 0.97 for Bethesda III+ classification, with prospective validation approaching 0.98 (10). Particularly noteworthy was the increase in specificity from 0.887 to 0.993 among young cytopathologists when AI assistance was used. This is one of the clearest examples in the literature demonstrating a significant improvement when human interpretation is supported by algorithmic output.

Similarly, patch-based WSI models using Inception-ResNet-v2 achieved a test accuracy of .9.4.9% and 100% sensitivity for the detection of papillary thyroid carcinoma (11). Compared to many imaging-based studies, this study stands out for being strengthened by the inclusion of multi-center datasets.

Overall, cytology-based AI offers numerous advantages over imaging and endoscopic applications. Studies in this field typically involve larger datasets, more frequent multicenter validation, occasional prospective components, and clearer workflow-related endpoints. For these reasons, digital cytopathology is currently the diagnostic field best positioned for routine clinical integration.

2.4. Multimodal Integration: From Diagnosis to Risk Characterization

Recently, there has been a significant shift toward studies focusing on the integration of multiple data streams within a single predictive framework. New models combine features derived from CT, WSI-based information, and structured clinical variables, rather than relying solely on imaging or pathology.

In a multicenter cohort of 1,087 patients, integrated CT + WSI + clinical models yielded internal validation AUC values of approximately 0.78 to 0.79 for overall survival prediction, while external validation performance ranged from 0.64 to 0.84 (12). Although these systems are generally discussed as prognostic models, they also have diagnostic implications. By converting basic imaging and pathological data into clinically relevant risk profiles, they may begin to shape discussions regarding adjuvant therapy and surveillance planning. Therefore, while their effects are indirect, they are potentially significant.

In conclusion, performance metrics alone are insufficient for any of these systems to be clinically useful. Calibration is crucial, as the predicted risk must align reasonably well with observed outcomes. Regulatory expectations are moving in the same direction. The FDA guidance on Clinical Decision Support software and Good Machine Learning Practices (GMLP) principles emphasizes human oversight and auditability. In head and neck surgery, these technologies should likely be evaluated not as standalone diagnostic systems, but as tools that support specific decisions within existing workflows. Margin definition layers, lymph node risk maps, or Bethesda risk recalibration results may be useful, but they remain auxiliary elements to clinical judgment rather than independent decision-makers.

3. Artificial Intelligence in Treatment Guidance

The transition from diagnostic support to treatment guidance represents one of the most critical and frequently discussed stages in the integration of artificial intelligence into head and neck surgery. While diagnostic models primarily predict probabilities such as lymph node metastasis, HPV status, or risk of recurrence, treatment-focused systems have the potential to influence surgical thresholds, surgical planning, and the selection of multimodal treatment approaches. Therefore, moving from predictions to clinical action requires a much higher level of evidence, as algorithmic recommendations can directly impact patient morbidity, functional outcomes, and long-term survival.

3.1. Surgical Eligibility and Organ-Preserving Decisions

One of the most challenging decisions in head and neck oncology, particularly in oropharyngeal and laryngeal malignancies, is choosing between primary surgery and organ-preserving strategies such as chemoradiotherapy. New multimodal artificial intelligence models that integrate imaging, pathology, and clinical parameters have shown promising results in classifying patients into different survival risk categories (12). Internal validation studies reported AUC values of approximately 0.78–0.79 for overall survival prediction, while external validation revealed a broader performance range of 0.64 to 0.84, highlighting the impact of data set heterogeneity and institutional variability.

From a surgical perspective, these findings raise an important clinical question: should patients predicted to have a higher risk of recurrence undergo more aggressive primary surgery or intensified adjuvant therapy? However, at present, there are no prospective interventional studies demonstrating that AI-based risk stratification improves clinical decision-making compared to traditional multidisciplinary tumor board discussions. Consequently, these systems should currently be viewed as probabilistic decision-support tools rather than definitive treatment decision-makers.

The distinction between prediction and decision-making remains fundamental. Calculated survival or recurrence probabilities do not automatically determine the optimal

treatment strategy. Instead, such predictions should be interpreted within a broader context—including functional outcomes, patient comorbidities, and individual treatment preferences—and ultimately support, rather than replace, the shared decision-making process.

3.2. Thresholds for Elective Neck Dissection and Lymph Node Risk Modeling

Elective neck dissection (END) is traditionally performed when the probability of occult lymph node metastasis exceeds approximately 15–20%. Artificial intelligence models designed to predict lymph node disease or imaging-based extranodal extension (iENE) have raised the possibility of refining or recalibrating these thresholds.

In HPV-positive oropharyngeal squamous cell carcinoma, AI-based iENE prediction demonstrated an AUC of approximately 0.81 and was shown to be independently associated with survival outcomes (6). If validated in external cohorts, such tools could potentially inform decisions regarding strategies for intensifying or reducing adjuvant therapy. However, modifying established surgical thresholds based solely on algorithmic predictions would require robust supporting evidence, including prospective outcome data, consistent calibration across institutions, and clear demonstration that the model reduces both overtreatment and undertreatment.

Without these safeguards, algorithm-guided neck management could inadvertently introduce bias or increase calibration errors.

3.3. Margin Estimation and Intraoperative Decision Support

Margin status remains one of the strongest predictors of local recurrence in head and neck cancer surgery. Emerging artificial intelligence systems aim to support margin-related decision-making through two complementary approaches: preoperative risk prediction based on imaging features and intraoperative support using real-time visualization technologies.

Endoscopic segmentation models such as SegMENT-Plus have reported Dice similarity coefficients of approximately 0.83 while maintaining a real-time processing speed of about 25 frames per second. Although initially developed as diagnostic tools, these systems can assist surgeons in identifying superficial tumor margins during endoscopic procedures, which may potentially influence surgical planning and intraoperative navigation (13).

Changes in automated PET-derived tumor volume metrics (ΔPET-GTV) have been associated with differences in locoregional control, suggesting potential implications for postoperative treatment planning (8).

Despite these advancements, fully integrated intraoperative AI systems capable of real-time frozen section evaluation or optical margin analysis remain largely in the experimental stage. To date, no randomized clinical trial has demonstrated that AI-assisted systems significantly reduce positive margin rates in head and neck surgery.

3.4. Reconstruction Planning and Functional Outcome Prediction

Treatment planning in head and neck surgery extends beyond oncological resection. Microvascular reconstruction requires careful evaluation of the defect size, tissue characteristics, anticipated radiation therapy, and patient-specific comorbidities.

Although the literature remains limited compared to oncological prediction models, early-stage studies have explored the use of machine learning to predict functional outcomes such as the recovery of swallowing function or long-term dependence on gastrostomy(14,15,16). By integrating clinical and imaging variables, these models may ultimately assist surgeons in selecting reconstructive strategies or determining the extent of surgical resection.

However, robust multicenter validation studies remain scarce. Furthermore, the reconstructive decision-making process involves aesthetic, psychosocial, and patient-specific considerations that cannot be fully captured through structured datasets. Therefore, algorithmic recommendations in this field should be interpreted as supportive tools rather than prescriptive guidelines.

3.5. Multimodal Decision Engines: Toward Integrated Risk Scoring

Perhaps the most ambitious vision for AI-guided treatment decision-making is the development of multimodal decision engines capable of integrating various clinical data sources. Such systems combine CT-derived imaging features, whole-slide pathology representations, structured clinical variables, and potentially genomic information within a single predictive framework.

In a large multicenter cohort, integrated modeling demonstrated moderate survival prediction performance but exhibited significant variability across external datasets (12). In particular, performance declined in validation cohorts derived from publicly available datasets such as TCIA.

Before such systems can meaningfully guide treatment decisions, they must undergo reliable calibration across diverse populations and be validated through prospective studies to mitigate demographic and institutional biases.

Without these precautions, algorithmic risk scores may unintentionally misclassify patients or lead to inappropriate treatment recommendations.

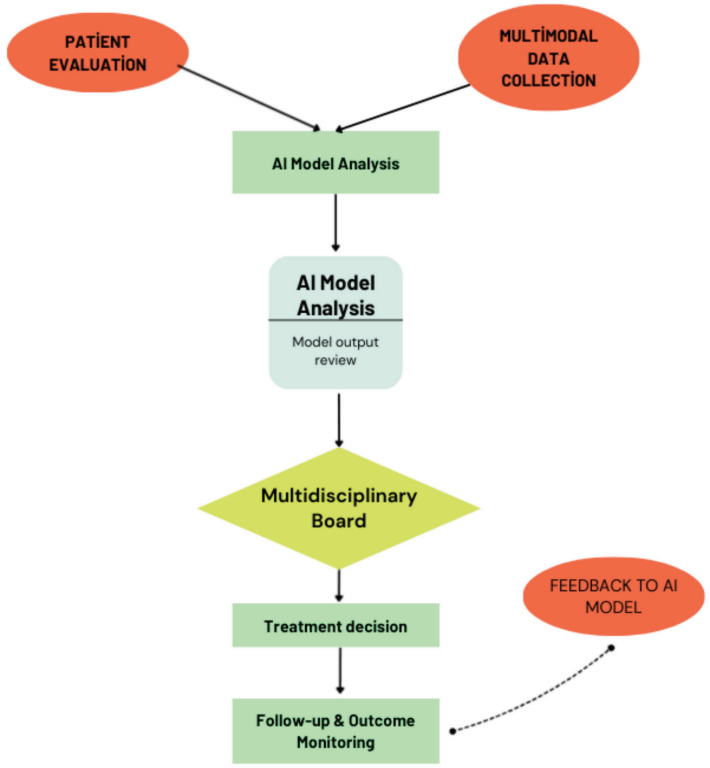
3.6. Conclusions on Treatment Guidance

As a result, as AI systems gain a foothold within clinical workflows, surgeons may place excessive trust in algorithmic outputs, particularly when these outputs are presented through visually appealing interfaces such as heat maps or probability scores.

This risk becomes particularly pronounced in borderline scenarios; for example, when the predicted risk of occult lymph node involvement is close to traditional intervention thresholds. Without transparent calibration and result validation, relying on such predictions can gradually shift clinical practice in directions not supported by evidence.

Table 1. The limitations of artificial intelligence		
Issue	**Description**	**Clinical Risk**
Domain shift	Model fails across centers	Wrong decisions
Overfitting	High internal performance	False confidence
Lack of validation	No prospective trials	Unsafe adoption
Black-box models	Low interpretability	Trust issues
Automation bias	Over-reliance	Clinical errors

For AI systems guiding treatment to be clinically meaningful, their evaluations must go beyond traditional performance metrics such as AUC. Receiver operating characteristic (ROC) curve analysis, net reclassification improvement, and demonstrable improvements in patient outcomes are key indicators of clinical value. However, currently, these metrics are largely absent from the existing head and neck AI literature. The limitations of artificial intelligence are presented in Table .1. Ultimately, the surgeon remains the individual legally and ethically responsible for final clinical decisions.



Algorithm 1. This algorithm outlines an AI-assisted decision-making framework in head and neck surgery, integrating multimodal clinical data with artificial intelligence–based risk estimation while preserving surgeon oversight as the final decision authority.

4. Future Perspectives: The Augmented Surgeon

The future of AI in head and neck surgery does not appear to be shaped by fully autonomous surgical systems. Instead, the emerging paradigm is the "augmented surgeon" model; this refers to a clinician whose cognitive and technical performance is enhanced through real-time data processing, multimodal visualization, and context-aware decision support. This model acknowledges the socio-technical complexity of surgical care and positions artificial intelligence not as a replacement for expertise, but as a layer integrated into the perioperative process.

4.1. Autonomous Surgical Robots

Despite rapid technological advancements, real-world surgical robotics remains predominantly at low levels of autonomy. Analyses of FDA-approved surgical robotic systems indicate that most operate under continuous human- e control (Level 1 assistance), with rare examples of conditional autonomy, and no Level 4–5 autonomous platforms currently available for clinical use (17). The levels of AI integration of surgery are presented in Table .2. In head and neck surgery, this empirical reality suggests that short-term gains will stem from planning optimization, visualization improvements, and intraoperative feedback rather than independent robotic decision-making.

This distinction is clinically significant. Autonomous surgery requires robust causal reasoning and dynamic adaptation to bleeding, tissue variability, and anatomical distortion; these remain challenging conditions for current AI systems. In contrast, assistance enhances decision quality while preserving the surgeon's control.

Table 2. The levels of AI integration of surgery

Level	Description	Example
Level 0	No AI	Standard care
Level 1	Assistance	Image segmentation
Level 2	Decision support	Risk prediction
Level 3	Conditional guidance	AR navigation
Level 4–5	Autonomy	(Not in use)

4.2. Short-Term Outlook (1–5 Years)

One of the most mature AI fields intersects with radiation therapy planning. Head and neck radiation therapy requires comprehensive contouring of organs at risk (OARs) and lymph node levels; these tasks are time-consuming and prone to inter-observer variability. Deep learning-based automatic contouring systems have yielded significant workflow gains.

In a multicenter study involving seven institutions, automated contouring reduced total contouring time by 42–49% while also decreasing inter-observer variability (18). However, time savings varied by ROI and institution, and the benefit remained minimal at

certain lymph node levels. Importantly, commercial systems have generally reported "true failure" rates of approximately 1% associated with dental artifacts or atypical anatomy (19). The fact that these rates are at such low levels holds promise for the feasibility of autosegmentation using AI models. However, it can be argued that combining it with expert review is necessary to minimize error rates in the early stages.

Real-time endoscopic AI-based imaging systems also have the potential to enter routine clinical practice in the short term, provided they undergo more comprehensive validation studies, as described in the diagnostic and therapeutic sections of this chapter.

4.3. Mid-Term Outlook (5–10 Years)

Multimodal AI models hold promise for integration into clinical practice within the next 5–10 years. The next significant advancement may be achieved through multimodal foundational models capable of integrating imaging, pathology, video, and clinical data under a single umbrella. The ability of models like MedSAM to ensure cross-modal consistency suggests that, in the future, radiation therapy planning, surgical planning, and intraoperative navigation processes could be integrated into a single system(20).

Augmented reality (AR) holds potential for the intraoperative visualization of tumor margins and critical structures. Studies in the otolaryngology field emphasize the importance of reliable image accuracy and ergonomic integration (21). This is an area where research is ongoing and results may be available in the medium term; however, dynamic updates that account for tissue deformation are necessary for it to be integrated into clinical routine.

Although full autonomy does not appear feasible in the near term, conditional robotic assistance for limited sub-tasks—such as camera stabilization, instrument tracking, and collision avoidance—may become increasingly widespread. Furthermore, regulatory analyses indicate that the vast majority of FDA-approved robotic systems still operate under human control. Therefore, mid-term robotic advancements in head and neck surgery are expected to focus on enhancing safety and performance rather than decision autonomy.

In head and neck oncology, personalized decision support systems could contribute to more precise determination of adjuvant therapy decisions. However, confounding factors, indication bias, and heterogeneous outcome definitions present significant methodological challenges. Reporting frameworks such as TRIPOD+AI and PROBAST+AI are of critical importance in mitigating exaggerated performance claims (22). Nevertheless, the routine clinical adoption of such systems is likely to be facilitated by prospective randomized controlled trials.

Federated learning is a distributed learning approach that enables the training of a shared machine learning model using data sources from different institutions without requiring the centralization of data in a single repository. In this method, the model is initially distributed to different centers, and each center trains the model on its own local data. Subsequently, only the model parameters or updates are consolidated on a central server; raw data, however, is never transferred outside the institution where it is located.

This feature makes federated learning a particularly prominent method in the healthcare field, where data privacy is critical (23).

In the context of head and neck surgery and oncology, federated learning has the potential to enhance model performance and generalizability by enabling the use of multicenter datasets. Especially in situations where imaging, pathology, and clinical data are scattered across different institutions, this approach facilitates collaboration without violating ethical and legal constraints on data sharing. This enables the development of models that represent more diverse patient populations.

However, federated learning also has some significant limitations. The heterogeneous distribution of data across different centers does not eliminate the "domain shift" issue, which can lead to variability in model performance. Additionally, the security of model updates, communication costs, and technical infrastructure requirements are factors that must be considered. Therefore, it is of great importance that models developed using federated learning are validated on independent datasets (external validation) before being put into clinical use.

Based on the current level of technological maturity:

- **2026–2028:** Widespread pilot use of automated contouring systems with quality control integration; pragmatic clinical trials for endoscopic artificial intelligence
- **2028–2030:** Standardization of optical boundary detection technologies; development of early-stage multimodal decision support systems
- **2030–2032:** Expansion of federated data networks and widespread adoption of conditional robotic assistance for limited tasks

The "augmented surgeon" of 2032 will not have been replaced by algorithms. Instead, the operating room will be equipped with integrated systems featuring calibrated risk predictions, real-time visual overlays, and adaptive radiation therapy feedback loops; the final decision-making authority will remain with the surgeon.

5. Conclusion

Artificial intelligence applications in head and neck surgery have made significant advancements in recent years, spanning a broad spectrum from diagnostic support to treatment guidance. The analysis of high-dimensional data derived from imaging, pathology, and clinical data has enabled more accurate risk prediction and patient classification, particularly through radiomics and deep learning approaches. However, the vast majority of current AI systems remain at the level of diagnostic augmentation and prognostic prediction; clinical evidence sufficient to directly guide treatment decisions remains limited.

In the context of treatment guidance, artificial intelligence offers potential in critical areas such as surgical candidate selection, decisions regarding elective neck dissection, determination of surgical margins, and adjuvant treatment planning. However, for this

potential to be safely integrated into clinical practice, not only high accuracy rates but also calibration, generalizability, and demonstration of clinical benefit through prospective studies are required. The distinction between "prediction" and "decision" is of central importance here; a high-performance model cannot be accepted as a treatment guide unless it demonstrates that it improves clinical outcomes.

In the future, the role of artificial intelligence will be shaped within the framework of the "augmented surgeon" approach rather than autonomous systems. In this model, artificial intelligence is positioned as a tool that reduces the surgeon's cognitive load, integrates complex datasets, and supports decision-making processes. Technologies such as augmented reality, real-time image analysis, multimodal foundational models, and federated learning are paving the way for a more integrated and data-driven approach in the operating room environment. However, fundamental methodological challenges such as domain shift, data heterogeneity, and model transparency remain significant obstacles that need to be addressed.

Regulatory and ethical frameworks also play a decisive role in this transformation. FDA guidelines, the European Union AI Act, and reporting standards like TRIPOD+AI mandate that AI systems be developed in a safe, transparent, and clinically meaningful manner. In particular, ensuring human oversight and maintaining the surgeon's role as the ultimate decision-maker stand out as fundamental requirements from both ethical and legal perspectives.

In conclusion, while artificial intelligence has the potential to transform decision-making processes in head and neck surgery, the surgeon remains at the center of this transformation. The surgeon of the future will not be replaced by algorithms; rather, they will be a clinician enhanced by algorithms. Therefore, the true value of artificial intelligence lies not in replacing the surgeon, but in making the surgical decision-making process more reliable, consistent, and personalized.

6. References

1. van Dijk, L. V., & Fuller, C. D. (2021). Artificial Intelligence and Radiomics in Head and Neck Cancer Care: Opportunities, Mechanics, and Challenges. *American Society of Clinical Oncology educational book. American Society of Clinical Oncology. Annual Meeting*, *41*, 1–1.1. https://doi.org/10.1200/EDBK_3209
2. Alabi, R. O., Elmusrati, M., Leivo, I., Almangush, A., & Mäkitie, A. A. (2024). Artificial Intelligence-Driven Radiomics in Head and Neck Cancer: Current Status and Future Prospects. *International Journal of Medical Informatics*, *188*, 1054.6.4. https://doi.org/10.1016/j.ijmedinf.202.4.105464
3. Broggi, G., Maniaci, A., Lentini, M., Palicelli, A., Zanelli, M., Zizzo, M., Koufopoulos, N., Salzano, S., Mazzucchelli, M., & Caltabiano, R. (2024). Artificial Intelligence in Head and Neck Cancer Diagnosis: A Comprehensive Review with Emphasis on Radiomics, Histopathological, and Molecular Applications. *Cancers*, *16*(21), 362.3. https://doi.org/10.3390/cancers16213623
4. Lang, D. M., Peeken, J. C., Combs, S. E., Wilkens, J. J., & Bartzsch, S. (2021). Deep Learning-Based HPV Status Prediction for Oropharyngeal Cancer Patients. *Cancers*, *13*(4), 7.8.6. https://doi.org/10.3390/cancers13040786
5. Leijenaar, R. T., Bogowicz, M., Jochems, A., Hoebers, F. J., Wesseling, F. W., Huang, S. H., Chan, B., Waldron, J. N., O'Sullivan, B., Rietveld, D., Leemans, C. R., Brakenhoff, R. H., Riesterer, O., Tanadini-Lang, S., Guckenberger, M., Ikenberg, K., & Lambin, P. (2018). Development and validation of a radiomic signature to predict HPV (p16) status from standard CT imaging: a multicenter study. *The British Journal of Radiology*, *91*(1086), 201704.9.8. https://doi.org/10.1259/bjr.20170498
6. Dayan, G. S., Hénique, G., Bahig, H., Nelson, K., Brodeur, C., Christopoulos, A., Filion, E., Nguyen-Tan, P. F., O'Sullivan, B., Ayad, T., Bissada, E., Tabet, P., Guertin, L., Desilets, A., Kadoury, S., & Letourneau-Guillon, L. (2026). Artificial Intel-

ligence Model for Imaging-Based Extranodal Extension Detection and Outcome Prediction in Human Papillomavirus-Positive Oropharyngeal Cancer. *JAMA Otolaryngology—Head & Neck Surgery*, *152*(1), 7–1.7. https://doi.org/10.1001/jamaoto.202.5.3225

7. Oreiller, V., Andrearczyk, V., Jreige, M., Boughdad, S., Elhalawani, H., Castelli, J., Vallières, M., Zhu, S., Xie, J., Peng, Y., Iantsen, A., Hatt, M., Yuan, Y., Ma, J., Yang, X., Rao, C., Pai, S., Ghimire, K., Feng, X., Naser, M. A., … Depeursinge, A. (2022). Head and neck tumor segmentation in PET/CT: The HECKTOR challenge. *Medical Image Analysis*, *77*, 10233.6. https://doi.org/10.1016/j.media.20.2.1.102336
8. Kovacs, D. G., Aznar, M., Van Herk, M., Mohamed, I., Price, J., Ladefoged, C. N., Fischer, B. M., Andersen, F. L., McPartlin, A., Osorio, E. M. V., & Abravan, A. (2025). External validation of deep learning-derived 18F-FDG PET/CT delta biomarkers for loco-regional control in head and neck cancer. *Acta Oncologica (Stockholm, Sweden)*, *64*, 1143–11.5.1. https://doi.org/10.2340/1651-226X.202.5.43977
9. Azam, M. A., Sampieri, C., Ioppi, A., Africano, S., Vallin, A., Mocellin, D., Fragale, M., Guastini, L., Moccia, S., Piazza, C., Mattos, L. S., & Peretti, G. (2022). Deep Learning Applied to White Light and Narrow Band Imaging Videolaryngoscopy: Toward Real-Time Laryngeal Cancer Detection. *The Laryngoscope*, *132*(9), 1798–180.6. https://doi.org/10.1002/lary.29960
10. Wang, J., Zheng, N., Wan, H., Yao, Q., Jia, S., Zhang, X., Fu, S., Ruan, J., He, G., Chen, X., Li, S., Chen, R., Lai, B., Wang, J., Jiang, Q., Ouyang, N., & Zhang, Y. (2024). Deep learning models for thyroid nodule diagnosis in fine-needle aspiration biopsy: a retrospective, prospective, multicenter study in China. *The Lancet. Digital Health*, *6*(7), e458–e46.9. https://doi.org/10.1016/S2589-7500(24)00085-2
11. Lee, Y., Alam, M. R., Park, H., Yim, K., Seo, K. J., Hwang, G., Kim, D., Chung, Y., Gong, G., Cho, N. H., Yoo, C. W., Chong, Y., & Choi, H. J. (2024). Improved Diagnostic Accuracy of Thyroid Fine-Needle Aspiration Cytology with Artificial Intelligence Technology. *Thyroid: Official Journal of the American Thyroid Association*, *34*(6), 723–73.4. https://doi.org/10.1089/thy.202.3.0384
12. Tian, R., Hou, F., Zhang, H., Yu, G., Yang, P., Li, J., Yuan, T., Chen, X., Chen, Y., Hao, Y., Yao, Y., Zhao, H., Yu, P., Fang, H., Song, L., Li, A., Liu, Z., Lv, H., Yu, D., Cheng, H., … Song, X. (2025). Multimodal fusion model for prognostic prediction and radiotherapy response assessment in head and neck squamous cell carcinoma. *NPJ Digital Medicine*, *8*(1), 30.2. https://doi.org/10.1038/s41746-025-01712-0
13. Sampieri, C., Azam, M. A., Ioppi, A., Baldini, C., Moccia, S., Kim, D., Tirrito, A., Paderno, A., Piazza, C., Mattos, L. S., & Peretti, G. (2024). Real-Time Laryngeal Cancer Boundaries Delineation on White Light and Narrow-Band Imaging Laryngoscopy with Deep Learning. *The Laryngoscope*, *134*(6), 2826–283.4. https://doi.org/10.1002/lary.31255
14. Costantino, A., Sampieri, C., Pace, G. M., Festa, B. M., Cerri, L., Giordano, G. G., Dalè, M., Spriano, G., Peretti, G., & De Virgilio, A. (2024). Development of machine learning models for the prediction of long-term feeding tube dependence after oral and oropharyngeal cancer surgery. *Oral Oncology*, *148*, 106.6.4.3. https://doi.org/10.1016/j.oraloncology.202.3.106643
15. Dohopolski, M., Wang, K., Morgan, H., Sher, D., & Wang, J. (2022). Use of deep learning to predict the need for aggressive nutritional supplementation during head and neck radiotherapy. *Radiotherapy and Oncology: Journal of the European Society for Therapeutic Radiology and Oncology*, *171*, 129–13.8. https://doi.org/10.1016/j.radonc.202.2.0.4.016
16. Pu, Y., Yang, J., Shui, L., Tang, Q., Zhang, X., & Liu, G. (2025). Risk prediction models for dysphagia after radiotherapy among patients with head and neck cancer: a systematic review , and meta-analysis. *Frontiers in Oncology*, *15*, 150240.4. https://doi.org/10.3389/fonc.202.5.1502404
17. Lee, A., Baker, T. S., Bederson, J. B., & Rapoport, B. I. (2024). Levels of autonomy in FDA-cleared surgical robots: a systematic review. *NPJ Digital Medicine*, *7*(1), 10.3. https://doi.org/10.1038/s41746-024-01102-y
18. Pang, E. P. P., Tan, H. Q., Wang, F., Niemelä, J., Bolard, G., Ramadan, S., Kiljunen, T., Capala, M., Petit, S., Seppälä, J., Vuolukka, K., Kiitam, I., Zolotuhhin, D., Gershkevitsh, E., Lehtiö, K., Nikkinen, J., Keyriläinen, J., Mokka, M., & Chua, M. L. K. (2025). Multicenter evaluation of deep learning-based CT autosegmentation of the head and neck region for radiotherapy. *NPJ Digital Medicine*, *8*(1), 31.2. https://doi.org/10.1038/s41746-025-01624-z
19. Temple, S. W. P., & Rowbottom, C. G. (2024). Gross failure rates and failure modes for a commercial AI-based auto-segmentation algorithm in head and neck cancer patients. *Journal of Applied Clinical Medical Physics*, *25*(6), e142.7.3. https://doi.org/10.1002/acm.2.14273
20. Ma, J., He, Y., Li, F., Han, L., You, C., & Wang, B. (2024). Segment anything in medical images. *Nature Communications*, *15*(1), .6.5.4. https://doi.org/10.1038/s41467-024-44824-z
21. Williams, M. A., McVeigh, J., Handa, A. I., & Lee, R. (2020). Augmented reality in surgical training: a systematic review. *Postgraduate Medical Journal*, *96*(1139), 537–.5.4.2. https://doi.org/10.1136/postgradmedj-2020-137600
22. Collins, G. S., Dhiman, P., Andaur Navarro, C. L., Ma, J., Hooft, L., Reitsma, J. B., Logullo, P., Beam, A. L., Peng, L., Van Calster, B., van Smeden, M., Riley, R. D., & Moons, K. G. (2021). Protocol for the development of a reporting guideline (TRIPOD-AI) and risk of bias tool (PROBAST-AI) for diagnostic and prognostic prediction model studies based on artificial intelligence. *BMJ Open*, *11*(7), e04800.8. https://doi.org/10.1136/bmjopen-2020-048008
23. Sheller, M. J., Edwards, B., Reina, G. A., Martin, J., Pati, S., Kotrotsou, A., Milchenko, M., Xu, W., Marcus, D., Colen, R. R., & Bakas, S. (2020). Federated learning in medicine: facilitating multi-institutional collaborations without sharing patient data. *Scientific Reports*, *10*(1), 125.9.8. https://doi.org/10.1038/s41598-020-69250-1

CHAPTER 38

Artificial Intelligence in Orthopedics and Traumatology: Fundamental Concepts, Clinical Applications, and Future Perspectives

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1. Introduction

In the 1990s, as orthopedic surgeons embraced digital radiography, the idea that software could one day outperform them in interpreting radiographs seemed highly improbable (1). Artificial intelligence encompassing algorithms that mimic human cognitive functions such as perception, reasoning, and decision-making has subtly integrated into nearly every aspect of orthopedic practice, revolutionizing clinicians' approaches to diagnosing injuries, planning surgeries, and tracking recovery (2). The speed and scale of this transformation are unprecedented in the history of the specialty.

AI in medicine relies on three core technologies: machine learning, which detects patterns in structured data; deep learning, which uses layered processing to extract features from raw images or text; and natural language processing, which handles unstructured data like clinical notes and radiology reports (3–5). Each of these pillars has found exceptionally fertile ground in orthopedics, a field defined by rich imaging data, reproducible surgical procedures, and quantifiable functional outcomes.

The extent of unmet clinical needs even more strongly emphasizes the importance of this trend. Musculoskeletal disorders are the world's leading cause of physical disability, impacting an estimated 1.71 billion people globally (6). Emergency departments frequently overlook a significant proportion of fractures during initial assessments; inconsistencies in osteoarthritis staging undermine the integrity of clinical trials; and complications following arthroplasty impose substantial burdens on healthcare resources. These deficiencies represent prime opportunities for AI-enhanced interventions (7).

The expansion of scholarly output in this domain closely parallels this accelerating momentum. A systematic search of the Web of Science (WoS) database integrating the terms "artificial intelligence" or "machine learning" with "orthopedic" or "bone fracture" dis-

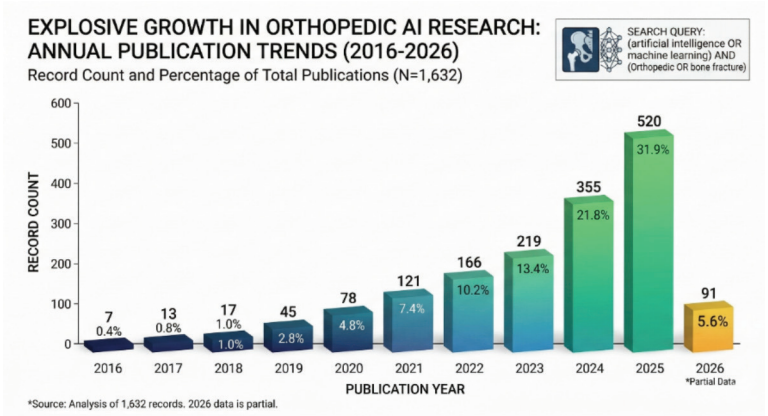


Figure 1. Annual publication trends of research involving artificial intelligence and machine learning in the context of orthopedics and bone fractures (2016–2026).

closes a remarkable progression: eligible articles numbered merely 7 in 2016, but surged to 520 by 2025, signifying a more than seventyfold increase across a decade (Figure 1). This chapter is intended for orthopedic surgeons who encounter AI tools in the clinical setting or evaluate the AI literature and require a reliable conceptual framework. Beginning with foundational methodology, it extends across major subspecialty domains including imaging and diagnostics, arthroplasty, spinal surgery, trauma care, sports medicine, robotics, and rehabilitation, before addressing the limitations that the field must confront and the directions in which research is advancing.

2. Fundamental Concepts of Artificial Intelligence in Clinical Medicine

2.1. Machine Learning: Learning from Patterns

Machine learning is most readily apprehended through its contrast with conventional software. Traditional programs follow explicit rules programmed by developers, whereas a machine learning model processes vast datasets iteratively to independently detect the associations that most accurately predict the desired outcome. In orthopedics, relevant outcomes might encompass the detection of a fracture on a radiograph, implant failure within five years, or the likelihood of attaining a clinically significant functional improvement after surgery (8).

Supervised learning wherein algorithms are trained on labeled datasets featuring known outcomes represents the predominant paradigm in the field. Canonical supervised techniques encompass logistic regression, random forest, gradient boosting machines, and support vector machines. These methods proficiently manage tabular data and are routinely deployed in outcome prediction models derived from registry databases. Their superior interpretability relative to deep learning positions them as

especially compelling for clinical risk stratification instruments, wherein articulating the rationale underlying a prediction to patients or payers holds equivalent importance to the prediction itself (9).

Unsupervised learning methods operate without labeled targets, instead discovering latent structure within the data (10,11). Clustering algorithms such as k-means and hierarchical clustering have been employed in orthopedics to identify phenotypically distinct patient subgroups within ostensibly homogeneous diagnostic categories(12–14). Principal component analysis (PCA) and dimensionality reduction techniques have been applied to visualize high-dimensional biomechanical or gait data (15).

2.2. Deep Learning and Convolutional Neural Networks

Deep learning encompasses neural networks comprising multiple hidden layers, where the term "deep" signifies architectural depth rather than inherent conceptual sophistication—though the two often align. Convolutional neural networks (CNN), the preeminent architecture for image processing, acquire visual feature recognition via iterative convolution operations that enable progressive hierarchical abstraction, evolving from rudimentary edges and textures in initial layers to clinically salient structures in subsequent ones (16,17). The practical implication is that a CNN trained on a sufficient number of labeled radiographs can learn to detect fractures, measure joint spaces, or grade bone quality without any programmer explicitly defining what a fracture looks like (18).

Notable CNN architectures that have shaped the field include VGGNet, ResNet (with residual skip connections that enable training of very deep networks), Inception, DenseNet, and EfficientNet (19,20). Each has been benchmarked on orthopedic imaging tasks; transfer learning—initializing a network with weights pre-trained on ImageNet and subsequently fine-tuning on medical images has substantially reduced the labeled data requirements that would otherwise render medical AI impracticable (21). More recently, transformer-based architectures, including Vision Transformer (ViT) and Swin Transformer, have demonstrated competitive performance in medical image classification, offering advantages in modeling long-range spatial dependencies that CNNs handle less naturally (22).

Generative models, an increasingly important category encompassing diffusion models and generative adversarial networks (GANs), have found their primary orthopedic applications in data augmentation: synthesizing realistic yet novel radiographic examples to balance underrepresented classes such as rare fracture types or pediatric cases (23,24). Preliminary studies suggest that GAN-augmented training datasets can improve downstream classifier performance by 3 to 8 percentage points in low-data regimes (25).

The hierarchical architecture of a typical CNN applied to orthopedic image classification Figure 2 illustrates, highlighting the sequential processing stages from raw radiographic input through successive convolution, pooling, and fully connected layers to the diagnostic output.

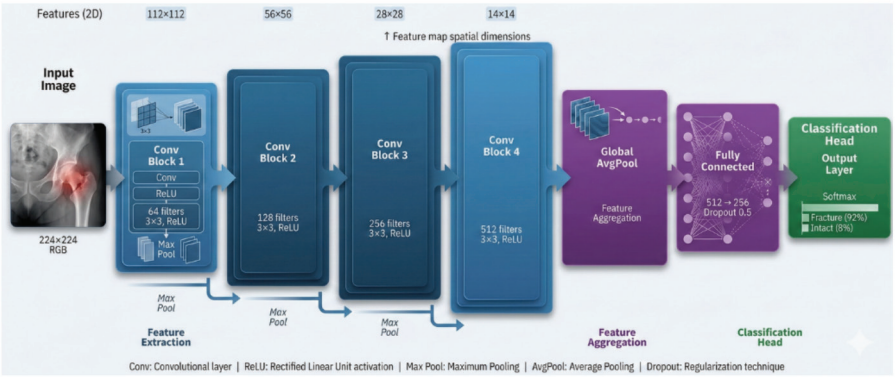


Figure 2. Schematic architecture of a convolutional neural network (CNN) for orthopedic fracture detection and classification on radiographic images. Conv: Convolutional layer; ReLU: Rectified Linear Unit; AvgPool: Average Pooling.

2.3. Natural Language Processing and Large Language Models

Orthopedic practice generates a vast quantity of unstructured text: operative notes documenting surgical approaches and findings, radiology reports describing imaging pathology, and patient-reported outcome questionnaires capturing subjective functional status (26,27). Natural language processing extracts structured, computable information from this text through techniques such as named entity recognition, relation extraction, and document classification. Practical applications range from the automated extraction of complication events from operative notes for quality assurance purposes to the phenotyping of surgical cohorts from free-text electronic health records for research (28–30).

Large language models (LLMs) such as GPT-4 and PaLM 2 represent a qualitative advance over prior NLP systems through emergent competencies arising from training on internet-scale text corpora (31). Multiple groups have evaluated LLM performance on orthopedic board examination questions and clinical scenario reasoning, with results sometimes approaching or exceeding the performance of average examination candidates (32–34). However, a critical caveat remains: LLMs exhibit a propensity for confident confabulation—generating statements that are confidently presented yet factually erroneous—which is particularly hazardous in the clinical setting; deployment without robust validation and human oversight would be premature (35,36).

2.4. Multimodal Fusion Architectures

Patients in reality are not isolated data modalities but holistic biological entities, prompting the development of multimodal AI systems. These architectures process imaging, laboratory, genomic, and clinical tabular data concurrently via parallel encoding pathways, fusing the representations before a shared final prediction layer. Several orthope-

dic studies comparing unimodal and multimodal models for outcomes such as aseptic implant loosening, periprosthetic joint infection, and revision surgery have reported improvements in AUC ranging from 0.04 to 0.12 for the multimodal approach—a clinically meaningful gain in discriminative performance (37,38). The challenge is that multimodal systems require all input modalities to be available at inference time, creating practical difficulties when data are missing or incomplete (39).

3. Artificial Intelligence in Orthopedic Imaging and Diagnostics

Prior to a detailed examination of specific diagnostic applications, it proves instructive to outline the overarching architecture facilitating the integration of AI tools within orthopedic clinical workflows. As depicted in Figure 3, the standard AI-augmented pathway leverages diverse input modalities—including imaging, electronic health record data, and patient-reported outcomes—routes these through a processing pipeline incorporating explainability mechanisms, and delivers the outputs to the surgeon for final decision-making (40,41). This human-in-the-loop design lies at the center of responsible clinical AI deployment and distinguishes validated decision support tools from autonomous systems (42–44).

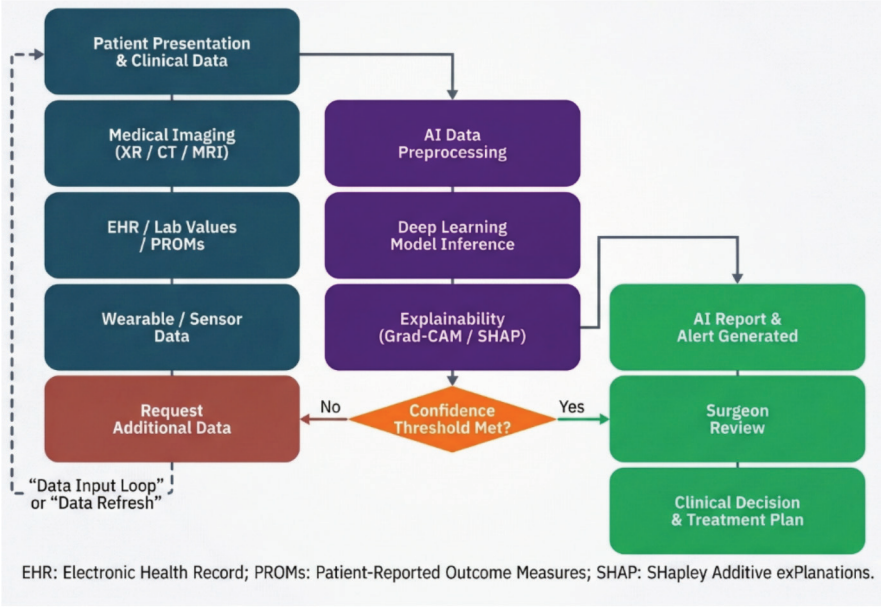


Figure 3. AI-integrated clinical decision support workflow in orthopedics. The diagram illustrates the data input streams, AI processing pipeline, explainability layer, and surgeon review pathways. EHR: Electronic Health Record; PROMs: Patient-Reported Outcome Measures; SHAP: SHapley Additive exPlanations.

3.1. Fracture Detection: From Proof of Concept to Clinical Tools

Experienced emergency medicine physicians overlook roughly one-fifth of fractures on plain radiographs—a sobering fact that spurred much of the pioneering AI research in this field (45). The first compelling evidence that deep learning could match or exceed radiologist performance in fracture detection came from, who trained a CNN on 135,471 wrist radiographs and reported an AUC of 0.994 for fracture identification. More significantly, the study demonstrated that radiologists using AI output as a second opinion substantially reduced their miss rates, a finding that shifted the conceptual framework of much subsequent AI imaging research from artificial replacement to human-AI collaboration (46).

Hip fractures constitute a particularly high-stakes detection problem as delayed diagnosis in elderly adults is directly associated with increased mortality trained a DenseNet architecture on 3,198 pelvic radiographs and achieved 92.5% sensitivity and 97.7% specificity for hip fracture detection; this performance was statistically indistinguishable from that of fellowship-trained orthopedic surgeons when evaluated under equivalent conditions (47). The systematic review and meta-analysis by, which pooled fracture detection studies across anatomical regions, reported 92% sensitivity and 91% specificity for deep learning models, supporting the contention that AI now meets a threshold for clinical decision support use (48). Occult fractures—not visible on radiographs but detectable on MRI or CT—pose a distinct challenge. A recent study showed a ResNet model trained on MRI detected femoral neck stress fractures with 93.7% sensitivity—potentially preventing unnecessary repeat imaging if used in clinical triage (49).

3.2. Fracture Classification

Detecting a fracture and classifying it are distinct problems. The AO/OTA classification system serves as the international standard, yet inter-observer agreement among experienced trauma surgeons for complex fracture patterns seldom exceeds a kappa value of 0.70. Automated classification offers the possibility of a consistent, reproducible classifier that could standardize registry data and trial enrollment. Pediatric fractures present unique classification challenges because growth plate anatomy complicates interpretation. Costa et al. (2026) introduced a deep learning model for Salter–Harris fracture classification using pediatric elbow radiographs, achieving 88% accuracy on an external validation cohort from a distinct institution. The model demonstrated reduced performance for types III and IV—the subtypes conferring the highest clinical risk—thereby identifying a key opportunity for augmented training data in these categories (50).

3.3. Bone Tumors and Metabolic Bone Disease

Differentiating benign from malignant bone lesions on radiographs remains challenging, particularly for indeterminate lesions measuring 1 to 5 cm. Osteoporosis screening represents a related but distinct application that shares the principle of extracting diagnostic

value from routinely acquired imaging. Yamamoto et al. (2020) demonstrated that a deep learning model applied to opportunistic CT data could predict bone mineral density obtained by DXA with a correlation coefficient of r = 0.89 and identify patients meeting World Health Organization osteoporosis criteria with an AUC of 0.91. Crucially, the CT scans in question had been obtained for unrelated indications such as abdominal pathology—meaning that bone health information was being recovered from data already present in the radiology archive without imposing additional radiation or cost on the patient (51).

3.4. Osteoarthritis Staging and Cartilage Assessment

The Kellgren–Lawrence grading system for knee osteoarthritis represents one of the most prevalent radiographic assessment tools in orthopedics; however, its reliability is undermined by marked inter-observer variability, which has persistently hindered clinical trials of disease-modifying osteoarthritis therapies over decades. Convolutional neural network–based automated grading approaches have effectively mitigated this limitation, achieving Cohen's kappa values of 0.70–0.75 or higher relative to expert radiologists across diverse independent validation cohorts (52). A particularly striking finding from the Osteoarthritis Initiative dataset, which has served as a benchmark for several groups, reveals that AI-derived cartilage thickness measurements from MRI can predict symptomatic progression 24 months in advance with accuracy superior to baseline clinical parameters (53).

4. Artificial Intelligence in Arthroplasty

4.1. Preoperative Templating and Component Sizing

Total hip and knee arthroplasty together account for more than seven million procedures annually in the United States (54). Preoperative templating accuracy directly affects operative efficiency, limb length restoration, and implant availability in the operating room. Manual digital templating, while an improvement over acetate overlay methods, remains time-intensive and dependent on radiographic technique and surgeon experience (55,56). AI-based templating systems learn the relationship between bone morphology and optimal implant dimensions from large postoperative radiograph databases in which implant selections are known (57,58).

A related and arguably more consequential question is patient selection. Determining which patients will benefit from arthroplasty—and which will remain dissatisfied despite a technically successful operation—is among the most important preoperative decisions. Conventional selection criteria based on radiographic severity and pain duration account for only a limited portion of outcome variance. The remainder is attributable to patient-specific biological, psychological, and social factors that are difficult to quantify during routine clinical examination. ML (models capable of integrating multiple predictors simultaneously offer potential added value in this domain (59). Fontana et al. (2019) applied

gradient boosting to a registry dataset of 14,000 total knee arthroplasty patients to predict failure to achieve the minimum clinically important difference (MCID) in Oxford Knee Score at one year. The gradient boosting model achieved an AUC of 0.71, significantly outperforming logistic regression (AUC 0.63), and provided clinically actionable risk stratification: MCID failure was 44% in the highest predicted nonresponder quintile compared to 7% in the lowest-risk quintile (60).

4.2. Computer Vision in Implant Identification

Revision arthroplasty surgeons frequently encounter implants from prior procedures whose brand and model are undocumented. This complicates compatible trial and modular component selection. CNN-based implant identification systems, trained on large radiographic databases, have addressed this problem effectively. Karnuta et al. (2021), using an ensemble CNN architecture evaluated on an external validation dataset from a different healthcare system, reported 97.3% top-1 accuracy for acetabular and femoral component identification across 17 implant brands. The clinical time savings in transitioning from hourly manual database searching to second-level automated identification represent an efficiency gain of direct operating-room relevance (61).

5. Artificial Intelligence in Traumatology

Trauma care requires high-stakes decisions under time pressure and informational uncertainty. Early identification of patients who will need massive transfusion, damage control surgery, or intensive care admission is essential for resource allocation and outcome optimization. Conventional triage scoring systems—including the Injury Severity Score and the Revised Trauma Score—leave considerable unexplained prediction variance.

ML models that integrate prehospital physiological data, injury mechanism, and initial laboratory values have demonstrated AUC values of 0.85 to 0.93 for 30-day mortality prediction in polytrauma cohorts. These models consistently outperform traditional scoring systems (62).

Rib fractures present a specific application area. Fracture number and pattern on chest CT carry implications for pulmonary complications, pain management, and the need for surgical stabilization. Zhou et al. (2021) developed a CNN trained on 5,169 CT examinations that achieved 95.2% sensitivity with a false-positive rate of 1.3 fractures per scan (63).

6. Limitations, Challenges, and Critical Appraisal

Interest in AI within orthopedics should be tempered by an objective assessment of the existing literature. Bini's (2018) systematic review of 48 AI studies in orthopedics found that only 4.3% included external validation. Retrospective single-institution studies with

train–test overlap are overrepresented. Prospective randomized evaluations comparing AI-assisted with conventional clinical workflows remain scarce. Without such evidence, it is uncertain in many areas whether AI confers real clinical benefit beyond existing tools (64). Reporting quality is a related concern. The TRIPOD guidelines (Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis) provide a standard framework for prediction model reporting (65). The TRIPOD-AI extension, currently under development, specifically addresses ML studies (66). Adherence to these standards has been insufficient in the orthopedic AI literature, complicating bias assessment, generalizability evaluation, and meta-analysis. Journal editors and reviewers play a key role in enforcing these standards (67).

7. Future Perspectives

Prior to considering future directions, it is valuable to evaluate the current position of the field across orthopedic subspecialties. Imaging and fracture detection, arthroplasty planning, and robotic surgery constitute the most advanced quadrant; rehabilitation AI and autonomous surgical systems remain at earlier stages of the evidence-toadoption pipeline (68). The next decade of AI in orthopedics will likely be shaped by three convergent developments: the maturation of foundation models, the expansion of realworld evidence generation, and the integration of AI into connected surgical ecosystems. Each merits brief consideration as a framework for interpreting the research publications that will emerge in the years ahead.

Foundation models are large-scale AI systems pre-trained on multimodal corpora and adaptable to downstream clinical tasks with minimal fine-tuning. These models are beginning to reach medical imaging. Google's Med-PaLM 2 has demonstrated expert-level performance on the United States Medical Licensing Examination and has shown early promise in medical visual question-answering, including radiograph interpretation. BioViL-T, a vision–language model trained on paired radiology images and reports, performs zero-shot disease detection on chest radiographs and is being adapted for musculoskeletal imaging. The practical implication is that a single pre-trained model may serve multiple orthopedic tasks—fracture detection, implant identification, deformity measurement, and surgical planning—with relatively modest institution-specific fine-tuning (69).

Augmented reality surgical guidance that integrates AI-generated preoperative plans with real-time intraoperative monitoring and holographic overlay arguably represents the most immediately applicable near-term development (70,71).

8. Conclusion

Artificial intelligence is not a future technology in orthopedics. It is already employed to flag missed fractures in emergency departments, guide robotic bone preparation in

operating rooms, and monitor postoperative recovery via smartphones in rehabilitation settings. The evidence base reviewed in this chapter encompasses more than thirty peer-reviewed studies published within the past decade. Collectively, these studies demonstrate that AI achieves clinically relevant performance gains over conventional methods in specific, well-defined tasks. Fracture detection, arthroplasty templating, implant identification, and Cobb angle measurement represent the best-supported applications.

Orthopedic surgeons who understand the methodological foundations of AI—what convolutional networks can and cannot recognize, how dataset bias affects generalizability, and what metrics such as AUC and sensitivity actually measure—will be better equipped to appraise AI evidence critically. They will also be better positioned to participate in clinical validation studies and to advocate for patients when AI tools enter institutional practice.

Looking ahead, the most consequential advances will likely arise not from incremental algorithmic improvements but from systemic integration. Achieving this will require collaboration across specialties, institutions, and industries. It will also demand a shared commitment to validation standards and equity principles ensuring that the benefits of AI extend to all patients, not only those who receive care at well-resourced academic centers.

9. References

1. Beyaz, S. (2020). A brief history of artificial intelligence and robotic surgery in orthopedics & traumatology and future expectations. *Joint Diseases and Related Surgery*, *31*(3), 653. https://doi.org/10.5606/ehc.2020.75300
2. Cabitza, F., Locoro, A., & Banfi, G. (2018). Machine Learning in Orthopedics: A Literature Review. *Frontiers in Bioengineering and Biotechnology*, *6*, 75. https://doi.org/10.3389/fbioe.2018.00075
3. Esteva, A., Robicquet, A., Ramsundar, B., Kuleshov, V., DePristo, M. A., Chou, K., Cui, C., Corrado, G. S., Thrun, S., & Dean, J. (2018). A guide to deep learning in healthcare. *Nature Medicine*, *25*(1), 24. https://doi.org/10.1038/s41591-018-0316-z
4. Kumari, J., Kumar, E., & Kumar, D. (2023). A Structured Analysis to study the Role of Machine Learning and Deep Learning in The Healthcare Sector with Big Data Analytics [Review of *A Structured Analysis to study the Role of Machine Learning and Deep Learning in The Healthcare Sector with Big Data Analytics*]. *Archives of Computational Methods in Engineering*, *30*(6), 3673. Springer Science+Business Media. https://doi.org/10.1007/s11831-023-09915-y
5. Quazi, F., Mohammed, A. S., & Gorrepati, N. (2024). *Transforming Treatment and Diagnosis in Healthcare through AI*. https://doi.org/10.21428/e90189c8.072ffbe8
6. Cieza, A., Causey, K., Kamenov, K., Hanson, S. W., Chatterji, S., & Vos, T. (2020). Global estimates of the need for rehabilitation based on the Global Burden of Disease study 2019: a systematic analysis for the Global Burden of Disease Study 2019. *The Lancet*, *396*(10267), 2006. https://doi.org/10.1016/s0140-6736(20)32340-0
7. Obermeyer, Z., & Emanuel, E. (2016). Predicting the Future — Big Data, Machine Learning, and Clinical Medicine. *New England Journal of Medicine*, *375*(13), 1216. https://doi.org/10.1056/nejmp1606181
8. LeCun, Y., Bengio, Y., & Hinton, G. E. (2015). Deep learning. *Nature*, *521*(7553), 436. https://doi.org/10.1038/nature14539
9. Breiman, L. (2001). Random Forests. *Machine Learning*, *45*(1), 5. https://doi.org/10.1023/a:1010933404324
10. Eckhardt, C., Madjarova, S. J., Williams, R. J., Ollivier, M., Karlsson, J., Pareek, A., & Nwachukwu, B. U. (2022). Unsupervised machine learning methods and emerging applications in healthcare [Review of *Unsupervised machine learning methods and emerging applications in healthcare*]. *Knee Surgery Sports Traumatology Arthroscopy*, *31*(2), 376. Springer Science+Business Media. https://doi.org/10.1007/s00167-022-07233-7
11. Friedman, S., Khurshid, S., Venn, R. A., Wang, X., Diamant, N., Achille, P. D., Weng, L., Choi, S. H., Reeder, C., Pirruccello, J. P., Singh, P., Lau, E. S., Philippakis, A., Anderson, C. D., Maddah, M., Batra, P., Ellinor, P. T., Ho, J. E., & Lubitz, S. A. (2025). Unsupervised deep learning of electrocardiograms enables scalable human disease profiling. *Npj Digital Medicine*, *8*(1), 23. https://doi.org/10.1038/s41746-024-01418-9
12. Karimi, A. H., Langberg, J., Malige, A., Rahman, O., Abboud, J. A., & Stone, M. A. (2024). Accuracy of machine learning to predict the outcomes of shoulder arthroplasty: a systematic review [Review of *Accuracy of machine learning to predict the outcomes of shoulder arthroplasty: a systematic review*]. *Arthroplasty*, *6*(1). BioMed Central. https://doi.org/10.1186/s42836-024-00244-4

13. Oettl, F. C., Oeding, J. F., Feldt, R., Ley, C., Hirschmann, M. T., & Samuelsson, K. (2024). The artificial intelligence advantage: Supercharging exploratory data analysis. *Knee Surgery Sports Traumatology Arthroscopy*, *32*(11), 3039. https://doi.org/10.1002/ksa.12389
14. Rani, S., Memoria, M., Choudhury, T., & Sar, A. (2024). A Comprehensive Review of Machine Learning's Role within KOA [Review of *A Comprehensive Review of Machine Learning's Role within KOA*]. *EAI Endorsed Transactions on Internet of Things*, *10*. European Alliance for Innovation. https://doi.org/10.4108/eetiot.5329
15. Federolf, P., Boyer, K. A., & Andriacchi, T. P. (2013). Application of principal component analysis in clinical gait research: Identification of systematic differences between healthy and medial knee-osteoarthritic gait. *Journal of Biomechanics*, *46*(13), 2173. https://doi.org/10.1016/j.jbiomech.2013.06.032
16. Dias, R., & Torkamani, A. (2019). Artificial intelligence in clinical and genomic diagnostics [Review of *Artificial intelligence in clinical and genomic diagnostics*]. *Genome Medicine*, *11*(1). BioMed Central. https://doi.org/10.1186/s13073-019-0689-8
17. Mienye, I. D., Swart, T. G., Obaido, G., Jordan, M., & Ilono, P. (2025). Deep Convolutional Neural Networks in Medical Image Analysis: A Review. *Information*, *16*(3), 195. https://doi.org/10.3390/info16030195
18. He, K., Zhang, X., Ren, S., & Sun, J. (2016). *Deep Residual Learning for Image Recognition*. 770. https://doi.org/10.1109/cvpr.2016.90
19. Suzuki, T., Maki, S., Yamazaki, T., Wakita, H., Toguchi, Y., Horii, M., Yamauchi, T., Kawamura, K., Aramomi, M., Sugiyama, H., Matsuura, Y., Yamashita, T., Orita, S., & Ohtori, S. (2021). Detecting Distal Radial Fractures from Wrist Radiographs Using a Deep Convolutional Neural Network with an Accuracy Comparable to Hand Orthopedic Surgeons. *Journal of Digital Imaging*, *35*(1), 39. https://doi.org/10.1007/s10278-021-00519-1
20. Zdolsek, G., Chen, Y., Bögl, H. P., Wang, C., Woisetschläger, M., & Schilcher, J. (2021). Deep neural networks with promising diagnostic accuracy for the classification of atypical femoral fractures. *Acta Orthopaedica*, *92*(4), 394. https://doi.org/10.1080/17453674.2021.1891512
21. Raghu, M., Zhang, C., Kleinberg, J., & Bengio, S. (2019). Transfusion: Understanding Transfer Learning for Medical Imaging. *arXiv (Cornell University)*. https://doi.org/10.48550/arxiv.1902.07208
22. Ahmad, K. J., Rehman, H. U., Shah, B., Ali, F., & Hussain, I. (2025). Dual-model approach for accurate chest disease detection using GViT and swin transformer V2. *Scientific Reports*, *15*(1). https://doi.org/10.1038/s41598-025-16422-6
23. Kunze, K. N. (2025). Generative Artificial Intelligence and Musculoskeletal Health Care. *HSS Journal® The Musculoskeletal Journal of Hospital for Special Surgery*, *21*(3), 248. https://doi.org/10.1177/15563316251335334
24. Mısır, A., & Yüce, A. (2025). AI in Orthopedic Research: A Comprehensive Review. *Journal of Orthopaedic Research®*, *43*(8), 1508. https://doi.org/10.1002/jor.26109
25. Frid-Adar, M., Diamant, I., Klang, E., Amitai, M. M., Goldberger, J., & Greenspan, H. (2018). GAN-based synthetic medical image augmentation for increased CNN performance in liver lesion classification. *Neurocomputing*, *321*, 321. https://doi.org/10.1016/j.neucom.2018.09.013
26. Caterson, J., Ambler, O., Cereceda-Monteoliva, N., Horner, M., Jones, A. M., & Poacher, A. (2024). Application of generative language models to orthopaedic practice. *BMJ Open*, *14*(3). https://doi.org/10.1136/bmjopen-2023-076484
27. Wyatt, J. M., Booth, G. J., & Goldman, A. H. (2021). Natural Language Processing and Its Use in Orthopaedic Research. *Current Reviews in Musculoskeletal Medicine*, *14*(6), 392. https://doi.org/10.1007/s12178-021-09734-3
28. Le, K. D. R., Tay, S., Choy, K. T., Verjans, J., Sasanelli, N., & Kong, J. C. (2024). Applications of natural language processing tools in the surgical journey [Review of *Applications of natural language processing tools in the surgical journey*]. *Frontiers in Surgery*, *11*. Frontiers Media. https://doi.org/10.3389/fsurg.2024.1403540
29. Mellia, J. A., Basta, M. N., Toyoda, Y., Othman, S., Elfanagely, O., Morris, M. P., Torre-Healy, L. A., Ungar, L., & Fischer, J. P. (2020). Natural Language Processing in Surgery [Review of *Natural Language Processing in Surgery*]. *Annals of Surgery*, *273*(5), 900. Lippincott Williams & Wilkins. https://doi.org/10.1097/sla.0000000000004419
30. Sagheb, E., Ramazanian, T., Tafti, A. P., Fu, S., Kremers, W. K., Berry, D. J., Lewallen, D. G., Sohn, S., & Kremers, H. M. (2020). Use of Natural Language Processing Algorithms to Identify Common Data Elements in Operative Notes for Knee Arthroplasty. *The Journal of Arthroplasty*, *36*(3), 922. https://doi.org/10.1016/j.arth.2020.09.029
31. Lonergan, R. M., Curry, J., Dhas, K., & Simmons, B. I. (2023). Stratified Evaluation of GPT's Question Answering in Surgery Reveals Artificial Intelligence (AI) Knowledge Gaps. *Cureus*, *15*(11). https://doi.org/10.7759/cureus.48788
32. Lubitz, M., & Latario, L. (2024). Performance of Two Artificial Intelligence Generative Language Models on the Orthopaedic In-Training Examination. *Orthopedics*, *47*(3). https://doi.org/10.3928/01477447-20240304-02
33. Nawari, A., Zahir, J., Kumar, S., Ocampo, L., Opara, O., Ahmad, H., Crawford, B., & Feeley, B. T. (2025). Artificial Intelligence Large Language Models Are Nearly Equivalent to Fourth-Year Orthopaedic Residents on the Orthopaedic In-Training Examination: A Cause for Concern or Excitement? *Journal of Orthopaedic Experience & Innovation*, *6*(1). https://doi.org/10.60118/001c.124070
34. Zhang, C., Liu, S., Zhou, X., Zhou, S., Tian, Y., Wang, S., Xu, N., & Li, W. (2024). Examining the Role of Large Language Models in Orthopedics: Systematic Review. *Journal of Medical Internet Research*, *26*. https://doi.org/10.2196/59607
35. Kung, T. H., Cheatham, M., Medenilla, A., Sillos, C., Leon, L. D., Elepaño, C., Madriaga, M., Aggabao, R., Diaz-Candido, G., Maningo, J., & Tseng, V. (2023). Performance of ChatGPT on USMLE: Potential for AI-assisted medical education using large language models. *PLOS Digital Health*, *2*(2). https://doi.org/10.1371/journal.pdig.0000198
36. Shen, Y., Heacock, L., Elias, J., Hentel, K., Reig, B., Shih, G., & Moy, L. (2023, January 26). ChatGPT and Other Large Language Models Are Double-edged Swords. In *Radiology* (Vol. 307, Issue 2). Radiological Society of North America. https://doi.org/10.1148/radiol.230163

37. Li, R., Yang, F., Liu, X., & Shi, H. (2023). HGT: A Hierarchical GCN-Based Transformer for Multimodal Periprosthetic Joint Infection Diagnosis Using Computed Tomography Images and Text. *Sensors*, *23*(13), 5795. https://doi.org/10.3390/s23135795
38. Oettl, F. C., Zsidai, B., Oeding, J. F., Hirschmann, M. T., Feldt, R., Tischer, T., Samuelsson, K., & Group, E. A. I. W. (2025). Beyond traditional orthopaedic data analysis: AI, multimodal models and continuous monitoring. *Knee Surgery Sports Traumatology Arthroscopy*, *33*(6), 2269. https://doi.org/10.1002/ksa.12657
39. Ngiam, K. Y., & Khor, I. W. (2019). Big data and machine learning algorithms for health-care delivery. *The Lancet Oncology*, *20*(5). https://doi.org/10.1016/s1470-2045(19)30149-4
40. GUMMADI, H. S. B. (2025). AI-driven multimodal workflow optimization for personalized patient-centered care. *World Journal of Advanced Engineering Technology and Sciences*, *15*(2), 555. https://doi.org/10.30574/wjaets.2025.15.2.0604
41. Varghese, C., Harrison, E. M., O'Grady, G., & Topol, E. J. (2024). Artificial intelligence in surgery. *Nature Medicine*, *30*(5), 1257. https://doi.org/10.1038/s41591-024-02970-3
42. Protserov, S., Hunter, J., Zhang, H. C., Mashouri, P., Masino, C., Brudno, M., & Madani, A. (2024). Development, deployment and scaling of operating room-ready artificial intelligence for real-time surgical decision support. *Npj Digital Medicine*, *7*(1), 231. https://doi.org/10.1038/s41746-024-01225-2
43. Fosch-Villaronga, E., Khanna, P., Drukarch, H., & Custers, B. (2021). A human in the loop in surgery automation. *Nature Machine Intelligence*, *3*(5), 368. https://doi.org/10.1038/s42256-021-00349-4
44. Williams, S. C., Khan, D. Z., Bano, S., Blandford, A., Clarkson, M. J., Costanza, E., Mazomenos, E. B., Stoyanov, D., McCulloch, P., & Marcus, H. J. (2025). A surgical approach to building impactful artificial intelligence. *Npj Digital Medicine*, *8*(1), 709. https://doi.org/10.1038/s41746-025-02073-4
45. Guly, H. R. (2001). Diagnostic errors in an accident and emergency department. *Emergency Medicine Journal*, *18*(4), 263. https://doi.org/10.1136/emj.18.4.263
46. Lindsey, R., Daluiski, A., Chopra, S., Lachapelle, A. S., Mozer, M. C., Sicular, S., Hanel, D. P., Gardner, M. J., Gupta, A., Hotchkiss, R., & Potter, H. G. (2018). Deep neural network improves fracture detection by clinicians. *Proceedings of the National Academy of Sciences*, *115*(45), 11591. https://doi.org/10.1073/pnas.1806905115
47. Cheng, C., Ho, T., Lee, T.-Y., Chang, C. C., Chou, C.-C., Chen, C.-C., Chung, I., & Liao, C. (2019). Application of a deep learning algorithm for detection and visualization of hip fractures on plain pelvic radiographs. *European Radiology*, *29*(10), 5469. https://doi.org/10.1007/s00330-019-06167-y
48. Langerhuizen, D. W. G., Janssen, S. J., Mallee, W. H., Bekerom, M. P. J. van den, Ring, D., Kerkhoffs, G. M. M. J., Jaarsma, R. L., & Doornberg, J. N. (2019). What Are the Applications and Limitations of Artificial Intelligence for Fracture Detection and Classification in Orthopaedic Trauma Imaging? A Systematic Review. *Clinical Orthopaedics and Related Research*, *477*(11), 2482. https://doi.org/10.1097/corr.0000000000000848
49. Urakawa, T., Tanaka, Y., Goto, S., Matsuzawa, H., Watanabe, K., & Endo, N. (2018). Detecting intertrochanteric hip fractures with orthopedist-level accuracy using a deep convolutional neural network. *Skeletal Radiology*, *48*(2), 239. https://doi.org/10.1007/s00256-018-3016-3
50. Costa, J., Vrignaud, B., Frampas, É., Decante, C., Meurice, L., Levieux, K., Guen, C. G., & Lorton, F. (2025). Assessing deep learning artificial intelligence support for detecting elbow fractures in the pediatric emergency department. *European Journal of Radiology*, *194*, 112498. https://doi.org/10.1016/j.ejrad.2025.112498
51. Yamamoto, N., Sukegawa, S., Kitamura, A., Goto, R., Noda, T., Nakano, K., Takabatake, K., Kawai, H., Nagatsuka, H., Kawasaki, K., Furuki, Y., & Ozaki, T. (2020). Deep Learning for Osteoporosis Classification Using Hip Radiographs and Patient Clinical Covariates. *Biomolecules*, *10*(11), 1534. https://doi.org/10.3390/biom10111534
52. Tiulpin, A., & Saarakkala, S. (2020). Automatic grading of individual knee OA features in plain radiographs using deep CNNs. *Diagnostics*, *10*(11), 932. https://doi.org/10.3390/diagnostics10110932
53. Tolpadi, A., Lee, J. J., Pedoia, V., & Majumdar, S. (2020). Deep Learning Predicts Total Knee Replacement from Magnetic Resonance Images. *Scientific Reports*, *10*(1), 6371. https://doi.org/10.1038/s41598-020-63395-9
54. Andriollo, L., Picchi, A., Iademarco, G., Fidanza, A., Perticarini, L., Rossi, S. M. P., Logroscino, G., & Benazzo, F. (2025). The Role of Artificial Intelligence and Emerging Technologies in Advancing Total Hip Arthroplasty. *Journal of Personalized Medicine*, *15*(1), 21. https://doi.org/10.3390/jpm15010021
55. Surroca, M., Álvarez, S. M. M., Bartra, A., Núñez, J. H., & Angles-Crespo, F. (2024). Surgeon's Experience and Accuracy of Preoperative Digital Templating in Primary Total Hip Arthroplasty. *Hip & Pelvis*, *36*(2), 129. https://doi.org/10.5371/hp.2024.36.2.129
56. Wheeler, A., & Gradisar, I. M. (2021). Accuracy of Digital Templating for Non-Cemented Total Hip Arthroplasty: A Large Series by a Single Surgeon. *Research Square (Research Square)*. https://doi.org/10.21203/rs.3.rs-154468/v1
57. Garcia, A. V., Bukowiec, L. G., Yang, L., Nishikawa, H., Fitzsimmons, J. S., Larson, A. N., Taunton, M. J., Sánchez-Sotelo, J., O'Driscoll, S. W., & Wyles, C. C. (2024). Artificial intelligence–based three-dimensional templating for total joint arthroplasty planning: a scoping review. *International Orthopaedics*, *48*(4), 997. https://doi.org/10.1007/s00264-024-06088-6
58. Park, J., Kim, S. E., Kim, B., Lee, S., Lee, J., & Ro, D. H. (2024). A deep learning based automatic two-dimensional digital templating model for total knee arthroplasty. *Knee Surgery and Related Research*, *36*(1), 38. https://doi.org/10.1186/s43019-024-00240-7
59. Collins, G. S., Dhiman, P., Navarro, C. L. A., Ma, J., Hooft, L., Reitsma, J. B., Logullo, P., Beam, A. L., Peng, L., Calster, B. V., Smeden, M. van, Riley, R. D., & Moons, K. G. M. (2021). Protocol for development of a reporting guideline (TRIPOD-AI)

and risk of bias tool (PROBAST-AI) for diagnostic and prognostic prediction model studies based on artificial intelligence. *BMJ Open*, *11*(7). https://doi.org/10.1136/bmjopen-2020-048008

60. Fontana, M. A., Lyman, S., Sarker, G. K., Padgett, D. E., & MacLean, C. H. (2019). Can Machine Learning Algorithms Predict Which Patients Will Achieve Minimally Clinically Important Differences From Total Joint Arthroplasty? *Clinical Orthopaedics and Related Research*, *477*(6), 1267. https://doi.org/10.1097/corr.0000000000000687
61. Karnuta, J. M., Haeberle, H. S., Luu, B. C., Roth, A., Molloy, R. M., Nystrom, L. M., Piuzzi, N. S., Schaffer, J. L., Chen, A. F., Iorio, R., Krebs, V. E., & Ramkumar, P. N. (2020). Artificial Intelligence to Identify Arthroplasty Implants From Radiographs of the Hip. *The Journal of Arthroplasty*, *36*(7). https://doi.org/10.1016/j.arth.2020.11.015
62. Stonko, D. P., Guillamondegui, O. D., Fischer, P. E., & Dennis, B. M. (2020). Artificial intelligence in trauma systems. *Surgery*, *169*(6), 1295. https://doi.org/10.1016/j.surg.2020.07.038
63. Zhou, Q.-Q., Wang, J., Tang, W., Hu, Z.-C., Xia, Z.-Y., Li, X., Zhang, R., Yin, X., Zhang, B., & Zhang, H. (2020). Automatic Detection and Classification of Rib Fractures on Thoracic CT Using Convolutional Neural Network: Accuracy and Feasibility. *Korean Journal of Radiology*, *21*(7), 869. https://doi.org/10.3348/kjr.2019.0651
64. Bini, S. A. (2018). Artificial Intelligence, Machine Learning, Deep Learning, and Cognitive Computing: What Do These Terms Mean and How Will They Impact Health Care? *The Journal of Arthroplasty*, *33*(8), 2358. https://doi.org/10.1016/j.arth.2018.02.067
65. Collins, G. S., Moons, K. G. M., & Dhiman, P. (2021). TRIPOD+AI statement. *BMJ*, *375*. https://doi.org/10.1136/bmj.n2085
66. Kelly, C., Karthikesalingam, A., Suleyman, M., Corrado, G. S., & King, D. (2019). Key challenges for delivering clinical impact with artificial intelligence. *BMC Medicine*, *17*(1). https://doi.org/10.1186/s12916-019-1426-2
67. Zsidai, B., Hilkert, A., Kaarre, J., Narup, E., Senorski, E. H., Grassi, A., Ley, C., Longo, U. G., Herbst, E., Hirschmann, M. T., Kopf, S., Seil, R., Tischer, T., Samuelsson, K., & Feldt, R. (2023). A practical guide to the implementation of AI in orthopaedic research – part 1: opportunities in clinical application and overcoming existing challenges [Review of *A practical guide to the implementation of AI in orthopaedic research – part 1: opportunities in clinical application and overcoming existing challenges*]. *Journal of Experimental Orthopaedics*, *10*(1). Springer Nature. https://doi.org/10.1186/s40634-023-00683-z
68. Mohamed, A., Elasad, A., Fuad, U., Pengas, I., El-Sayed, A. E.-K. B., Bhamidipati, P., & Salib, P. (2025). Artificial Intelligence in Trauma and Orthopaedic Surgery: A Comprehensive Review From Diagnosis to Rehabilitation. *Cureus*, *17*(9). https://doi.org/10.7759/cureus.92280
69. Tu, T., Azizi, S., Driess, D., Schaekermann, M., Amin, M., Chang, P.-C., Carroll, A., Lau, C. T., Tanno, R., Ktena, S. I., Palepu, A., Mustafa, B., Chowdhery, A., Liu, Y., Kornblith, S., Fleet, D. J., Mansfield, P., Prakash, S., Wong, R., … Natarajan, V. (2024). Towards Generalist Biomedical AI. *NEJM AI*, *1*(3). https://doi.org/10.1056/aioa2300138
70. Kowal, M., Ibrahim, M., Mihaljević, A. L., Kron, P., & Lodge, P. (2025). Technological Advances in Pre-Operative Planning [Review of *Technological Advances in Pre-Operative Planning*]. *Journal of Clinical Medicine*, *14*(15), 5385. Multidisciplinary Digital Publishing Institute. https://doi.org/10.3390/jcm14155385
71. Necker, F. N., Cholok, D., Shaheen, M. S., Fischer, M. J., Gifford, K., Chemaly, T. E., Leuze, C., Scholz, M., Daniel, B. L., & Momeni, A. (2025). Holographic Deep Inferior Epigastric Perforator Exploration in Mixed Reality using Real-Time Cinematic Rendering. *Aesthetic Plastic Surgery*, *50*(1), 183. https://doi.org/10.1007/s00266-025-05167-2

CHAPTER 39

Artificial Intelligence in the Diagnosis of Retinal Diseases

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1. Introduction

Ophthalmology, particularly the subspecialty of retina, is heavily reliant on digital imaging technologies within the medical sciences and therefore relies heavily on artificial intelligence. Ophthalmology is considered one of the branches most open to AI integration (1, 2). The fact that the retina is one of the few nerve tissues in the human body where a nerve tissue can be directly observed using a non-invasive method has placed ophthalmology at the center of artificial intelligence (AI) research (2). Optical coherence tomography (OCT), color fundus imaging and the recently developed OCT angiography (OCTA) provide the high-resolution and standardized large-scale datasets required for training deep learning algorithms (2, 3). This chapter comprehensively examines the current state, technical infrastructure, clinical successes and ethical challenges of AI in the diagnosis, monitoring and treatment processes of retinal diseases considering current literature.

2. Computer Engineering And Software Fundamentals: Algorithmic Architecture

Correlates with changes in computer engineering and software architecture. Modern medical image analysis is fundamentally built upon the principles of machine learning (ML) and its more advanced form DL.

2.1. Programming Languages and Development Environments

In retinal imaging projects, Python stands out as the dominant programming language due to its rich ecosystem and library support (4). In particular, the PyTorch and Ten-

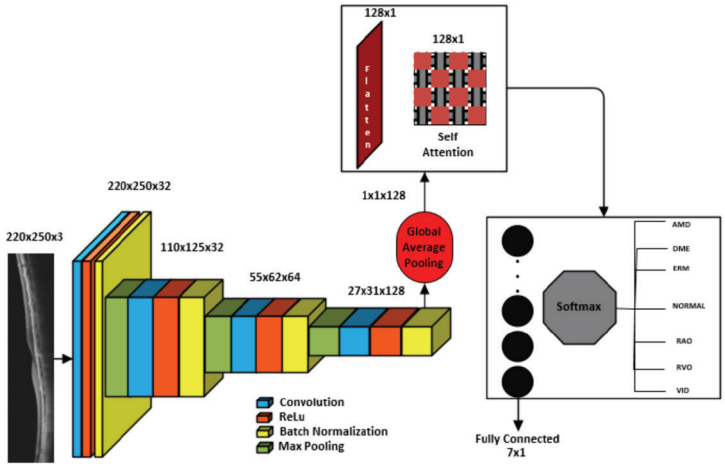


Figure 1. A Deep Learning Model Proposed For The Classification Of Multi-Class OCT İmages.

sorFlow libraries, developed by Google and Meta for the design and training of neural networks, have become industry standards. These libraries dramatically shorten training times by shifting the computational load from traditional central processing units (CPUs) to graphics processing units (GPUs) capable of parallel processing on thousands of cores. For example, processing a 640x640 pixel resolution image for high-resolution retinal vessel segmentation requires approximately 8 GB of video memory (VRAM) on an optimized GPU (5).

2.2. Deep Learning and Convolutional Neural Networks (CNN)

DL is the process of extracting features from data through multilayer artificial neural networks. The most used architecture in retinal image analysis is " Convolutional Neural Networks ". Neural Networks-CNNs (3). CNNs are designed to capture spatial relationships between local pixels, rather than seeing the image as just a stack of pixels. The working principle of a CNN architecture is mathematically based on the convolution operation. Through the convolution operation between the image and a filter, the algorithm learns complex pathological lesions such as (6) (Figure 1).

3. Specific Model Architectures and Performance Dynamics

DL models used in ophthalmology are optimized for specific tasks:

- **ResNet (Residual Networks):** "Gradient vanishing" that occurs as the number of layers increases. gradient problem, shortcuts between layers (skip) It solves by adding (7). ResNet-50 and ResNet-101 variants achieved high accuracy rates of 96.69% in disease classification from OCT sections (8).

- **U-Net:** It is the cornerstone of medical image segmentation. Thanks to its symmetrical expansion and contraction pathway, it can determine the boundaries of pathological fluid cysts or retinal layers with pixel-level precision (7).
- **Vision Transformers (ViT):** This architecture, which has recently developed as an alternative to CNNs, processes the image by dividing it into small patches and using a "self-attention" mechanism. It achieves 95.7% AUC values, especially in diabetic retinopathy (DRP) screenings (9).

4. Diabetic Retinopathy: Automated Diagnosis and Screening with Artificial Intelligence

DDR is the leading cause of blindness in working-age adults worldwide (10). The asymptomatic nature of the disease in the early stages makes regular screening critical, but the number of specialist physicians is insufficient to meet this need (4).

AI algorithms have made rapid progress, from recognizing fundus images to progression analysis for DRP screening. These systems are trained on large datasets consisting of thousands of color fundus photographs and OCT images collected from cloud systems worldwide, enabling the detection of moderate non-proliferative DR, DME and DR requiring treatment with high diagnostic accuracy.

Models used to identify referralable DRP from fundus images analyze fundus images to identify characteristic lesions such as microaneurysms, hemorrhages and exudates and determine the need for referral. Additionally, In addition, it can perform staging according to the internationally valid ICDR (International Clinical Diabetic Retinopathy) (11).

IDx-DR (LumineticsCore), the first FDA-approved autonomous system, can identify DR cases requiring referral with 87.2% sensitivity and 90.7% specificity without the need for intervention by a specialist ophthalmologist (12). Similarly, the EyeArt system is used in large-scale screening programs due to its compatibility with different fundus cameras and its 91.3% sensitivity (12). In similar modeling studies, it was reported that the convolutional neural network (CNN) achieved 90.3% sensitivity and 98.1% specificity and the result was close to the performance of retina specialists (13).

Then autonomous AI systems were evaluated and showed 87.2% sensitivity and 90.7% specificity for mild to more severe DR, these results paved the way for the first FDA approval of an autonomous diagnostic system using AI in the medical field in the world in 2018 (14). Similarly, EyeArt ® (Eyenuk Woodland Inc.) In a multicenter clinical trial, the Hills, CA, USA, achieved 96% sensitivity and 88% specificity for referral DR and soon after received FDA approval. Currently, with this and similar integrated systems, since October 2018, in Germany Mergentheim Diabetes Center EyeArt® offers DRP screening services using its EyeScan System. Each year, approximately 4000 diabetic patients have their eyes easily visualized using a fundus camera that doesn't require pupil dilation. The images are sent to EyeArt and a screening report is quickly forwarded to the relevant center. Similarly, the Eyecheckup® model, developed in Antalya, Turkey, is one of the pioneering systems in

this field. EyeCheckup® provides automatic diagnosis without the need for expert doctor's opinion or the use of eye drops. Because it is easily accessible, screening can be done without the need to go to the hospital for a private examination and early diagnosis can be applied early. In this system, 900 diabetic patients who did not receive a DR diagnosis were evaluated and as a result, the diagnostic rates of the patients were found to be 96.57%, 100% and 100% respectively using (15).

All these autonomous systems analyze fundus images to identify characteristic lesions such as microaneurysms, hemorrhages, exudates and determine the need for referral. By 2030, many of these tools will have been deployed in real-world settings, including primary care hospitals and community health centers, aiming to expand access to DRP detection.

AI is its ability to predict the future course of disease, beyond diagnosing the current condition (16). Accurate staging of DRP and DME is crucial for making appropriate treatment decisions. DR severity is typically classified using the Early Treatment Diabetic Retinopathy Study (ETDRS) scale, ranging from mild to moderate non-proliferative DR to proliferative DR ; DME is assessed by OCT and is generally categorized as centrally involved and non-centrally involved based on macular thickness (CST)(Figure 2). Recent advances in DL have made it possible to directly stage DR in addition to diagnosing it. For example, one study categorized OCT images of DRP according to severity using an AI model and reported a classification accuracy of nearly 95% (17). Complex assessments, including laboratory results and other accompanying systemic conditions, of DR patients with determined severity also significantly determine disease progression.

DL models can predict (13). This capability allows for the efficient use of health resources by enabling the screening intervals to be safely extended for low-risk patients (e.g., 24 months) and for high-risk patients to be followed up more closely. It also provides an opportunity for priority examination of patients who are autonomously triaged and followed up.

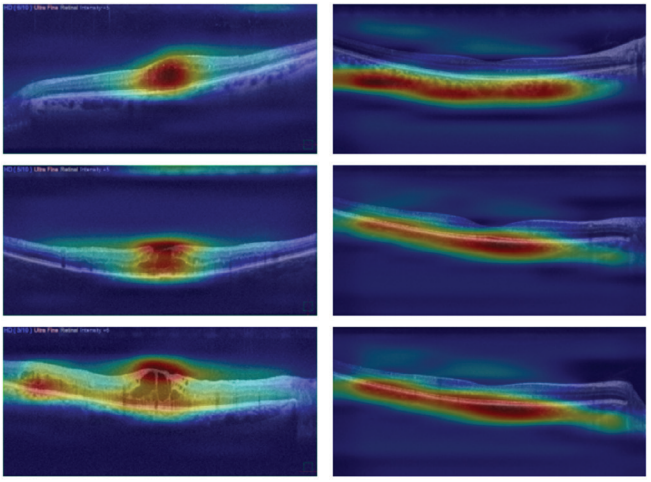


Figure 2. Detection of cystoid macular edema on OCT imaging with AI.

AI shows the clearest results in the diagnosis and monitoring of DRP is undoubtedly OCT. OCT is a rapidly developing examination that has revolutionized retinal evaluation in the last 20 years. It is particularly effective in diagnosing cystoid lesions in DR. OCT is used to identify key biomarkers such as macular thickening, subretinal fluid, macular edema, inner retinal layer irregularity (DRIL), hyperreflective foci and ellipsoid zone disruption, all of which are associated with visual prognosis in DME. In one study, a DL model achieved 88% accuracy in detecting (18). Another system measured loss of photoreceptor integrity to aid in outcome prediction (19).

OCT-based AI systems have significantly higher sensitivity than extensive meta-analyses, DL models based on OCT images show very high accuracy in diagnosing DME (AUROC: 0.985, sensitivity: 95.9%, specificity: 97.9%) (20).

AI models can measure critical parameters in seconds that would take clinicians hours to calculate manually. By segmenting intraretinal and subretinal fluid volumes at the pixel level, they track treatment response at the micron level. Disorganization of inner retinal layers (DRIL), ellipsoid zone, integrity and hyperreflective retinal foci are automatically identified by DL models (21). In cohort studies involving more than 2300 eyes, it has been shown that AI can identify four different morphological phenotypes based on fluid distribution and these phenotypes exhibit different treatment prognoses. A DL system was trained on 73,746 B-scans and obtained area under the curve (AUC) values between 0.94 and 0.97 for detecting and classifying DME (22). However, large-scale scanning using OCT is still impractical due to the high cost of OCT devices and the technical complexity of image acquisition. However, OCT is still the gold standard for planning intravitreal steroid and anti-VEGF injections.

Intravitreal anti-VEGF injections, particularly those administered over extended periods, are the first-line treatment in the management of DRP and DME. Treatment outcomes are highly variable: some patients experience rapid resolution of retinal fluid, while others experience recurrence of edema despite regular injections. AI enables earlier prediction of treatment response and replanning of treatment. "Random forest models" achieved 90.0% sensitivity and 85.1% specificity (AUC 0.923) in identifying patients showing both anatomical and functional improvement after three anti-VEGF injections (23). Intravitreal anti-VEGF administration, the primary treatment method and assess whether injection is appropriate or whether intravitreal corticosteroids are necessary. Ultimately, they can alert the ophthalmologist to unnecessary injections or unpredictable treatment outcomes.

Basic prognosis, AI is also applied to analyze follow-up OCT scans and measure fluid dynamics throughout the treatment process. Demonstrated that volumetric segmentation algorithms can reliably measure fluid volume changes between visits and provide clinicians with consistent metrics to guide retreatment decisions (24).

5. Retinopathy of Prematurity (ROP): Artificial Intelligence in Neonatal Screening

Retinopathy of prematurity (ROP), ROP is a vasoproliferative disorder characterized by retinal vascularization arrest followed by pathological neovascularization in low birth

weight and premature infants. ROP remains one of the leading causes of preventable childhood blindness worldwide (25). The prevalence of ROP in premature infants worldwide is approximately 31.9% and the prevalence of "severe ROP" (requiring treatment) is 7.5%. According to the World Health Organization (WHO), ROP is responsible for 6% to 18% of infantile blindness (26).

The epidemiology of the disease is on an upward trajectory, referred to as the "third epidemic," particularly in middle-income countries, due to the increase in the number of surviving infants with the development of neonatal care. In a large cohort study of 8,503 infants in Turkey between 2021 and 2024, it was reported that approximately 19% of the infants screened were diagnosed with ROP (27). ROP is diagnosed by pediatric ophthalmologists in neonatal intensive care units (NICUs) by screening at-risk infants with indirect ophthalmoscopy after pupillary dilation. According to the International Classification of Retinopathy of Prematurity 3rd Edition (ICROP3) criteria, the severity, location and activity of the disease are standardized based on three basic parameters: Anatomical Location is expressed in zones and determines the location of the disease from the center to the periphery and is the most critical determinant in terms of prognosis. Disease Severity: Classified from stage 1 to stage 5, considering the morphological progression of vascular structures on the retina and vitreous humor. Finally, the progression of ROP is determined by the characterization of Plus disease by vascular activity. Plus disease is characterized by significant vascular dilation (venous dilation) and tortuosity (arterial tortuosity) in at least two quadrants of the retinal vessels in the posterior pole. This is the strongest biomarker indicating that ROP is active and progressive and may require urgent treatment.

The most critical stage in diagnosing ROP is " plus " The detection of " arterial tortuosity and venous dilation" is the result of traditional examination methods showing 17-19% variation among clinicians, leading to diagnostic inconsistencies (28). The AI-based e-ROP system evaluates vessel diameters and tortuosity with an objective score (risk scale of 1-9) by analyzing wide-angle retinal images (25).

Meta-analyses have shown that DL algorithms achieve an average sensitivity of 95.72% and a specificity of 98.15% in ROP detection (28). In studies conducted in Turkey, it was observed that the Random Forest model, a predictive model based on risk factors for ROP, could detect infants with stage II ROP (90% accuracy, 96% specificity) and region III ROP (93% accuracy, 99% specificity) with higher accuracy and specificity. This success allows for critical screenings to be carried out via telemedicine in remote areas where there is no specialist ROP physician and for the timely identification of ROP cases that "need to be referred" (25). Similarly, the i-ROP DL algorithm, trained with 227,326 images under the KIDROP program in India, has proven its clinical reliability by achieving 91.46% sensitivity, 91.22% specificity and 0.970 AUROC success in independent test sets (29). Automated ROP screening application called DeepROP, which includes a CNN classifier (Id-Net) to determine the presence or absence of ROP features and another CNN to grade ROP cases as mild or severe. For plus-disease classification, the Imaging & Informatics ROP (i-ROP) consortium created the i-ROP DL (i-ROP-DL) system, which uses two

CNN strategies, the first for vessel segmentation and the second for classification (30). Both the DeepROP and i-ROP-DL approaches utilize the publicly available ImageNet It has been pre-trained using the database and demonstrates high performance as well as strong agreement with expert opinion. Recent studies have shown the potential use of a deep learning-derived ROP severity score based on the i-ROP-DL classifier for disease screening. Furthermore in studies that analyze fundus images Plus disease diagnosis achieved 84% sensitivity, 43% specificity and 96% negative predictive value (31). OHSU Casey Eye Institute developed the world's first portable system that can scan a 140-degree area in awake infants and process images with real-time AI to generate an automatic "severity score" (32).

In approximately 80% of infants in the screening population, ROP is not detected or is mild enough not to require referral. AI can autonomously filter out this low-risk group, reducing the workload of specialist physicians by 80%. In regions where there is a shortage of specialist physicians, images taken by technicians are analyzed using cloud-based AI and "ROP cases requiring referral" are quickly directed to treatment centers. Especially in areas where access to tertiary healthcare is difficult, the analysis of fundus images that are referred to distant centers enables the detection and referral of ROP.

6. Pathology Analysis and Automated Segmentation from OCT Sections

OCT has become an indispensable part of ophthalmological diagnosis by providing microscopic-level sections of the retina. While a manual OCT assessment can take hours on a data cube containing more than 100 sections, AI reduces this process to seconds.

6.1. Cystoid Detection of Macular Edema and Subretinal Fluids

Retinal edema is a common consequence of many diseases, from diabetes to vascular occlusions. Cystic macular edema (CME) is a painless condition affecting the central retina, often associated with inflammation, venous occlusion, DRP, or cataract surgery. Chronic CME, lasting 6–9 months, causes permanent central vision damage. It may be asymptomatic or present as blurred vision, central field distortion, or changes in color perception. AI systems cystoid Macular edema can measure intraretinal (IRF) and subretinal fluid (SRF) volumes separately. ML, a subset of artificial intelligence, is a branch of AI where computers identify patterns in data without explicit programming, build statistical models from this data and make predictions. It is based on mathematical optimization and statistical inference. The algorithm evaluates the image by layering. The first layers find edges, corners and contrast differences, while the deeper layers recognize abnormalities in retinal layers and the morphology of intraretinal cysts. The integration of ML in ophthalmology has helped in early disease diagnosis by increasing the accuracy of interpreting eye imaging data. The correlation (ICC) between the fluid volume measurements of the models and the manual measurements of expert physicians is quite high, ranging from 0.94 to 0.99. This value has paved the way for integrated services without ignoring ethical problems in medical terms.

U-Net-based models can identify fluid cysts with a high accuracy rate of 96.5% using the Dice coefficient, defined as a high overlap rate (33). AI tracks the change in fluid volume at the micron level, providing the clinician with objective data on the response to anti-VEGF treatment. Platforms such as Altris AI can identify cystoid cysts. It can analyze more than 70 pathological signs, including (34).

6.2. Vitreomacular Interface Diseases: ERM, MH and PVD

Vitreomacular interface pathologies are characterized by mechanical traction and detachment of the inner surface of the retina. The vitreomacular interface (VMA) represents the complex interaction region between the vitreous gel and the inner retinal layers and pathologies in this region are among the main causes of irreversible vision loss and metamorphopsia in the elderly population. Traditionally, the diagnosis of these diseases relies on fundus examination and OCT imaging, which has become the gold standard in the last two decades. However, the volume of data generated because of the intensive integration of OCT devices into clinical practice makes it difficult for specialists to examine each slice (B-scan) with the same precision. At this point, AI and especially DL algorithms offer revolutionary opportunities not only to automate the diagnostic process but also to predict surgical outcomes and create personalized treatment plans (35).

Epiretinal membrane (ERM) is an avascular, fibrocellular tissue that forms on the inner surface of the retina ; it can be idiopathic but may also be associated with conditions such as DRP or retinal vascular occlusions. The presence of ERM creates traction forces in the retina, causing edema in the macula, cystic changes and distortion in the retinal layers. AI models have achieved very high-performance values in ERM detection and classification. In a large-scale study using deep neural networks (DNNs), analyses of 11,061 OCT images proved that the models demonstrated flawless success in detecting particularly large membranes (36). AI models can detect the presence of ERM with 93% accuracy and predict the expected increase in visual acuity (BCVA) after surgery. The data show that detecting small and extrafoveal ERMs is the biggest challenge for AI, but the fact that the AUC value remains at a high level of 0.92 shows that the models are clinically reliable even in early-stage disease. Analyses through saliency maps revealed that the models focus on features such as (36).

Macular hole is characterized by a partial or full-thickness retinal defect in the center of the fovea and, if left untreated, leads to severe central vision loss. MH management involves accurate diagnosis, characterization and prediction of the likelihood of surgical closure. AI can automatically measure the hole diameter and predict the probability of surgical success (anatomical closure) with an accuracy of up to 84.3%. Accessible diagnostic tools such as the Teachable Machine have achieved 91.67% sensitivity, 100% specificity and 0.958 AUC in MH diagnosis. Expert-designed models for full-thickness macular holes (FTMH) have achieved 100% sensitivity and recall, reducing the margin of error to almost zero (37).

Random Forest models, when trained on 33,260 OCT data points, were able to predict the MH shutdown with 92% accuracy. In these models, the Macular Hole Area (MHA) index was identified as the strongest predictor of surgical success (F-score: 0.96). The importance of MHA stems from the fact that it represents a three-dimensional space encom-

passing both the base and minimum diameter and height of the hole; this includes both anteroposterior and tangential aspects.

Posterior vitreous detachment (PVD) is a natural change that occurs in adulthood, where the vitreous gel separates from the retina. Floaters are a common reason for presentation to community primary eye care services. Diagnosis and treatment are important because they can be associated with retinal tears and rhegmatogenous retinal detachment (RRD), which can lead to blindness if left untreated. Despite playing a role in the pathogenesis of many VMA diseases, it is one of the most difficult structures to detect in OCT images. The poor reflectivity and mobile nature of the vitreous cortex create diagnostic uncertainty for both humans and algorithms. PVD detection is vital for vitreoretinal surgical planning. Algorithms developed using the ResNet-50 architecture can classify PVD status from OCT volume scans with 90.7% accuracy.

6.3. Age-Related Macular Degeneration

Age-related macular degeneration (AMD) is the leading cause of irreversible blindness in individuals over 60 in developed countries. This progressive degeneration, occurring in the macula region responsible for central vision, severely reduces the quality of life and places a significant economic burden on healthcare systems. AMD is showing a dramatic increase in parallel with the growing elderly population worldwide. The number of cases, approximately 196 million in 2020, is projected to reach 288 million in 2040, affecting 8.7% of the world's population. Between 1990 and 2021, the absolute number of cases increased by 121%. More than 11% of individuals over 80 are affected by AMD, with women bearing a higher disease burden than men.

Although the disease begins as the "dry type" characterized by drusen and pigment changes in the early stages, approximately 10-15% of cases progress to the "wet type" (exudative), accompanied by neovascularization, leading to sudden vision loss.

DL algorithms developed in recent years are used in OCT and Fundus imaging. Detection, monitoring and progression prediction of dry type (38, 39). In scans performed on color fundus photographs, DL algorithms have been compared to the AREDS (Age-Related Eye Disease Study) rating system, which is considered the "Gold Standard". Studies by Google DeepMind and other research groups show that the algorithms achieve an accuracy rate of (40). The area under the ROC curve (AUC) is the most important measure of success for diagnostic tests. CNN models developed for the detection of dry type AMD (especially Inception-v3 based) consistently produce AUC values in the range of 0.96-0.99 (41). In Geographic Atrophy(GA), the final stage of dry type AMD, precise measurement of the atrophy area is critical for disease severity and treatment monitoring of new FDA-approved drugs (e.g., Syfovre,Izervay).

In age-related macular degeneration, segmentation performed in OCT scans are important in the long term both for ease of follow-up and for the prognosis of the progressing disease. AI models automatically segment specific structures in eye scans in a digital environment and perform intelligible staining. The Dice coefficient measures the accuracy of this staining. In this metric, which measures the success of segmentation, a score close to 1

between 0 and 1 means perfect overlap. U-Net based models obtain Dice coefficient scores between 0.90 and 0.95. In addition, while it takes an average of 10-15 minutes for a specialist to manually calculate the GA area in OCT sections, AI can do this in 1.2 seconds and in a way that is free from human error. The area where AI most clearly surpasses humans is progression and future prediction. While the human eye sees current damage, AI can deduce future damage from mathematical patterns in pixels. By analyzing photoreceptor integrity and sub-RPE (Retinal Pigment Epithelium) reflections in OCT, it was able to predict how much geographic atrophy would expand in a patient after 1 year with a high correlation of 0.85%. Some DL models have reported high AUC/accuracy for short-term progression (42).

Real-world integration examples are increasing. Home-OCT and cloud analytics platforms (e.g., Notal) Vision + NOA), mobile/ handheld camera + AI combinations and some FDA/CE approvals have been reported. The patient-friendly SCANLY Home OCT device captures spectral domain OCT images in a 10x10 degree area centered on the fixation point. A scan typically takes less than a minute per eye. The images are automatically transmitted to Notal via the built-in wireless connection for analysis. The proprietary, AI-based Notal OCT Analyzer (NOA) estimates the segmentation and volume of hyporeflective spaces (HRS), which are key biomarkers in the management of neovascular age-related macular degeneration (nvAMD) in OCT images. Physicians can review the data, define eye-specific reporting criteria including volume thresholds and receive notifications via a HIPAA-compliant web portal (43, 44). However, routine, widespread and validated AMD-focused AI solutions are still limited and most tools are used as research or limited screening tools. In addition, DL models are seen as a potential benefit in high-volume image analysis, reproducibility, scalability for screening and progression prediction (45).

6.4. Choroidal Diseases and Central Serous Chorioretinopathy

The choroid is the most vascular structure, supplying the outer layers of the retina and its diseases typically manifest as fluid accumulation beneath the retina. Central serous Chorioretinopathy (CSCR) is a macular disorder (46). RD manifests as subretinal fluid accumulation in the macular region, while PED causes structural separation of the RPE-Bruch membrane complex. These anatomical features are associated with visual impairments and serve as critical biomarkers for diagnosis and staging.

Choroidal Vascularity Index (CVI) is the ratio of the area of vessels in the choroid to the total area and its manual calculation is extremely laborious. AI-based CVI-Net and Deeplabv3+ models can automatically calculate this index by (47). AI models exhibit near-perfect accuracy of 99.78% in distinguishing SSK patients from healthy individuals (33, 48).

7. Treatment Management: Predicting Anti-VEGF Response

Vascular endothelial growth factor (VEGF) is a key regulator in the proliferation and migration of vascular endothelial cells, as well as in promoting vasodilation and vascu-

lar permeability (49). It plays a critical role in angiogenesis and endothelial proliferation, which in turn is involved in many physiological processes such as wound healing, reproduction and organ development. However, when hypoxia develops in retinal tissue, the tissue produces more VEGF than normal. This leads to neovascularization instead of nerve tissue. Eventually, hyperpermeability and leakage develop. At this point, anti-VEGF agents are applied to reduce leakage and cause regression of abnormal vessels. Anti-VEGF injections are the cornerstone of AMD and DME treatment; they are also effectively used in (21). At this point, AI goes from being just a "diagnostic tool" to becoming a "treatment (16).

With personalized injection scheduling, DL models, particularly NGBoost and Random Forest algorithms, can predict the need for injections in the next year by analyzing the patient's response to OCT images during the first three dose loading phases (MAE ~2.6 injections/year) (50). Thanks to newly developed models, disease recurrence prediction is also successfully performed beyond injection scheduling. Using the DenseNet architecture, it is possible to predict when the retina will accumulate fluid again after injection with a 74.4% AUC success rate (51). These predictions provide the clinician with a data-driven guide on how often to call the patient.

- **Drug Selection:** Anti-VEGF drug selection is critical, especially in DRP and neovascular age-related macular degeneration. According to the Protocol T study, Aflibercept is superior to bevacizumab and ranibizumab in diabetic patients with low visual acuity, but all three drugs have similar efficacy in those with good vision. Researchers have developed models to predict anatomical treatment outcomes using AI and thus help clinicians choose the most appropriate anti-VEGF agent for each patient. In the studies conducted, a GAN-based model, which is one of the generative AI models, simulates the anatomical outcome that will be obtained when using Ranibizumab or Aflibercept and determines which drug will be more effective for the patient (in terms of anatomical response) with 87.8% accuracy (52).

8. Clinical Integration: Global and Local Systems

AI has moved beyond being just an academic subject and is beginning to be integrated into real-world clinics. In addition to the topics mentioned, anterior chamber angle assessment, primary angle closure disease, visual electrophysiology, Fields such as intraocular tumors, eye oncology, cataracts and anterior segment disorders are still evolving. Successful examples around the world are encouraging for other researchers and hospital management units. Moorfields, based in the UK. Eye As a result of the collaboration with (53). Singapore National Eye The Centre (Singapore) SELENA+ system is integrated into the national DRP screening program and has proven its reliability by being tested on 5 different ethnic groups (54). Altris AI IMS, a cloud-based platform, is used by over 500 businesses in 34 countries and reduces workload by 50% by automatically analyzing OCT data.



Figure 3. Analysis Of Fundus Image With Eyecheckup

8.1. Developments in Türkiye and Local Software

- **EyeCheckup® :** This domestic software, developed at Akdeniz University Technopark, automatically screens for DRP, glaucoma and AMD from fundus images. EyeCheckup® has achieved clinical validation successes at international standards by exhibiting sensitivity in the range of 95-98% (15)(Figure 3). The biggest advantage of the system is that it can take on the screening burden in primary healthcare services by providing a detailed report in under 60 seconds.

8.2. Ethical, Legal and Socio-Technical Issues

The unpredictable spread of AI has brought with it ethical and legal debates. The integration of image-based data has provided significant advantages and conveniences such as time savings and accurate decision-making in the fields of disease screening, diagnosis and treatment in ophthalmology (55). Ophthalmology generates a large amount of data with its multi-layered anatomical structures and non-invasive examination methods, providing a robust resource for the application of AI in this field. However, this also brings with it significant ethical issues, particularly privacy. Ophthalmic AI uses data from various sources, including images and electronic health records, to improve diagnostic accuracy, but it also increases the risk of misidentification (56). This data contains sensitive personal information such as anterior segment, iris and retina images, further increasing the risk of privacy breaches during AI processing. Therefore, it is necessary to strengthen research and discussions on the ethical issues of ophthalmic AI and to establish clear guidelines and regulatory frameworks. GDPR (General Data Protection Regulation) Regulation and HIPAA (Health Insurance Portability and Accountability Regulations) such as the GDPR

require the anonymization and secure storage of patients' retinal images. The fact that retinal images are unique to everyone, like a "biometric" identity card, makes the anonymization processes more complex. In our country, the Personal Data Protection Law (KVKK) defines health data as "special categories of data"; it prohibits the processing of this data without the explicit consent of the data subject, except for exceptions such as public health and medical diagnosis. Within this framework, researchers and management units in our country must also pay attention to GDPR-compliant (KVKK) guidelines and avoid privacy violations.

8.3. "Black Box" and Transparency

DL models often cannot explain how they arrive at a decision. This situation carries the risk of the system "making the right decision for the wrong reasons". Although DL models achieve high accuracy, especially in medical image analysis, their decision-making processes are mostly "black box". AI methods do not fully explain the model's true causal logic; they only offer an interpretable window into the diagnostic process (57).

Not knowing which characteristics, the model relies on for diagnosis can lead the system to produce the correct result based on incorrect reasoning (shortcut learning). This creates a risk of mislead learning. This situation is a significant problem in terms of clinical reliability, generalizability and physician-algorithm trust. To mitigate this problem, Explainable AI (XAI) approaches have been developed (57, 58). Gradient-based methods such as Grad-CAM and LayerCAM visualize which regions of the image the model focuses on when making decisions through heat maps. These visualizations help to question whether the model outputs are clinically acceptable and partially compare the AI's decision-making process with the physician's opinion. Thus, the physician can directly assess whether the algorithm is based on pathological areas or clinically insignificant areas. Therefore, AI should be considered a tool that supports, rather than replaces, clinical decision-making in real life.

8.4. Data Neutrality and Privacy

The existing global datasets (EyePACS) are of US and Chinese origin and are limited in terms of ethnic diversity. One study showed that a model trained only with images of light-skinned individuals had an accuracy rate that dropped from 73% to 60% in dark-skinned individuals (due to differences in retinal pigmentation). This situation risks exacerbating health inequality against certain populations instead of addressing it. As a result, it may also bring about problems of ethnic bias (59).

9. Future Vision: Multimodal and Prescriptive Artificial Intelligence

The combination of retina and AI is evolving from the "diagnosis" phase to the "management" phase. Key developments expected from AI systems in the future are as follows:

Generalized Models: The increasing use of comprehensive models that can learn about general retinal morphology, not just a single disease and detect all types of anomalies (including rare diseases). Multimodal Integration: In addition to OCT and fundus images, the patient's genetic data, medical profile and real-time blood sugar/blood pressure data from wearable smart devices are synthesized by AI to create a "personalized treatment plan" and communicate it to the physician. Analytical decision-making: AI not only identifies the disease and prognosis but also provides direct guiding recommendations by determining the most appropriate treatment agent and injection interval. In conclusion, AI is positioned in ophthalmology not as a competitor replacing the physician, but rather as a "super-assistant" that expands the physician's senses and analytical abilities. The responsible, transparent and inclusive development of this technology will be one of the biggest breakthroughs in history in reducing preventable blindness worldwide.

10. References

1. Parmar, U. P. S., Surico, P. L., Singh, R. B., Romano, F., Salati, C., Spadea, L., ... & Group, R. (2024). Artificial Intelligence (AI) for early diagnosis of retinal diseases. *Medicina, 60*(4), 527.
2. Robinson, E., Guidoboni, G., Vercellin, A. V., Zukerman, R., Keller, J., Siesky, B., ... & Clinical Study Group. (2025). Integrating artificial intelligence in ophthalmology: A pilot study of clinical understanding and adoption. *Artificial Intelligence in Vision and Ophthalmology, 1*(1).
3. Wang, J., Wang, Y. X., Zeng, D., Zhu, Z., Li, D., Liu, Y., ... & Jonas, J. B. (2025). Artificial intelligence-enhanced retinal imaging as a biomarker for systemic diseases. *Theranostics, 15*(8), 3223.
4. Padhy, S. K., Takkar, B., Chawla, R., & Kumar, A. (2019). Artificial intelligence in diabetic retinopathy: A natural step to the future. *Indian Journal of Ophthalmology, 67*(7), 1004–1009.
5. Ma, Y., Hao, H., Xie, J., Fu, H., Zhang, J., Yang, J., ... & Zhao, Y. (2020). ROSE: A retinal OCT-angiography vessel segmentation dataset and new model. *IEEE Transactions on Medical Imaging, 40*(3), 928–939.
6. Mateen, M., Zhu, W., Shi, F., Xiang, D., Nie, B., Peng, T., ... & Chen, X. (2025). The role of artificial intelligence in the diagnosis of diabetic retinopathy through retinal lesion features: A narrative review. *Quantitative Imaging in Medicine and Surgery, 15*(5), 4816.
7. Khan, N., & Das, A. (2024). Deep learning models for tumor detection and segmentation in medical image analysis: A comprehensive review of ResNet, U-Net, DETR, and Inception variants. *IP Journal of Diagnostic Pathology and Oncology, 9*(4), 195–206.
8. Gencer, K., Gencer, G., & Cizmeci, İ. H. (2024). Deep learning approaches for retinal image classification: A comparative study of GoogLeNet and ResNet architectures. *International Scientific and Vocational Studies Journal, 8*(2), 123–128.
9. Goh, J. H. L., Ang, E., Srinivasan, S., Lei, X., Loh, J., Quek, T. C., ... & Tan, G. S. (2024). Comparative analysis of vision transformers and conventional convolutional neural networks in detecting referable diabetic retinopathy. *Ophthalmology Science, 4*(6), 100552.
10. Beals, D., Simon, L., Rogers, F., & Pogroszewski, S. (2025). Revolutionizing diabetic retinopathy screening: Integrating AI-based retinal imaging in primary care. *Journal of CME, 14*(1), 2437294.
11. Rajesh, A. E., Davidson, O. Q., Lee, C. S., & Lee, A. Y. (2023). Artificial intelligence and diabetic retinopathy: AI framework, prospective studies, head-to-head validation, and cost-effectiveness. *Diabetes Care, 46*(10), 1728–1739.
12. Fan, Q., Teo, Y. Y., & Saw, S. M. (2011). Application of advanced statistics in ophthalmology. *Investigative Ophthalmology & Visual Science, 52*(9), 6059–6065.
13. Jukić, A., Pavan, J., Kalauz, M., Kopić, A., Markušić, V., & Jukić, T. (2025). Artificial intelligence in diabetic retinopathy and diabetic macular edema: A narrative review. *Bioengineering, 12*(12), 1342.
14. Abràmoff, M. D., Lavin, P. T., Birch, M., Shah, N., & Folk, J. C. (2018). Pivotal trial of an autonomous AI-based diagnostic system for detection of diabetic retinopathy in primary care offices. *NPJ Digital Medicine, 1*(1), 39.
15. Doğan, M. E., Bilgin, A. B., Sari, R., Bulut, M., Akar, Y., & Aydemir, M. (2024). Head to head comparison of diagnostic performance of three non-mydriatic cameras for diabetic retinopathy screening with artificial intelligence. *Eye, 38*(9), 1694–1701.
16. Hashemian, H., Peto, T., Ambrósio Jr, R., Lengyel, I., Kafieh, R., Noori, A. M., ... & Jafari, M. (2024). Application of artificial intelligence in ophthalmology: An updated comprehensive review. *Journal of Ophthalmic & Vision Research, 19*(3), 354.

17. Prahs, P., Radeck, V., Mayer, C., Cvetkov, Y., Cvetkova, N., Helbig, H., ... & Märker, H. (2018). OCT-based deep learning algorithm for the evaluation of treatment indication with anti-vascular endothelial growth factor medications. *Graefe's Archive for Clinical and Experimental Ophthalmology, 256*(1), 91–98.
18. Schmidt-Erfurth, U., Mulyukov, Z., Gerendas, B. S., Reiter, G. S., Lorand, D., Weissgerber, G., ... & Bogunović, H. (2023). Therapeutic response in the HAWK and HARRIER trials using deep learning in retinal fluid volume and compartment analysis. *Eye, 37*(6), 1160–1169.
19. Orlando, J. I., Seeböck, P., Bogunović, H., Klimscha, S., Grechenig, C., Waldstein, S., ... & Schmidt-Erfurth, U. (2019, April). *U2-net: A Bayesian U-net model with epistemic uncertainty feedback for photoreceptor layer segmentation in pathological OCT scans*. Paper presented at the 2019 IEEE 16th International Symposium on Biomedical Imaging (ISBI), Venice, Italy.
20. Lam, C., Wong, Y. L., Tang, Z., Hu, X., Nguyen, T. X., Yang, D., ... & Pang, C. P. (2024). Performance of artificial intelligence in detecting diabetic macular edema from fundus photography and optical coherence tomography images: A systematic review and meta-analysis. *Diabetes Care, 47*(2), 304–319.
21. Al-Harbi, F. A., Alkuwaiti, M. A., Alharbi, M. A., Alessa, A. A., Alhassan, A. A., Aleidan, E. A., ... & Al-Dhibi, H. A. (2025). Diagnostic accuracy of artificial intelligence in predicting anti-VEGF treatment response in diabetic macular edema: A systematic review and meta-analysis. *Journal of Clinical Medicine, 14*(22), 8177.
22. Tang, F., Wang, X., Ran, A. R., Chan, C. K., Ho, M., Yip, W., ... & Cheung, C. Y. (2021). A multitask deep-learning system to classify diabetic macular edema for different optical coherence tomography devices: A multicenter analysis. *Diabetes Care, 44*(9), 2078–2088.
23. Cao, J., You, K., Jin, K., Lou, L., Wang, Y., Chen, M., ... & Ye, J. (2021). Prediction of response to anti-vascular endothelial growth factor treatment in diabetic macular oedema using an optical coherence tomography-based machine learning method. *Acta Ophthalmologica, 99*(1), e19–e27.
24. Rasti, R., Biglari, A., Rezapourian, M., Yang, Z., & Farsiu, S. (2022). RetiFluidNet: A self-adaptive and multi-attention deep convolutional network for retinal OCT fluid segmentation. *IEEE Transactions on Medical Imaging, 42*(5), 1413–1423.
25. He, D., Luo, X., Ying, B., Quinn, G. E., Baumritter, A., Chen, Y., ... & G-ROP Study Group. (2025). Machine learning models for predicting treatment-requiring retinopathy of prematurity in the e-ROP study. *Translational Vision Science & Technology, 14*(8), 14.
26. Blazon, M. N., Rezar-Dreindl, S., Wassermann, L., Neumayer, T., Berger, A., & Stifter, E. (2024). Retinopathy of prematurity: Incidence, risk factors, and treatment outcomes in a tertiary care center. *Journal of Clinical Medicine, 13*(22), 6926.
27. Kizilay, O., Karaca, S., Oto, B. B., & Celik, G. (2025). Incidence of retinopathy of prematurity between 2021 and 2024: Results from a single center. *Beyoglu Eye Journal, 10*(3), 142.
28. Rao, D. P., Savoy, F. M., Tan, J. Z. E., Fung, B. P. E., Bopitiya, C. M., Sivaraman, A., ... & Gopal, L. (2023). Development and validation of an artificial intelligence based screening tool for detection of retinopathy of prematurity in a South Indian population. *Frontiers in Pediatrics, 11*, 1197237.
29. Brown, J. M., Campbell, J. P., Beers, A., Chang, K., Ostmo, S., Chan, R. P., ... & Chiang, M. F. (2018). Automated diagnosis of plus disease in retinopathy of prematurity using deep convolutional neural networks. *JAMA Ophthalmology, 136*(7), 803–810.
30. Jafarizadeh, A., Farabi Maleki, S., Pouya, P., Sobhi, N., Abdollahi, M., Pedrammehr, S., ... & Ghasemi-Falavarjani, K. (2025). Current and future roles of artificial intelligence in retinopathy of prematurity. *Artificial Intelligence Review, 58*, 188.
31. Bai, A., Dai, S., Hung, J., Kirpalani, A., Russell, H., Elder, J., ... & ROP.AI Consortium. (2023). Multicenter validation of deep learning algorithm ROP.AI for the automated diagnosis of plus disease in ROP. *Translational Vision Science & Technology, 12*(8), 13.
32. Campbell, J. P., Nudleman, E., Yang, J., Tan, O., Chan, R. P., Chiang, M. F., ... & Jia, Y. (2017). Handheld optical coherence tomography angiography and ultra–wide-field optical coherence tomography in retinopathy of prematurity. *JAMA Ophthalmology, 135*(9), 977–981.
33. Shojaeinia, M., Hosseini, A., Naderi, M., Baloutch, B., Yekta, M. S., Akbarpour, L., ... & Moghimi, S. (2025). A comprehensive overview: Deep learning approaches to central serous chorioretinopathy diagnosis. *BMC Ophthalmology, 25*(1), 1–22.
34. Dahrouj, M., & Miller, J. B. (Eds.). (2021). *Artificial intelligence (AI) and retinal optical coherence tomography (OCT)*. Philadelphia, PA: Taylor & Francis.
35. Herath, H., Yasakethu, S., Madusanka, N., Yi, M., & Lee, B. I. (2025). Comparative analysis of deep learning architectures for macular hole segmentation in OCT images: A performance evaluation of U-Net variants. *Journal of Imaging, 11*(2), 53.
36. Ayhan, M. S., Neubauer, J., Uzel, M. M., Gelisken, F., & Berens, P. (2024). Interpretable detection of epiretinal membrane from optical coherence tomography with deep neural networks. *Scientific Reports, 14*(1), 8484.
37. Kirik, F., Ozbas, C., Aslanoglu, C. E., Koytak, I. A., & Ozdemir, H. (2024). Efficiency of web-based code-free artificial intelligence platform in classification of vitreomacular interface diseases. *European Eye Research, 4*(1).
38. Borrelli, E., Serafino, S., Ricardi, F., Coletto, A., Neri, G., Olivieri, C., ... & Reibaldi, M. (2024). Deep learning in neovascular age-related macular degeneration. *Medicina, 60*(6), 990.
39. Schmidt-Erfurth, U., Sadeghipour, A., Gerendas, B. S., Waldstein, S. M., & Bogunović, H. (2018). Artificial intelligence in retina. *Progress in Retinal and Eye Research, 67*, 1–29.
40. Burlina, P. M., Joshi, N., Pacheco, K. D., Freund, D. E., Kong, J., & Bressler, N. M. (2018). Use of deep learning for detailed severity characterization and estimation of 5-year risk among patients with age-related macular degeneration. *JAMA Ophthalmology, 136*(12), 1359–1366.

41. Hwang, D. K., Hsu, C. C., Chang, K. J., Chao, D., Sun, C. H., Jheng, Y. C., ... & Lin, C. H. (2019). Artificial intelligence-based decision-making for age-related macular degeneration. *Theranostics, 9*(1), 232.
42. Dow, E. R., Keenan, T. D., Lad, E. M., Lee, A. Y., Lee, C. S., Loewenstein, A., ... & Ophthalmic Imaging Collaborative Community. (2022). From data to deployment: The collaborative community on ophthalmic imaging roadmap for artificial intelligence in age-related macular degeneration. *Ophthalmology, 129*(5), e43–e59.
43. Heier, J. S., Holekamp, N. M., Busquets, M. A., Elman, M. J., Schechet, S. A., Ladd, B. S., ... & Home OCT Study Group. (2025). Pivotal trial validating usability and visualization performance of home OCT in neovascular age-related macular degeneration: Report 1. *Ophthalmology Science, 2025*, 100772.
44. Schneider, E. W., Heier, J. S., Holekamp, N. M., Busquets, M. A., Wagner, L. L., Mukkamala, S. K., ... & Home OCT Study Group. (2025). Pivotal trial toward effectiveness of self-administered OCT in neovascular age-related macular degeneration: Report 2—Artificial intelligence analytics. *Ophthalmology Science, 5*(2), 100662.
45. Le, N. T., Le Truong, T., Pongsachareonnont, P. F., Suwajanakorn, D., Mavichak, A., Itthipanichpong, R., ... & Chaitanuwong, P. (2023). Deep learning approach for age-related macular degeneration detection using retinal images: Efficacy evaluation of different deep learning models. *Egyptian Informatics Journal, 24*(4), 100402.
46. Wang, M., Munch, I. C., Hasler, P. W., Prünte, C., & Larsen, M. (2008). Central serous chorioretinopathy. *Acta Ophthalmologica, 86*(2), 126–145.
47. Sah, R. P., Patel, N. B., Queener, H. M., Narra, P. K., & Ostrin, L. A. (2025). Deep learning-based segmentation of OCT images for choroidal thickness. *Journal of Optometry, 18*(2), 100556.
48. Alhalafi, A. M. (2023). Applications of artificial intelligence in choroid visualization for myopia: A comprehensive scoping review. *Middle East African Journal of Ophthalmology, 30*(4), 189–202.
49. Leung, D. W., Cachianes, G., Kuang, W. J., Goeddel, D. V., & Ferrara, N. (1989). Vascular endothelial growth factor is a secreted angiogenic mitogen. *Science, 246*(4935), 1306–1309.
50. Pfau, M., Sahu, S., Rupnow, R. A., Romond, K., Millet, D., Holz, F. G., ... & Fleckenstein, M. (2021). Probabilistic forecasting of anti-VEGF treatment frequency in neovascular age-related macular degeneration. *Translational Vision Science & Technology, 10*(7), 30.
51. Jang, B., Lee, C. H., Kim, S. J., Yoon, C. K., Park, U. C., Choi, J., ... & Humayun, M. S. (2026). Artificial intelligence based prediction of first recurrence in neovascular age related macular degeneration with validation by 19 experts. *Scientific Reports*.
52. Moon, S., Lee, Y., Hwang, J., Kim, C. G., Kim, J. W., Yoon, W. T., ... & Lee, C. S. (2023). Prediction of anti-vascular endothelial growth factor agent-specific treatment outcomes in neovascular age-related macular degeneration using a generative adversarial network. *Scientific Reports, 13*(1), 5639.
53. Sharma, A., Hussain, R., Learoyd, A. E., Aristidou, A., Soomro, T., Blandford, A., ... & HERMES Study Group. (2025). *Teleophthalmology and artificial intelligence for community optometry referrals: A cluster superiority randomised controlled trial with a linked prospective AI validation—The HERMES study*. Manuscript submitted for publication.
54. Ting, D. S. W., Cheung, C. Y. L., Lim, G., Tan, G. S. W., Quang, N. D., Gan, A., ... & Wong, T. Y. (2017). Development and validation of a deep learning system for diabetic retinopathy and related eye diseases using retinal images from multiethnic populations with diabetes. *JAMA, 318*(22), 2211–2223.
55. Iqbal, S., Khan, T. M., Naveed, K., Naqvi, S. S., & Nawaz, S. J. (2022). Recent trends and advances in fundus image analysis: A review. *Computers in Biology and Medicine, 151*, 106277.
56. Huang, A., Liu, P., Nakada, R., Zhang, L., & Zhang, W. (2023). *Safeguarding data in multimodal AI: A differentially private approach to CLIP training*. arXiv preprint arXiv:2306.08173.
57. Yuan, H., Kang, L., & Li, Y. (2025). *Opening the black box of deep learning: Validating the statistical association between explainable artificial intelligence (XAI) and clinical domain knowledge in fundus image-based glaucoma diagnosis*. arXiv preprint arXiv:2504.04549.
58. Saky, S., & Tshering, U. (2025). *Enhanced SegNet with integrated Grad-CAM for interpretable retinal layer segmentation in OCT images*. arXiv preprint arXiv:2509.07795.
59. Burlina, P., Joshi, N., Paul, W., Pacheco, K. D., & Bressler, N. M. (2021). Addressing artificial intelligence bias in retinal diagnostics. *Translational Vision Science & Technology, 10*(2),

CHAPTER 40

Artificial Intelligence in the Management of Periodontal Diseases: Diagnosis and Treatment

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1. Introduction

The periodontium consists of cementum, periodontal ligament, alveolar bone, and gingiva (1). Periodontal disease is defined as chronic inflammatory diseases that occur in the tissues supporting the teeth as a result of the host's immune-inflammatory response to microorganisms found in dental plaque on the teeth and gums (2). The disease is characterized by clinical attachment loss, radiographic alveolar bone loss, periodontal pocket formation, and gingival bleeding (Figure 1) (3). The classification of periodontal diseases has undergone numerous revisions over time, driven by advances in understanding of disease etiology, pathogenesis, and clinical presentation (4). Most recently, a staging and grading system was established in 2017, in which stages (Stage I–IV) reflect disease severity and extent, while grades (Grade A–C) assess the rate of progression and individual risk factors (5).

The integration of artificial intelligence (AI) into healthcare has fundamentally transformed diagnostic and therapeutic practices across many medical disciplines (6), and dentistry has begun to follow this trend (7). Despite the growing number of AI applications in medicine and dental sciences, adoption in periodontology has been limited (8). Dental professionals and researchers increasingly recognize that artificial intelligence can help improve patient care and make clinical work more efficient. Nevertheless, there is growing recognition that AI can enhance patient care and streamline clinical workflows. In periodontology, AI-driven image analysis may facilitate earlier detection of disease and more effective treatment planning (9), while risk stratification tools enable clinicians to implement more targeted preventive strategies for individual patients (10).

2. The Clinical Significance of Periodontal Disease

The Global Oral Health Status Report published by the World Health Organization in 2022 indicates that approximately %19 of the global adult population is affected by severe periodontal diseases, representing over one billion cases worldwide (12). Although periodontal disease primarily affects the oral cavity, significant evidence suggests it can also impact systemic health through mechanisms involving both innate and adaptive immune response (13). Severe periodontitis has been associated with multiple systemic diseases, including diabetes, cardiovascular disease (14), chronic obstructive pulmonary disease (15), and chronic kidney disease (16). Beyond local tissue damage, periodontitis increases the systemic inflammatory load through the continuous release of pro-inflammatory mediators into the circulation. Elevated systemic inflammatory markers associated with periodontal disease can affect overall health and complicate the management of chronic systemic conditions (17). These findings have prompted growing interest in AI-based tools for the diagnosis and management of periodontal disease, particularly in the context of systemic health. An instrumental see below Figure 1 (11).

2.1. Artificial Intelligence Applications in Periodontal and Peri-Implant Diagnosis

The diagnosis of periodontitis relies primarily on clinical examination and imaging findings, including periodontal pocket assessment, detection of bleeding on probing, and

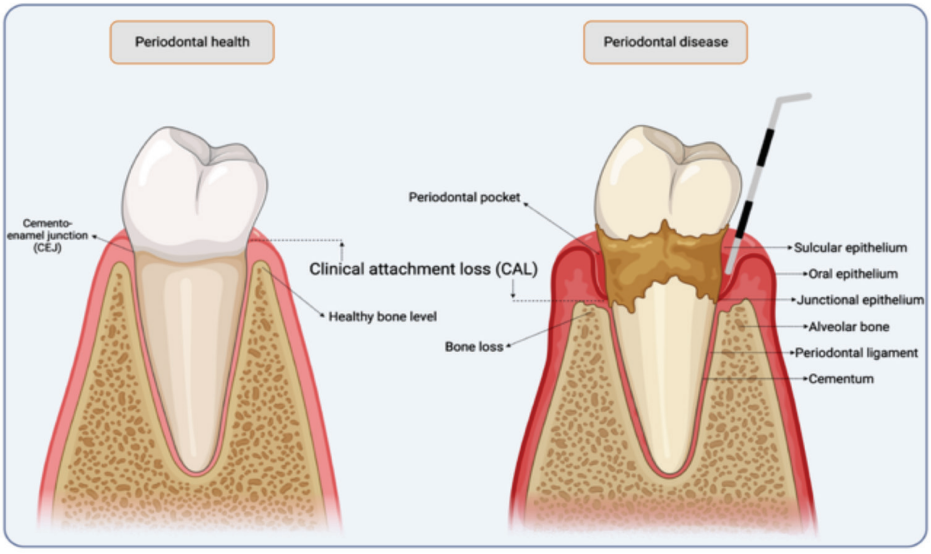


Figure 1. Graphical representation of periodontal health and periodontal disease. Adapted from Lima et al. , Clin Oral Investig, 2024. Original image created on BioRender.com. Licensed under CC BY 4.0. (11)

radiographic evaluation of alveolar bone levels (18). However, periodontal clinical examinations are inherently subjective, and differences in clinical experience and judgment among clinicians may lead to variability in diagnostic accuracy (19). These limitations have driven interest in more objective and reproducible approaches, including AI-assisted diagnostic systems.

Several studies have evaluated the diagnostic performance of AI-based systems in periodontitis classification, with generally promising results. A systematic review demonstrated that AI models achieve diagnostic accuracy comparable to that of general dentists and periodontists, with overall accuracy exceeding 70 %and reaching 80 – 90% in some studies, suggesting that these approaches may help reduce subjectivity and support more consistent disease classification (20). Similarly, a deep learning-based ensemble model trained on panoramic radiographs achieved approximately %89 accuracy in periodontitis staging and showed strong agreement with periodontist assessments, indicating its potential as a clinical decision-support tool (21). A meta-analysis further reported that AI models may diagnose and stage periodontitis from dental radiographs with accuracy generally above %80, with panoramic imaging appearing more suitable for screening and staging, and periapical radiographs demonstrating higher sensitivity for early bone loss detection (22). AI-based approaches have also been explored for the detection and risk prediction of peri-implant diseases. Deep learning models using radiographic and clinical data have shown promising results in detecting peri-implant bone loss and identifying peri-implantitis. These systems may support earlier detection and risk assessment of peri-implant complications in clinical practice (23).

2.2. Evaluation of Clinical Periodontal Parameters Using Artificial Intelligence

In clinical practice, periodontal probing remains the primary screening tool for detecting periodontal disease (24). This method involves placing a calibrated probe below the gingival margin to measure periodontal pocket depth (PPD); pockets of < 3 mm generally indicate periodontal health, while depths of > 3 mm suggest inflammation and possible periodontitis. However, the accuracy and reproducibility of probing can be affected by factors such as clinician experience, probe angulation, and applied force (25,26). These limitations have prompted interest in more objective, technology-driven alternatives. In this context, Tan and colleagues introduced PerioAI, an AI-based digital system that integrates intraoral scans (IOS) with CBCT imaging to assess periodontal status without manual probing. The system automates the assessment of gingiva–bone distance (GBD) by combining soft tissue morphology with three-dimensional alveolar bone segmentation, enabling standardized and reproducible periodontal evaluation. Validation on a large multicenter cohort demonstrated high diagnostic performance with reduced operator dependency (27), suggesting that AI-supported systems may serve as practical adjuncts for standardizing periodontal diagnosis in clinical settings.

2.3. Artificial Intelligence Applications in Radiographic and Three-Dimensional Imaging

In periodontology, radiographic evaluation complements clinical assessment by providing objective information on alveolar bone levels, bone defects, and furcation involvement. This reduces the subjectivity of manual clinical measurements and supports a more reliable assessment of periodontal status (28,29).

In periodontitis diagnosis, periapical and bitewing radiographs are generally preferred for their high resolution and localized diagnostic accuracy. Panoramic radiographs, while not the primary diagnostic tool, are widely used in general dental practice for initial screening and treatment planning due to their broad anatomical coverage and practicality. CBCT offers detailed three-dimensional imaging and is reserved for complex cases where conventional radiographs are insufficient, though its higher cost and radiation dose limit routine use (30).

In recent years, AI has shown promise in interpreting dental radiographs (31). A meta-analysis demonstrated that AI models provide high diagnostic accuracy in the diagnosis and staging of periodontitis across periapical, panoramic, bitewing, and CBCT images, with AI-supported approaches offering more consistent performance compared to manual evaluation (22). These findings suggest that AI may reduce inter-examiner variability and support more standardized radiographic assessment, contributing to its growing role as a clinical decision-support tool in periodontal imaging (31).

2.4. Artificial Intelligence in Periodontal Treatment and Follow-Up

AI applications may reduce clinical workload by streamlining routine tasks, allowing clinicians to focus more on direct patient care, and contribute to more personalized, predictive, and preventive approaches in dentistry (32). In the context of home-based monitoring, AI-assisted tools have shown potential for improving key clinical parameters in patients with periodontitis, including periodontal pocket depth (PPD), clinical attachment level (CAL) and plaque control record (PCR) (33,34). Patient motivation and self-care behaviors are equally important for the long-term sustainability of periodontal health; however, conventional health education approaches have shown limited impact on sustained behavior change (35). AI-supported digital tools may therefore help facilitate treatment compliance and reinforce self-care practices in patients with periodontitis.

A randomized controlled trial demonstrated that an AI-supported dental monitoring application for home use improved key periodontal clinical parameters, including PPD and PCR, in patients with periodontitis, with additional benefits observed in those receiving AI - assisted health counseling (33) . These findings support the potential role of AI - based digital tools in enhancing long-term treatment adherence and follow-up in periodontal care.

2.5. AI-Based Risk Prediction and Personalized Periodontal Care

Untreated periodontitis places a significant economic burden on healthcare systems, especially as the global population continues to age (12). Thus, early identification of patients at greatest risk of periodontitis progression and timely intervention are crucial. Conventional risk assessment models primarily rely on clinical parameters and patient-specific factors such as diabetes and smoking; however, their predictive performance and clinical applicability remain limited (36). AI-based applications can streamline periodontal care by automating routine and time-consuming tasks, thereby reducing the workload of dental professionals. By improving efficiency and optimizing resources, these technologies may help deliver care to a larger population at lower cost. In the long term, artificial intelligence can support more personalized, predictive, preventive, and participatory approaches in dentistry (32). A longitudinal cohort study demonstrated that artificial intelligence–based predictive models can identify patients at higher risk of periodontitis progression using clinical periodontal parameters, supporting individualized risk assessment and more personalized follow-up strategies (37). Machine learning – based predictive models have demonstrated promising performance in identifying periodontal disease risk and supporting personalized treatment planning. However, comparative studies evaluating multiple algorithms indicate that strong results observed during internal validation may not always translate into robust performance in external populations. These findings highlight the importance of large-scale datasets, appropriate feature selection, and rigorous external validation when developing artificial intelligence models for clinical risk prediction. Integrating such approaches into periodontal care may support individualized risk assessment and more tailored treatment strategies (38).

2.6. AI-Assisted Biomarker Analysis in Periodontology

Beyond imaging and clinical parameters, AI-based approaches have shown growing promise in the analysis of biological markers for periodontal diagnosis. Machine learning models can integrate salivary biomarkers, oral microbiome profiles, and immunological indicators to predict a patient's periodontal status non-invasively (39,40). A systematic review and meta-analysis evaluating AI models based on non-invasive biological markers reported that machine learning algorithms trained on salivary, gingival crevicular fluid, and immunological biomarkers demonstrated high accuracy and strong discriminative performance in the diagnosis of periodontitis (41). Longitudinal evidence further suggests that combining clinical parameters with salivary biomarkers — particularly IL-1β — may enhance predictive performance in machine learning models and support the earlier identification of individuals at risk for disease progression (37). These findings indicate that multimodal AI approaches integrating biological and clinical data represent a promising direction for more precise and individualized periodontal care.

2.7. Artificial Intelligence in Dental Education and Training

Artificial intelligence (AI) has increasingly been integrated into educational environments in recent years, offering important opportunities for personalized learning, automated teaching support, and the improvement of assessment systems (42). A recent review highlighted the growing use of AI and immersive technologies in dental education, noting that tools such as ChatGPT, virtual reality/augmented reality (VR/AR) simulations, and virtual patients can support interactive learning, clinical reasoning, and skill development, though they are regarded as complementary to traditional teaching methods rather than replacements (43). In the context of educational assessment, evidence suggests that AI-generated exam questions can increase the efficiency and scope of test development; however, human-designed assessments appear to better capture complex clinical reasoning, pointing to the value of hybrid AI–human approaches in dental education (44). In periodontology specifically, AI tools may support the development of diagnostic competencies by enabling repeated exposure to diverse case scenarios, standardized feedback, and objective performance evaluation areas where traditional clinical training alone may be insufficient.

3. Conclusion

The accumulated evidence suggests that artificial intelligence is progressively reshaping periodontal disease management by enhancing diagnostic precision, standardization, and risk stratification rather than replacing clinical expertise. Across diagnostic applications, AI-based systems demonstrate performance comparable to clinicians, particularly in radiographic interpretation and automated staging. A consistent finding across studies is the reduction of inter-examiner variability, highlighting AI's potential to standardize periodontal assessment in both clinical and educational settings.

In clinical parameter evaluation, digital and multimodal systems integrating intraoral scans and three-dimensional imaging represent a shift from manual, operator-dependent probing toward reproducible and data-driven measurements. These developments suggest a transition from subjective assessment toward quantifiable and automated periodontal evaluation.

Radiographic and three-dimensional imaging applications further indicate that AI systems are particularly effective in detecting advanced bone loss and assisting with disease staging. However, diagnostic performance may vary depending on imaging modality and dataset characteristics, underscoring the importance of validation across heterogeneous populations.

In treatment monitoring and follow-up, AI-supported digital platforms appear to enhance patient engagement and improve selected clinical parameters, supporting a more preventive and participatory care model. Risk prediction models based on longitudinal data demonstrate the feasibility of individualized progression assessment, although generalizability remains dependent on dataset size, feature quality, and robust external validation.

Despite the promising findings reviewed here, several limitations warrant consideration. Most studies included in this review are based on single-center datasets with limited demographic diversity, which may affect generalizability. Furthermore, the heterogeneity of AI methodologies, imaging protocols, and outcome measures across studies complicates direct comparisons. Prospective clinical trials and standardized reporting frameworks are needed to establish the clinical readiness of AI-based tools in periodontal practice.

Collectively, current findings position artificial intelligence as a clinical decision-support tool that strengthens personalization, consistency, and efficiency in periodontal care. Future advancements will likely depend on the integration of multimodal datasets, longitudinal validation, and thoughtful clinical implementation strategies to ensure reliability and ethical use. Alongside these advancements, broader considerations including data privacy, algorithmic transparency, and regulatory oversight will be essential to ensure the responsible and ethical integration of AI into periodontal practice.

4. References

1. Carranza, F. A., & Newman, M. G. (2018). *Newman and Carranza's clinical periodontology* (13th ed.). Elsevier Health Sciences.
2. Loesche, W. J., & Grossman, N. S. (2001). Periodontal disease as a specific, albeit chronic, infection: Diagnosis and treatment. *Clinical Microbiology Reviews*, *14*(4), 727–752. https://doi.org/10.1128/CMR.14.4.727-752.2001
3. Papapanou, P. N., Sanz, M., Buduneli, N., Dietrich, T., Feres, M., Fine, D. H., ... & Tonetti, M. S. (2018). Periodontitis: Consensus report of workgroup 2 of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions. *Journal of Periodontology*, *89*(S1), S173–S182. https://doi.org/10.1002/JPER.17-0721
4. Armitage, G. C. (1999). Development of a classification system for periodontal diseases and conditions. *Annals of Periodontology*, *4*(1), 1–6. https://doi.org/10.1902/annals.1999.4.1.1
5. Tonetti, M. S., Greenwell, H., & Kornman, K. S. (2018). Staging and grading of periodontitis: Framework and proposal of a new classification and case definition. *Journal of Periodontology*, *89*(S1), S159–S172. https://doi.org/10.1002/JPER.18-0006
6. Rajpurkar, P., Chen, E., Banerjee, O., & Topol, E. J. (2022). AI in health and medicine. *Nature Medicine*, *28*(1), 31–38. https://doi.org/10.1038/s41591-021-01614-0
7. Ahmed, N., Abbasi, M. S., Zuberi, F., Qamar, W., Halim, M. S. B., Maqsood, A., & Alam, M. K. (2021). Artificial intelligence techniques: Analysis, application, and outcome in dentistry—A systematic review. *BioMed Research International*, *2021*, 9751564. https://doi.org/10.1155/2021/9751564
8. Revilla-León, M., Gómez-Polo, M., Barmak, A. B., Inam, W., Kan, J. Y. K., Kois, J. C., & Akal, O. (2023). Artificial intelligence models for diagnosing gingivitis and periodontal disease: A systematic review. *The Journal of Prosthetic Dentistry*, *130*(6), 816–824. https://doi.org/10.1016/j.prosdent.2022.01.026
9. Shan, T., Tay, F. R., & Gu, L. (2021). Application of artificial intelligence in dentistry. *Journal of Dental Research*, *100*(3), 232–244. https://doi.org/10.1177/0022034520969115
10. Ghaffari, M., Zhu, Y., & Shrestha, A. (2024). A review of advancements of artificial intelligence in dentistry. *Dentistry Review*, *4*(2), 100081. https://doi.org/10.1016/j.dentre.2024.100081
11. Lima, L., Gaspar, S., Rocha, B. S., Alves, R., & Almeida, M. G. (2024). Current clinical framework on nitric oxide role in periodontal disease and blood pressure. *Clinical Oral Investigations*, *28*(10), 521. https://doi.org/10.1007/s00784-024-05913-x
12. Jain, N., Dutt, U., Radenkov, I., & Jain, S. (2024). WHO's global oral health status report 2022: Actions, discussion and implementation. *Oral Diseases*, *30*(2), 73–79. https://doi.org/10.1111/odi.14516
13. Huang, D., Wang, Y.-Y., Li, B.-H., Wu, L., Xie, W.-Z., Zhou, X., & Ma, B. (2024). Association between periodontal disease and systemic diseases: A cross-sectional analysis of current evidence. *Military Medical Research*, *11*(1), 74. https://doi.org/10.1186/s40779-024-00583-y
14. Sanz, M., Marco Del Castillo, A., Jepsen, S., Gonzalez-Juanatey, J. R., D'Aiuto, F., Bouchard, P., ... & Wimmer, G. (2020). Periodontitis and cardiovascular diseases: Consensus report. *Journal of Clinical Periodontology*, *47*(3), 268–288. https://doi.org/10.1111/jcpe.13189
15. Linden, G. J., & Herzberg, M. C. (2013). Periodontitis and systemic diseases: A record of discussions of working group 4 of the Joint EFP/AAP Workshop on Periodontitis and Systemic Diseases. *Journal of Periodontology*, *84*(4S), S20–S23. https://doi.org/10.1902/jop.2013.1340020

16. Zhang, J., Jiang, H., Sun, M., & Chen, J. (2017). Association between periodontal disease and mortality in people with CKD: A meta-analysis of cohort studies. *BMC Nephrology*, *18*(1), 269. https://doi.org/10.1186/s12882-017-0680-9
17. Tonetti, M. S., & Van Dyke, T. E. (2013). Periodontitis and atherosclerotic cardiovascular disease: Consensus report of the Joint EFP/AAP Workshop on Periodontitis and Systemic Diseases. *Journal of Periodontology*, *84*(4S), S24–S29. https://doi.org/10.1902/jop.2013.1340019
18. Preshaw, P. M. (2015). Detection and diagnosis of periodontal conditions amenable to prevention. *BMC Oral Health*, *15*(S1), S5. https://doi.org/10.1186/1472-6831-15-S1-S5
19. Renatus, A. (2016). Evaluation of an electronic periodontal probe versus a manual probe. *Journal of Clinical and Diagnostic Research*. https://doi.org/10.7860/JCDR/2016/22603.8886
20. Zhang, J., Deng, S., Zou, T., Jin, Z., & Jiang, S. (2025). Artificial intelligence models for periodontitis classification: A systematic review. *Journal of Dentistry*, *156*, 105690. https://doi.org/10.1016/j.jdent.2025.105690
21. Xue, T., Chen, L., & Sun, Q. (2024). Deep learning method to automatically diagnose periodontal bone loss and periodontitis stage in dental panoramic radiograph. *Journal of Dentistry*, *150*, 105373. https://doi.org/10.1016/j.jdent.2024.105373
22. Lee, J.-E., Choi, E., & Park, J.-B. (2025). Radiographic diagnosis of periodontitis using artificial intelligence: A meta-analysis comparing binary and staging classifications across imaging modalities. *BMC Oral Health*, *25*(1), 1921. https://doi.org/10.1186/s12903-025-07171-z
23. Roy, R., Chopra, A., Karmakar, S., & Bhat, S. G. (2025). Applications of artificial intelligence (AI) for diagnosis of periodontal/peri-implant diseases: A narrative review. *Journal of Oral Rehabilitation*, *52*(8), 1193–1219. https://doi.org/10.1111/joor.14045
24. Pihlstrom, B. L., Michalowicz, B. S., & Johnson, N. W. (2005). Periodontal diseases. *The Lancet*, *366*(9499), 1809–1820. https://doi.org/10.1016/S0140-6736(05)67728-8
25. Grossi, S. G., Dunford, R. G., Ho, A., Koch, G., Machtei, E. E., & Genco, R. J. (1996). Sources of error for periodontal probing measurements. *Journal of Periodontal Research*, *31*(5), 330–336. https://doi.org/10.1111/j.1600-0765.1996.tb00500.x
26. Lee, J.-S., Jeon, Y.-S., Strauss, F.-J., Jung, H.-I., & Gruber, R. (2020). Digital scanning is more accurate than using a periodontal probe to measure the keratinized tissue width. *Scientific Reports*, *10*(1), 3665. https://doi.org/10.1038/s41598-020-60291-0
27. Tan, M., Cui, Z., Li, Y., Fang, Y., Mei, L., Zhao, Y., ... & Shen, D. (2025). PerioAI: A digital system for periodontal disease diagnosis from an intra-oral scan and cone-beam CT image. *Cell Reports Medicine*, *6*(6), 102186. https://doi.org/10.1016/j.xcrm.2025.102186
28. Corbet, E., Ho, D., & Lai, S. (2009). Radiographs in periodontal disease diagnosis and management. *Australian Dental Journal*, *54*(s1), S11–S25. https://doi.org/10.1111/j.1834-7819.2009.01141.x
29. Scarfe, W. C., Azevedo, B., Pinheiro, L. R., Priaminiarti, M., & Sales, M. A. O. (2017). The emerging role of maxillofacial radiology in the diagnosis and management of patients with complex periodontitis. *Periodontology 2000*, *74*(1), 116–139. https://doi.org/10.1111/prd.12193
30. Jacobs, R., Fontenele, R. C., Lahoud, P., Shujaat, S., & Bornstein, M. M. (2024). Radiographic diagnosis of periodontal diseases – Current evidence versus innovations. *Periodontology 2000*, *95*(1), 51–69. https://doi.org/10.1111/prd.12580
31. Khalifa, M., & Albadawy, M. (2024). AI in diagnostic imaging: Revolutionising accuracy and efficiency. *Computer Methods and Programs in Biomedicine Update*, *5*, 100146. https://doi.org/10.1016/j.cmpbup.2024.100146
32. Schwendicke, F., Samek, W., & Krois, J. (2020). Artificial intelligence in dentistry: Chances and challenges. *Journal of Dental Research*, *99*(7), 769–774. https://doi.org/10.1177/0022034520915714
33. Shen, K., Huang, C., Lin, Y., Du, J., Chen, F., Kabasawa, Y., ... & Huang, H. (2022). Effects of artificial intelligence-assisted dental monitoring intervention in patients with periodontitis: A randomized controlled trial. *Journal of Clinical Periodontology*, *49*(10), 988–998. https://doi.org/10.1111/jcpe.13675
34. You, F., Lin, P., Huang, C., Wu, J., Kabasawa, Y., Chen, C., & Huang, H. (2025). Artificial intelligence with counseling on the treatment outcomes and quality of life in periodontitis patients. *Journal of Periodontology*, *96*(7), 781–793. https://doi.org/10.1002/JPER.24-0082
35. Ntoumanis, N., Ng, J. Y. Y., Prestwich, A., Quested, E., Hancox, J. E., Thøgersen-Ntoumani, C., ... & Williams, G. C. (2021). A meta-analysis of self-determination theory-informed intervention studies in the health domain: Effects on motivation, health behavior, physical, and psychological health. *Health Psychology Review*, *15*(2), 214–244. https://doi.org/10.1080/17437199.2020.1718529
36. Du, M., Bo, T., Kapellas, K., & Peres, M. A. (2018). Prediction models for the incidence and progression of periodontitis: A systematic review. *Journal of Clinical Periodontology*, *45*(12), 1408–1420. https://doi.org/10.1111/jcpe.13037
37. Furquim, C. P., Caruth, L., Chandrasekaran, G., Cucchiara, A., Kallan, M. J., Martin, L., ... & Teles, F. (2025). Developing predictive models for periodontitis progression using artificial intelligence: A longitudinal cohort study. *Journal of Clinical Periodontology*, *52*(10), 1478–1490. https://doi.org/10.1111/jcpe.14194
38. Bashir, N. Z., Rahman, Z., & Chen, S. L. (2022). Systematic comparison of machine learning algorithms to develop and validate predictive models for periodontitis. *Journal of Clinical Periodontology*, *49*(10), 958–969. https://doi.org/10.1111/jcpe.13692
39. Kim, E.-H., Kim, S., Kim, H.-J., Jeong, H., Lee, J., Jang, J., ... & Lee, S. (2020). Prediction of chronic periodontitis severity using machine learning models based on salivary bacterial copy number. *Frontiers in Cellular and Infection Microbiology*, *10*, 571515. https://doi.org/10.3389/fcimb.2020.571515

40. Xiang, J., Huang, W., He, Y., Li, Y., Wang, Y., & Chen, R. (2022). Construction of artificial neural network diagnostic model and analysis of immune infiltration for periodontitis. *Frontiers in Genetics*, *13*, 1041524. https://doi.org/10.3389/fgene.2022.1041524
41. Ardila, C. M., Vivares-Builes, A. M., & Yadalam, P. K. (2025). Artificial intelligence models for diagnosis of periodontitis using non-invasive biological markers: A systematic review and meta-analysis of patient-based studies. *Medical Sciences*, *13*(3), 159. https://doi.org/10.3390/medsci13030159
42. Erduran, S. (2023). AI is transforming how science is done. Science education must reflect this change. *Science*, *382*(6677), eadm9788. https://doi.org/10.1126/science.adm9788
43. Huang, S., Qu, Y., Sun, Y., Chen, S., & Gu, L. (2025). Application and development of artificial intelligence and immersive technologies in dental education: A scoping review. *BMC Medical Education*, *26*(1), 89. https://doi.org/10.1186/s12909-025-08420-z
44. Ma, X., Pan, W., & Yu, X. (2025). Evaluating AI-generated examination papers in periodontology: A comparative study with human-designed counterparts. *BMC Medical Education*, *25*(1), 1099. https://doi.org/10.1186/s12909-025-07706-6

CHAPTER 41

Artificial Intelligence in Physiotherapy and Rehabilitation: Clinical Applications and Future Perspectives

Assoc. Prof. Dr. Cigdem Cekmece

I. Introduction

Physiotherapy and rehabilitation is health disciplines aimed at maximizing lifelong mobility, function, and quality of life. Physiotherapy encompasses the assessment and evidence-based treatment of disorders related to the musculoskeletal, neurological, cardiopulmonary, and pediatric systems. In a broader perspective, rehabilitation is a multidisciplinary process aimed at restoring functional independence, increasing participation in social life, and improving overall well-being after illness, injury, or disability. Additionally, rehabilitation represents a comprehensive health approach designed to optimize the functional performance of individuals with disabilities and to increase their engagement in activities of daily living, thereby enhancing quality of life (1).

The increasing elderly population, higher survival rates following accidents and injuries due to improved medical care, and the prevalence of non-communicable chronic diseases have led to a growing demand for rehabilitation. The World Health Organization considers rehabilitation an integral component of universal health coverage and identifies its integration into health systems, particularly in low- and middle-income countries, as a strategic priority (2).

Physiotherapy and Rehabilitation practices require individualized assessment, regular monitoring, and interventions that are dynamically adapted according to the patient's clinical progress. The clinical decision-making process involves the integration of objective measurements, the therapist's clinical expertise, and patient-reported outcomes. In this respect, rehabilitation represents a complex and multidimensional field of healthcare.

Contemporary rehabilitation practices produce extensive datasets, including biomechanical measurements, movement analyses, physiological indicators, and functional per-

formance metrics. However, the systematic and efficient analysis of these data in clinical settings often remains limited. The increasing diversity of patients, the burden of chronic diseases, and the demand for personalized care have further highlighted the need for data-driven and innovative approaches in rehabilitation. Despite the World Health Organization defining rehabilitation as a global health priority, a significant proportion of individuals who could benefit from these services still lack Access (3) This situation necessitates the strengthening of existing clinical capacity and the development of more efficient and scalable solutions.

In this context, artificial intelligence emerges as an innovative tool with the potential to both enhance the clinical effectiveness of rehabilitation services and broaden their accessibility.

2. Artificial Intelligence

Artificial intelligence (AI) refers to computational systems capable of processing large volumes of data through models inspired by the neural network structure of the human brain. Moreover, AI refers to computer systems capable of imitating human cognitive processes and learning from data to make decisions, recognize patterns, and produce predictions (4).

AI technologies, encompassing subfields such as machine learning, deep learning, and natural language processing, can analyze complex relationships within large datasets and generate insights that support clinical decision-making (5). Machine learning methods, by analyzing relationships between data points, can predict specific outcomes and assist in clinical assessment processes. Advanced algorithms, particularly those used in the analysis of imaging, motion, and biosignal data, contribute to more objective and consistent results. Therefore, AI is regarded as a crucial tool for supporting clinical decision-making in healthcare domains that require intensive data generation and long-term patient monitoring.

Applications of AI in healthcare span a wide range, including diagnostic support systems, prognostic modeling, medical image analysis, and personalized treatment planning (6). AI technologies are increasingly adopted across various sectors due to their capacity to perform many tasks traditionally conducted by humans more rapidly, efficiently, and cost-effectively. This transformation is also clearly felt in healthcare. Through superior performance in data processing and decision-support mechanisms, AI is becoming increasingly central to the planning, delivery, and management of healthcare services. Accordingly, AI has become an integral component of the contemporary healthcare ecosystem, playing a critical role in restructuring service delivery models.

2.1. Artificial Intelligence in Healthcare

Technological advancements are significant determinants in improving quality of life and, in particular, are driving structural transformations in the delivery of healthcare services. Emerging technologies and methods in healthcare not only enhance the efficiency of di-

agnostic and therapeutic processes but also reshape patient–health professional interactions, strengthen preventive care practices, and facilitate more systematic organizational management of healthcare institutions.

Artificial intelligence (AI) technologies are increasingly being applied in healthcare to enable early detection of diseases, improve diagnostic accuracy, and support clinical decision-making with objective data. In particular, machine learning and deep learning algorithms provide high precision in the analysis of medical imaging data, contributing to the early identification of pathologies. Furthermore, through big data analytics, information obtained from electronic health records, biometric measurements, and remote monitoring systems can be integrated to develop predictive models and create personalized treatment plans. AI-based decision support systems also allow clinicians to make more consistent and evidence-based decisions in diagnostic and therapeutic processes. In this context, AI is positioned not merely as a tool supporting current clinical practice but as a fundamental component in the digital transformation of healthcare services (7).

2.2. Clinical Applications of Artificial Intelligence in Rehabilitation

Physiotherapy and rehabilitation are interventions aimed at restoring function and muscle strength, with the ultimate goal of enabling individuals to perform daily activities independently and effectively. Rehabilitation interventions can be delivered in hospital-based or community-based settings and may be guided by a clinician or conducted as self-managed programs. Although physiotherapy and rehabilitation services are accessible in many countries, their utilization remains insufficient on a global scale, and patient adherence to programs is often low. This situation highlights the need for innovative approaches that enhance the effectiveness of these services. In this context, artificial intelligence–based applications offer significant opportunities to both optimize patient care processes and expand the accessibility of rehabilitation services.

The use of artificial intelligence (AI) is reported to be rapidly increasing not only in healthcare services but also in the field of rehabilitation (8). Rehabilitation provides a suitable ground for AI applications due to its multidimensional clinical assessment processes, long-term patient monitoring, and need for individualized interventions. In particular, AI-based approaches are expected to support clinical decision-making and reduce the workload of physiotherapists and other healthcare professionals in processes such as analyzing functional performance data, predicting recovery progress, and personalizing treatment plans. In this context, AI in rehabilitation allows physiotherapists to conduct more comprehensive assessments of patients, identify their current performance, and receive support regarding prognosis, thereby enhancing the quality of patient care (9). Moreover, studies indicate that AI has various applications in physiotherapy and rehabilitation, including identifying patient problems, generating solutions, and planning individualized treatment protocols (10).

With the acceleration of technological developments, the impact of artificial intelligence (AI), robotic systems, and smart technologies on the workforce and service sectors is steadily increasing. In a study by Brougham and Haar, it was reported that futurists pre-

dict approximately one-third of current work could be performed by smart technologies, AI, robotic applications, and algorithms (11). Healthcare services are also significantly affected by this transformation, and the integration of AI-based applications into clinical processes is becoming increasingly widespread. In their study on technological transformation and AI applications in rehabilitation services, Akalın and Demirbaş emphasized that the use of AI offers various temporal, spatial, and economic advantages in rehabilitation processes. Furthermore, the study highlighted that AI-based applications enhance the organizational efficiency of healthcare services, improve the quality of service delivery, and support the efficient use of resources (12).

Neurological diseases are among the leading causes of mortality and long-term disability worldwide, imposing a significant burden on global healthcare systems. Stroke, in particular, ranks high among conditions that result in death and disability, profoundly affecting individuals' functional independence. Therefore, physical rehabilitation is recognized as a fundamental therapeutic approach for individuals with neurological conditions, aiming to enhance functional capacity, reduce disability, and improve quality of life. However, traditional rehabilitation services face several challenges, including high costs, substantial human resource requirements, and limited access to specialized healthcare professionals. At this point, AI-based systems offer innovative solutions that can help overcome these challenges by making clinical processes more accessible, personalized, and data-driven (13).

AI applications are employed in rehabilitation through various methods and algorithms. Among these approaches, machine learning and deep learning techniques play a particularly important role in analyzing clinical data, assessing patients' functional status, and predicting treatment outcomes. In this context, one of the most widely used approaches is artificial neural networks.

3. Artificial Neural Networks

Artificial neural networks (ANNs) are adaptive computational models inspired by the brain's information-processing mechanisms and are widely used for identifying patterns and analyzing complex datasets (14). These networks are based on systems composed of interconnected nodes arranged in layers, mimicking the neuronal structure of the human brain. ANNs are considered a form of machine learning known as deep learning. This architecture allows computers to create adaptive models that can update themselves based on feedback from errors and improve performance over time.

Neural networks can function even when the recorded data is incomplete. They can develop models based on existing examples to make predictions about previously unseen situations. In addition, they are capable of classification, pattern recognition, and self-organizing behaviors. These characteristics make artificial neural networks a powerful and preferred method, especially for analyzing complex and variable clinical data (14).

The theoretical foundation of artificial neural network (ANN) architecture is inspired by the structural and functional characteristics of the human brain. Neurons, the cells in

the human brain, communicate with each other through dense and complex connections, exchanging electrical signals to process information. This biological network forms the basis of cognitive processes such as learning, decision-making, and problem-solving. Accordingly, artificial neural networks are developed as computational models designed to emulate these information-processing mechanisms of the human brain.

The integration of artificial neural networks into rehabilitation applications has significantly facilitated the analysis and resolution of many clinical problems that were previously difficult to predict or complex in nature. These systems enable more efficient, systematic, and cost-effective planning of assessment and intervention processes in clinical settings. Consequently, they contribute both to optimizing resource utilization in healthcare and to enhancing the sustainability of rehabilitation services (12).

3.1. AI-Based Intelligent Rehabilitation Techniques

Rapid advancements in artificial intelligence (AI) technologies have enabled a diversification of methods and applications used in rehabilitation. In line with these developments, various AI-based intelligent systems have been introduced into physiotherapy and rehabilitation processes, becoming integral components of clinical practice.

Recent studies indicate that AI-supported rehabilitation technologies are increasingly being implemented in clinical settings and possess significant potential to enhance the effectiveness of rehabilitation interventions.

In physiotherapy and rehabilitation applications, AI systems can be integrated through both virtual (software-based) and robotic (hardware-based) platforms to facilitate patient training and to objectively monitor the rehabilitation process (15).

AI-based intelligent rehabilitation systems are considered integrated approaches that enhance rather than replace traditional methods, offering data-driven and sustainable solutions. These application techniques provide advantages such as personalized treatment, objective measurement, cost-effectiveness, and accessibility. Rather than substituting the therapist, these systems function as supportive tools that strengthen clinical decision-making processes.

One of the main strengths of AI-supported rehabilitation technologies lies in their ability to be tailored to an individual's functional level and skill capacity. Furthermore, parameters such as session duration, intensity, difficulty, and application speed can be flexibly adjusted for both the therapist and the patient. Reliable and valid sensing systems allow the collection of objective and measurable data. Additionally, real-time feedback contributes to the instantaneous evaluation of performance. Through simulations that mimic real-life activities, AI-based systems facilitate activity-based training and help reduce both physical and mental fatigue experienced by patients and therapists during the rehabilitation process (16).

Although AI technologies offer significant advantages in healthcare, their use also raises certain risks and ethical concerns. In particular, algorithmic errors or inaccurate predictions in AI systems may adversely affect clinical decision-making, posing potential

risks to patient safety. Additionally, the collection and analysis of large volumes of health data in AI applications raises ethical and legal issues related to patient privacy and data security. Algorithmic bias, lack of transparency in decision-making, and uncertainties regarding accountability are also key topics of concern in the use of AI in healthcare. Therefore, ensuring that AI-based systems are used safely and effectively in healthcare requires adherence to ethical principles, robust data security measures, and the development of regulatory frameworks (17).

Artificial intelligence encompasses a wide range of existing and emerging applications in rehabilitation, including the development of personalized treatment plans, real-time feedback systems, the expansion of tele-rehabilitation platforms, the use of wearable technologies, AI-assisted robotic applications, virtual reality-based therapeutic environments, and brain-computer interfaces. These technologies hold significant potential for optimizing treatment processes for individuals with physical impairments. In addition to enabling increased patient engagement and predicting treatment outcomes based on patient-specific data, AI-integrated robotic systems and advanced motion analysis tools facilitate remote and automated therapeutic interventions, thereby contributing to the transformation of traditional rehabilitation approaches (18-20).

The literature indicates that AI-based smart rehabilitation applications can be classified into different categories, with seven main areas of application identified (16). These technologies support more efficient, measurable, and individualized rehabilitation processes, securing a prominent role in modern physiotherapy practice.

- Robot-assisted therapy
- Brain–computer interfaces
- Orthotic and prosthetic technologies
- Tele-rehabilitation applications
- Mobile application-based technologies
- Virtual reality-based applications
- Video game–based therapy systems

3.2. Robot-Assisted Therapy

Robot-assisted therapy is an approach in rehabilitation that uses robotic devices, artificial intelligence, and sensor systems to support patient movements, deliver repetitive exercises with precision, and analyze treatment data. Research has shown that robot-assisted therapy contributes significantly to the recovery of motor functions, particularly after stroke, spinal cord injury, traumatic brain injury, and orthopedic injuries. These systems can adjust exercise intensity according to the patient, measure movement performance, and provide therapists with objective data (21).

With technological advancements, robotic devices have increasingly been incorporated into rehabilitation alongside traditional therapies. This approach allows patients to perform exercises for extended periods at consistent intensity, enhancing the effectiveness of rehabilitation programs (22).

Motor learning is an important concept in rehabilitation. Frequent repetition of an activity or exercise contributes to motor learning. In robot-assisted therapies, task-oriented movements can be repeated with visual and auditory feedback. Robot-assisted therapies are considered a promising approach in physiotherapy and rehabilitation because they move away from the monotonous flow of routine conventional exercises, capture the patient's interest, and enhance motivation (23).

Robotic-assisted rehabilitation technologies are among the innovative tools that promote neuroplasticity, the nervous system's capacity for reorganization. These systems provide patients with systematic, controlled, and high-repetition movement exercises, supporting motor learning processes. Particularly, task-oriented and high-intensity exercises contribute to the reorganization of neural networks, enabling the gradual recovery of lost motor skills. Therefore, robotic rehabilitation applications play a significant role in supporting functional recovery after neurological injuries. A study by Poli et al. demonstrated that post-stroke rehabilitation programs incorporating task-oriented exercises enriched with multimodal stimuli and repetitive practice support neuroplasticity and positively influence the recovery process (24).

Robot-assisted rehabilitation systems are increasingly used in clinical practice to support the recovery of motor functions in the treatment of neurological and orthopedic conditions. Different types of rehabilitation robots are employed for the treatment of the upper and lower extremities. Robotic systems used for lower extremity rehabilitation primarily contribute to gait training, balance, and postural control, while upper extremity rehabilitation robots play a crucial role in relearning normal movement patterns, improving muscle coordination, and enhancing functional use. Robots designed for the upper extremity are mostly intended for proximal segments (shoulder or elbow), whereas devices suitable for wrist and finger movements are produced less frequently.

Robot-assisted therapy systems include various technologies such as gait robots, arm rehabilitation robots, hand robots, exoskeletons, and soft robotic devices. These systems can be integrated with sensors, artificial intelligence, and virtual reality to provide more intensive, measurable, and individualized rehabilitation. Although rehabilitation robots are classified in various ways in the literature, the most common approach is based on their functions and mechanical structures. Most studies categorize rehabilitation robots into two main mechanical types: exoskeleton robots and end-effector robots. Additionally, based on their purpose, robots can also be classified as therapy robots or assistive robots (25).

3.2.1. Exoskeleton Rehabilitation Robots

Exoskeleton robots are mechanical devices worn externally on a patient's limbs that mimic the anatomical movements of joints. In these systems, the axes of the robot's joints are aligned with the human joints, allowing direct control of movements in joints such as the hip, knee, or elbow. This alignment enables movements to be guided in a more physiological manner. Such robots are particularly commonly used in gait training, balance exercises, and postural control interventions.

Table 1. Examples of rehabilitation robots, their types, and main clinical applications

Robotic System	Target Limb	Robot Type	Main Application
Lokomat	Lower extremity	Exoskeleton	Gait training, improving walking patterns
HAL (Hybrid Assistive Limb)	Lower extremity	Exoskeleton	Walking and mobility assistance
ReWalk	Lower extremity	Exoskeleton	Walking support for spinal cord injury patients
EksoGT	Lower extremity	Exoskeleton	Gait rehabilitation in neurological disorders
G-EO System	Lower extremity	End-effector	Walking and stair-climbing training
Gait Trainer GT I	Lower extremity	End-effector	Repetition of gait patterns
Armeo Power / Armeo Spring	Upper extremity	Exoskeleton-based	Arm movement and functional task training
MIT-Manus (InMotion Robot)	Upper extremity	End-effector	Rehabilitation of arm and hand motor control
ReoGo	Upper extremity	End-effector	Improvement of shoulder and arm movements
Amadeo	Hand and fingers	End-effector	Hand and finger rehabilitation

3.2.2. End-Effector Rehabilitation Robots

In these systems, the robot is not attached along the patient's joints; instead, movement is facilitated through a single platform or pedal that comes into contact with the foot or hand. The robot indirectly guides the movement of the entire limb by moving the distal segment. These systems are commonly used for repeating gait patterns and implementing task-oriented exercises.

The main types of robotic systems used in rehabilitation, along with their types and primary applications, are summarized in Table 1.

With the development of robotic rehabilitation systems, technologies have begun to emerge that go beyond merely providing mechanical support and are capable of directly interacting with the nervous system. One such technology is brain–computer interfaces, which enable the interaction of brain signals with computer systems.

3.3. Brain–Computer Interfaces

A brain–computer interface (BCI) is a technology that detects neural activity in the human brain and directly transmits it as commands to a computer or electronic device. These systems aim to enable device control through thought, without relying on muscles or the nervous system, and represent an important research area at the intersection of medicine, neuroscience, artificial intelligence, and engineering. BCIs began to gain prominence in the literature in the 1990s and were initially developed for individuals with functional brains but impaired motor abilities, primarily for pa-

tients with amyotrophic lateral sclerosis (ALS) and others who have lost motor function (26).

Brain–computer interfaces encompass applications such as software tools that allow users to communicate through thought, robotic arms for performing feeding and daily activities, and mobility systems including wheelchairs. Non-invasive measurement techniques such as EEG and fNIRS are widely used in these technologies, enabling users to effectively control devices through their neurological signals (27).

In recent years, BCIs have been enhanced with machine learning and artificial intelligence algorithms, providing significant advancements in personalized care and communication strategies. This has led to improved quality of life and substantially increased independence for individuals affected by ALS and other neurological disorders (28).

Brain–computer interfaces are not only important for individuals who have lost motor function but have also emerged as a significant technology in various medical applications. Today, BCIs are used in clinical settings for detecting motion and balance disorders, preventing behavioral disorders such as tobacco and alcohol addiction, early diagnosis of brain tumors and neurological diseases, and monitoring and evaluating sleep disorders. Additionally, they enable the implementation of personalized treatment and therapy programs in rehabilitation for conditions such as cerebral palsy, muscle or nerve injuries, congenital disabilities, and other physiological impairments (29).

With the acceleration of technological advancements in recent years, the precision and accuracy of BCIs have increased, allowing users' neurological activity to be measured more reliably through both non-invasive and invasive methods. These improvements have expanded the potential for both clinical research and everyday use, paving the way for innovative approaches in areas such as neuro-rehabilitation and addiction therapy (30).

New methods are being developed in rehabilitation using brain–computer interfaces (BCIs). In this context, robot-assisted motor imagery (MI) and BCI systems have emerged as advanced techniques that support faster recovery of motor functions in post-stroke patients. The motor imagery approach allows patients to mentally simulate movements without physically performing them. EEG-based BCI systems detect brain activity and enable interaction with the environment. The integration of robot-assisted MI and BCI systems, known as the motor imagery–brain–computer interface approach, allows stroke patients to control their impaired limbs via robotic arms using mental movement signals while providing multi-sensory feedback. This process accelerates motor learning and enhances the effectiveness of rehabilitation (31).

In stroke patients, EEG-based BCI systems have been shown to be effective in supporting voluntary movements. These systems play a critical role in bridging the essential link between movement planning and execution. Furthermore, interface applications developed by integrating functional electrical stimulation (FES) and electromyography (EMG) data are being effectively utilized in neurorehabilitation processes (16).

3.4. Orthotic and Prosthetic Technologies

Every day, congenital conditions, accidents, diseases, and an aging population contribute to functional impairments or losses in body parts such as the arms, legs, or trunk. To minimize or compensate for these functional or cosmetic deficits, orthoses or prostheses are required. Orthotic and prosthetic technologies are among the essential rehabilitation tools developed to enhance mobility, reduce functional loss, and enable individuals with physical impairments to perform daily activities more independently.

Orthotic devices in clinical practice are not limited to providing immobilization, support, alignment, or protection. They also play a crucial role in rehabilitation processes aimed at treating musculoskeletal injuries and addressing functional impairments. Consequently, orthoses are widely used as assistive medical devices to increase patients' mobility, preserve existing functions, and support greater independence in daily activities (32).

Assistive technologies, such as orthotic or prosthetic devices, have been effectively used in rehabilitation for centuries. Over the years, different applications and modifications have been applied to shape and improve the appearance of these orthoses. These developments have gradually enhanced not only their aesthetics but also their comfort. In the early 1980s, a significant advancement in manufacturing technology occurred with the emergence of additive manufacturing technologies (AMT), commonly known today as 3D printing. This innovation is based on the stereolithography method, which uses ultraviolet (UV) lasers to cure photopolymer resin layer by layer, enabling the production of three-dimensional models in a layered manner.

In subsequent years, the field of additive manufacturing rapidly advanced, and various production techniques such as Fused Deposition Modeling (FDM), Laminated Object Manufacturing (LOM), Selective Laser Sintering (SLS), 3D printing methods, and PolyJet technology were developed and implemented. These technologies have provided significant advantages in rapid prototyping and the production of complex geometries (33).

Recently, research on wearable robotic systems designed to enhance mobility, improve functional independence, and increase quality of life for individuals with physical impairments has significantly increased in the fields of physical medicine and rehabilitation. Among these wearable robots are powered prosthetic arms and legs for amputees (34) as well as exoskeleton systems and robotic orthoses designed for individuals with paresis, stroke, and various neuromuscular disorders.

Although numerous prototypes of these assistive and rehabilitation-oriented robotic systems have been developed, the majority of these technologies have not yet reached widespread clinical use or integration into daily life, remaining primarily in research and laboratory settings.

Orthotic and prosthetic technologies constitute an essential component of the rehabilitation process, enabling individuals with physical impairments to perform daily activities more independently. These technologies support mobility, mitigate the impact of functional loss, and facilitate more active interaction with the surrounding environment. Additionally, they enhance social participation, promote social integration, and support individuals' psychological confidence. Therefore, orthotic and prosthetic applications play

a crucial role not only in improving physical functions but also in enhancing overall quality of life.

3.5. Tele-rehabilitation Applications

The rapid development of digital technologies has profoundly transformed the delivery of healthcare services. One of the most notable examples of this transformation is telehealth, a model that enables healthcare to be provided remotely through digital tools. Telehealth refers to the delivery of health-related services to individuals who reside in different locations or are receiving care through established networks. It involves the sharing of health data, care information, and education between healthcare providers, patients, students, and other healthcare personnel using telephone, computer, interactive television, or a combination of these tools (35). The World Health Organization (WHO) defines telehealth as "the use of telecommunications and virtual technology to deliver health services outside traditional healthcare facilities" (36).

In telehealth applications, information and communication technologies such as data transmission, audio, still images, and video allow healthcare information to be shared over short or long distances without face-to-face contact between healthcare providers and patients. These technologies enable many healthcare services, including patient assessment, diagnosis, treatment planning, and monitoring, to be conducted remotely. In the field of physiotherapy, telehealth has been adapted as tele-rehabilitation, defined as "the provision of rehabilitation services via information and communication technologies" (37). Broadly, tele-rehabilitation refers to the remote delivery of rehabilitation services—including monitoring, intervention, supervision, education, and counseling—by rehabilitation specialists using tools such as information and communication technologies, with the aim of enhancing patients' independence according to specific procedures and protocols.

Tele-rehabilitation services are generally provided via either synchronous (real-time) or asynchronous (store-and-forward) methods. These approaches facilitate the delivery of physiotherapy services to a broader population and allow treatment processes to continue remotely (38). In synchronous methods, the physiotherapist and patient communicate online simultaneously, typically via video conferencing, live video sessions, or online platforms. This enables the physiotherapist to observe the patient's movements in real time, verify the correct performance of exercises, and provide immediate feedback and corrections if necessary. Synchronous tele-rehabilitation is particularly effective for exercise training, functional assessment, and treatment follow-up.

In asynchronous methods, the physiotherapist and patient do not need to communicate at the same time. Patient information—such as video recordings, exercise sessions, health data, or reports—is first recorded and then sent to the physiotherapist, who later reviews the data to assess the patient's status, update exercise programs, and provide feedback. This method is especially useful for follow-up, exercise monitoring, and evaluating patient progress.

The increasing use of tele-rehabilitation in the assessment and treatment of various conditions has brought significant benefits for both patients and rehabilitation teams. These applications improve efficiency in time and labor use while reducing treatment-related costs. Considering the time required to access healthcare services, tele-rehabilitation provides time and cost advantages for both physiotherapists and patients. Therefore, tele-rehabilitation is regarded as an effective approach that contributes to the more efficient and accessible delivery of rehabilitation services (39).

3.6. Mobile Application-Based Technologies

The use of mobile applications in rehabilitation has become increasingly important as individuals carry mobile devices such as smartphones or tablets with them in their daily lives. These applications enable users to easily record and regularly monitor health-related data in their own environments. Consequently, information such as exercise performance, physical activity levels, and adherence to treatment can be collected, creating a comprehensive database.

Mobile applications provide significant support to healthcare professionals in monitoring and evaluating patients' rehabilitation progress. Regular documentation of patient progress allows for timely updates to treatment programs and the development of more individualized rehabilitation approaches. These features make mobile applications an important tool for conducting rehabilitation processes more effectively and sustainably. Various mobile applications also facilitate postural assessment, joint range of motion measurement, physical activity tracking, educational guidance, and engagement in exercises and activities (16).

Studies have examined the usability of home-based mobile rehabilitation applications for improving upper extremity function in individuals with chronic stroke. In this context, a smartphone-based application was combined with 3D-printed objects such as cups, bowls, keys, and door handles for task-oriented activities. The developed application was capable of assessing both task completion time and movement quality during these activities. Findings indicate that smartphone-based portable technologies can support home rehabilitation programs and enhance upper extremity function in individuals with chronic stroke (40).

In recent years, mobile application-based technologies have increasingly been used as tools to support rehabilitation services. Mobile platforms designed for children with cerebral palsy, particularly for improving upper extremity function, facilitate the implementation of goal-oriented home programs. The GO Move mobile web platform, for instance, provides exercises and activities aimed at enhancing children's daily living skills and upper extremity movements (41). The platform offers features such as goal setting, exercise and activity selection, video-assisted instructions, and progress tracking, supporting active participation of both therapists and families in the rehabilitation process.

Research findings suggest that mobile application-based systems can improve adherence to home programs, enhance motivation, and contribute to the development of func-

tional skills. Therefore, mobile application-based technologies hold significant potential for increasing access to rehabilitation services and supporting the effectiveness of treatment processes.

3.7. Virtual Reality-Based Applications

The concept of virtual reality (VR) is broadly defined as the "reconstruction of reality" or the "combination of reality and imagination through technology," implying that real-world experiences can be simulated virtually (42). VR is an artificial environment created using software and hardware that allows users to interact with virtual patients and resources, providing experiences that closely resemble reality. In these applications, users perceive themselves as if they are in a real environment (43).

Virtual reality systems detect user movements and provide real-time feedback, creating an environment that simulates real-world experiences. Due to these capabilities, VR applications are increasingly utilized in education, entertainment, military simulations, and particularly in healthcare.

In healthcare, one prominent application of VR technology is in rehabilitation. Traditional rehabilitation programs often consist of repetitive and structured exercises, which some patients may perceive as monotonous or unengaging. This challenge is especially relevant in pediatric rehabilitation, where children have limited attention spans and motivation can decrease rapidly, potentially reducing participation in conventional therapy sessions and adherence to treatment. Insufficient exercise repetition may consequently limit treatment effectiveness. VR, through three-dimensional interactive environments generated via computer technologies, provides more engaging and immersive rehabilitation experiences, enhancing patient participation.

Recent advancements in healthcare technologies have led to increased use of VR applications, particularly in neurorehabilitation. These systems enable individuals to perform specific tasks in a virtual environment, supporting motor learning processes and making rehabilitation programs more interactive.

VR-based rehabilitation applications offer visual and auditory feedback, allowing users to assess their movements in real time. This feature is particularly advantageous during the relearning of motor skills. Additionally, VR can gamify exercises, increasing motivation and engagement, which allows for a higher number of repetitions and more effective motor learning.

Existing literature suggests that VR-based rehabilitation applications can serve as effective complementary therapies for improving motor functions in individuals with cerebral palsy, stroke, and other neurological disorders. Studies in pediatric rehabilitation indicate that VR-based exercise programs can positively impact balance, gait, and upper extremity functions (44,45. Moreover, VR systems can be used to assess motor performance and plan individualized treatment programs (46).

Another significant advantage of VR applications is their ability to extend rehabilitation programs beyond clinical settings. VR systems support home-based rehabilitation,

facilitating patient access to therapy and promoting continuity in the rehabilitation process. Current studies indicate that VR technology shows promising results in neurorehabilitation and highlight the need for larger-scale randomized controlled trials in this field (47).

3.8. Video-Based Game Therapy Systems

Video-based game therapy systems are a treatment modality frequently utilized by physiotherapists to enhance motor performance. These systems provide repetitive functional tasks combined with rich sensory (visual, auditory, tactile), cognitive feedback, and enhanced stimulation, and studies have shown that they can also increase task-focused motivation in patients (48).

Video-based game therapy systems are gaining attention among rehabilitation practitioners as innovative approaches that offer both a therapeutic and engaging environment. In these applications, individuals perform specified tasks in a virtual environment while simultaneously completing the movements required for therapy objectives. This gamified structure reduces monotony, particularly in patients requiring long-term rehabilitation, enhances motivation, and supports adherence to the treatment program (49).

These systems are typically integrated with motion-detecting sensors or camera-based tracking systems, enabling real-time monitoring and feedback of patient movements. Certain commercial gaming platforms, such as Nintendo Wii and Microsoft Kinect, have been shown to support motor control, coordination, and balance, providing effective exercise options for rehabilitation (50).

Research indicates that video-based game therapy systems can be particularly effective in neurological and pediatric rehabilitation. Systematic reviews and meta-analyses conducted on children with cerebral palsy demonstrate that virtual reality and video-based game therapy systems positively impact motor function, balance, and functional performance (51,52). Moreover, children who may become bored with conventional exercises and fail to complete sufficient repetitions have been reported to show increased engagement and more efficient performance of exercises when using these systems (53).

Randomized controlled trials provide additional evidence supporting these findings. For instance, (48) implemented a video-based game program to improve upper extremity function in children with cerebral palsy and observed significant improvements in motor performance. This study highlights that game-based therapies can serve as an effective adjunct to conventional rehabilitation methods. Furthermore, other recent studies suggest that video game–based rehabilitation may enhance hand function, upper extremity skills, and activities of daily living (54,55).

In conclusion, video-based game therapy systems emerge as a method that enhances motivation, provides feedback, and supports motor learning. Current literature indicates that these technologies can play a complementary role to traditional exercises, particularly in pediatric and neurological rehabilitation.

4. Misconceptions About the Use of Artificial Intelligence in Rehabilitation Practices

The use of artificial intelligence (AI) in rehabilitation is sometimes met with misunderstandings and concerns. In particular, some stakeholders fear that AI will completely replace human therapists, potentially leading to a decline in the quality of care provided to patients. However, current research and practical applications demonstrate that AI is not a "substitute" for therapists but rather a powerful tool that supports clinical decision-making processes (5). AI contributes significantly to critical functions such as monitoring patient progress, providing personalized feedback, and enhancing the effectiveness of interventions.

Another common misconception is that integrating AI into rehabilitation settings is inherently complex and costly. In reality, technological advancements are making AI solutions increasingly accessible and cost-effective, and integration with existing systems can be carried out more efficiently. The belief that AI systems are unreliable is also scientifically unfounded. Modern AI applications are designed with multi-stakeholder evaluation processes, adherence to ethical standards, and rigorous quality control methods. Nevertheless, responsible and effective AI integration requires ongoing research and development, ethical compliance, and stakeholder engagement. Additionally, contemporary AI systems possess transparent and explainable characteristics, meaning that they can provide justifications and evidence for the decisions and interventions they implement.

In conclusion, the role of AI in rehabilitation is not to replace human experts but to enhance their competencies and make care processes more effective. Addressing misconceptions and fostering the proper adoption of AI can provide significant benefits for both patients and therapists.

5. Conclusion and Future Perspectives

The use of AI-based technologies in physiotherapy and rehabilitation significantly contributes to transforming clinical practices into more data-driven, measurable, and personalized approaches. AI-supported systems assist clinicians in various areas, including movement analysis, functional performance assessment, monitoring of rehabilitation processes, and individualization of treatment programs. Innovative approaches such as robotic rehabilitation systems, virtual reality applications, tele-rehabilitation platforms, and wearable technologies enhance the accessibility of rehabilitation services and enable more effective management of treatment processes.

However, ensuring the safe and effective use of AI technologies in rehabilitation requires adherence to ethical principles, data security, and increased clinical validation studies. In the future, AI-based systems are expected to be further integrated with advanced algorithms, big data analytics, and intelligent sensor technologies. These developments are anticipated to contribute to making rehabilitation services more accessible,

sustainable, and patient-centered. In this context, increasing interdisciplinary research in physiotherapy and rehabilitation will play a critical role in demonstrating the clinical efficacy of AI applications more comprehensively.

6. References

1. World Health Organization. (2011). *World report on disability*. World Health Organization.
2. Heinemann, A. W., Feuerstein, M., Frontera, W. R., Gard, S. A., Kaminsky, L. A., Negrini, S., & Stucki, G. (2020). Rehabilitation is a global health priority. *Canadian Journal of Occupational Therapy*, 87(2), 89-90.
3. Cieza, A., Mikkelsen, B., & Ghaffar, A. (2022). Advancing rehabilitation through health policy and systems research. *Bulletin of the World Health Organization*, 100(11), 655.
4. Russell, S., & Norvig, P. (2021). *Artificial intelligence: A modern approach* (4th ed.). Pearson
5. Topol, E. (2019). *Deep medicine: How artificial intelligence can make healthcare human again*. Hachette UK.
6. Jiang, F., Jiang, Y., Zhi, H., Dong, Y., Li, H., Ma, S., Wang, Y., Dong, Q., Shen, H., & Wang, Y. (2017). Artificial intelligence in healthcare: past, present and future. *Stroke and Vascular Neurology*, 2(4), 230-243.
7. Akalın, B., & Veranyurt, Ü. (2020). Sağlıkta dijitalleşme ve yapay zekâ. *SDÜ Sağlık Yönetimi Dergisi*, 2(2), 128-137.
8. Davenport, T., & Kalakota, R. (2019). The potential for artificial intelligence in healthcare. *Future Healthcare Journal*, 6(2), 94-98.
9. Vélez-Guerrero, M. A., Callejas-Cuervo, M., & Mazzoleni, S. (2021). Artificial intelligence-based wearable robotic exoskeletons for upper limb rehabilitation: a review. *Sensors*, 21(6), 2146.
10. Ravali, R. S., Vijayakumar, T. M., Santhana Lakshmi, K., Mavaluru, D., Reddy, L. V., Retnadhas, M., & Sivakumar, V. (2022). A systematic review of artificial intelligence for pediatric physiotherapy practice: past, present, and future. *Neuroscience Informatics*, 2(4), 100045
11. Brougham, D., & Haar, J. (2017). Smart technology, artificial intelligence, robotics, and algorithms (STARA): Employees' perceptions of our future workplace. *Journal of Management & Organization*, 24(2), 239-257.
12. Akalın, B., & Demirbaş, M. B. (2022). Rehabilitasyon hizmetlerinde yapay zekâ uygulamaları. *Acta Infologica*, *6*(2), 141-161.
13. Martínez-Cid, S., Herrera, V., Schez-Sobrino, S., Monekosso, D., Glez-Morcillo, C., & Vallejo, D. (2025). Artificial intelligence in physical therapy for neurological rehabilitation: A systematic mapping study. *IEEE Access*. Advance online publication.
14. Grossi, E. (2011). Artificial neural networks and predictive medicine: a revolutionary paradigm shift. *Artificial Neural Networks-Methodological Advances and Biomedical Applications*, *10*, 15810.
15. Anderson, D. (2019). Artificial intelligence and applications in PM&R. *American journal of physical medicine & rehabilitation*, *98*(11), e128-e129.
16. Tarakçı, D. (2021, Haziran 3). Rehabilitasyonda yapay zekâ. *SD Platform*. https://www.sdplatform.com/Dergi/1420/Rehabilitasyonda-yapay-zek.aspx
17. Weiner, E. B., Dankwa-Mullan, I., Nelson, W. A., & Hassanpour, S. (2025). Ethical challenges and evolving strategies in the integration of artificial intelligence into clinical practice. *PLOS digital health*, *4*(4), e0000810.
18. Khalifa, A. A., & Ibrahim, M. A. (2025). Artificial Intelligence, Rehabilitation, and Physical Disabilities. In *The Palgrave Encyclopedia of Disability* (pp. 1-13). Cham: Springer Nature Switzerland.
19. Sumner, J., Lim, H. W., Chong, L. S., Bundele, A., Mukhopadhyay, A., & Kayambu, G. (2023). Artificial intelligence in physical rehabilitation: A systematic review. *Artificial Intelligence in Medicine*, *146*, 102693.
20. Mennella, C., Maniscalco, U., De Pietro, G., & Esposito, M. (2023). The role of artificial intelligence in future rehabilitation services: a systematic literature review. *IEEE Access*, *11*, 11024-11043.
21. Rad, O. L., & Brisan, C. (2025). Control algorithms in robot-assisted rehabilitation: A systematic review. *Applied Sciences*, 15(16), 9184.
22. Meng, W., Liu, Q., Zhou, Z., Ai, Q., Sheng, B., & Xie, S. S. (2015). Recent development of mechanisms and control strategies for robot-assisted lower limb rehabilitation. *Mechatronics*, 31, 132-145.
23. Iosa, M., Morone, G., Cherubini, A., & Paolucci, S. (2016). The three laws of neurorobotics: A review on what neurorehabilitation robots should do for patients and clinicians. *Journal of Medical and Biological Engineering*, 36(1), 1-11.
24. Poli, P., Morone, G., Rosati, G., & Masiero, S. (2013). Robotic technologies and rehabilitation: new tools for stroke patients' therapy. *BioMed research international*, *2013*(1), 153872.
25. Molteni, F., Gasperini, G., Cannaviello, G., & Guanziroli, E. (2018). Exoskeleton and end-effector robots for upper and lower limbs rehabilitation: Narrative review. *PM&R*, 10(9), S174-S188.
26. Cincotti, F., Mattia, D., Aloise, F., Bufalari, S., & Schalk, G. (2008). Non-invasive brain–computer interface system: Towards its application as assistive technology. *Brain Research*, 1233, 183-193.
27. Indumathi, G., & Sathananthavathi, V. (2021). Cost-effective assistive device for motor neuron disease. In *Handbook of decision support systems*. Elsevier.

28. Kew, S., Mok, S. Y., & Goh, C. H. (2024). Machine learning and brain-computer interface approaches in prognosis and individualized care strategies for individuals with amyotrophic lateral sclerosis. *MethodsX*. Advance online publication.

29. Büyükgöze, S. (2021). Beyin Bilgisayar Arayüzleri ve Uygulama Alanlari.

30. Jumphoo, T., Uthansakul, M., Duangmanee, P., Khan, N., & Uthansakul, P. (2021). Soft robotic glove controlling using brainwave detection for continuous rehabilitation at home. *Computers, Materials & Continua*, *66*(1), 961-976.

31. Ang, K. K., Chua, K. S. G., Phua, K. S., Wang, C., Chin, Z. Y., Kuah, C. W. K., ... & Guan, C. (2015). A randomized controlled trial of EEG-based motor imagery brain-computer interface robotic rehabilitation for stroke. *Clinical EEG and neuroscience*, *46*(4), 310-320.

32. Barrios-Muriel, J., Romero-Sánchez, F., Alonso-Sánchez, F. J., & Salgado, D. R. (2020). Advances in orthotic and prosthetic manufacturing: a technology review. *Materials*, *13*(2), 295.

33. Chia, H. N., & Wu, B. M. (2015). Recent advances in 3D printing of biomaterials. *Journal of Biological Engineering*, 9(1), 4.

34. Lingampally, P. K., Ramanathan, K. C., Shanmugam, R., Cepova, L., & Salunkhe, S. (2024). Wearable assistive rehabilitation robotic devices—a comprehensive review. *Machines*, *12*(6), 415.

35. Pazar, B., Taştan, S., & İyigün, E. (2015). Tele-sağlık sisteminde hemşirenin rolü. *Bakırköy Tıp Dergisi*, 11(1), 1-4.

36. Zischke, C., Simas, V., Hing, W., Milne, N., Spittle, A., & Pope, R. (2021). The utility of physiotherapy assessments delivered by telehealth: A systematic review. *Journal of global health*, *11*, 04072.

37. Brennan, D., Tindall, L., Theodoros, D., Brown, J., Campbell, M., Christiana, D., & Smith, D. (2010). A blueprint for telerehabilitation guidelines. *International Journal of Telerehabilitation*, 2(2), 31-34.

38. Cary Jr, M. P., Spencer, M., Carroll, A., Hand, D. H., Amis, K., Karan, E., ... & Hoenig, H. M. (2016). Benefits and challenges of delivering tele-rehabilitation services to rural veterans. *Home healthcare now*, *34*(8), 440-446.

39. Koh, G., et al. (2017). A time motion analysis... *Archives of Physical Medicine and Rehabilitation*, 98(10), e28. doi:10.1016/j.apmr.2017.08.087

40. Langan, J., et al. (2020). In-home rehabilitation... *JMIR mHealth and uHealth*, 8(7), e19582.

41. Shierk, A., Roberts, H., Habeeb, Y., Dursun, N., Cekmece, C., Bonikowski, M., ... & Delgado, M. R. (2024). Development of GO Move: A Website for Children With Unilateral Cerebral Palsy. *OTJR: Occupational Therapy Journal of Research*, *44*(4), 589-596.

42. Kayabaşı, Y. (2015). Sanal gerçeklik ve eğitim amaçlı kullanılması. *TOJET*, 4(3), 151-158.

43. Jenson, C. E., & Forsyth, D. M. (2012). Virtual reality simulation: Using three-dimensional technology to teach nursing students. *CIN: Computers, Informatics, Nursing*, *30*(6), 312-320. https://doi.org/10.1097/NXN.0b013e31824af6ae

44. Wang, Y., Tan, Y., Zheng, X., Wang, M., Li, H., & Zhou, X. A Scoping Review of the Application Scope of Digital Technologies in Lower Limb Rehabilitation and Balance Training for Children with Cerebral Palsy. *Frontiers in Pediatrics*, *14*, 1786311.

45. Schless, S. H., Sorek, G., Schurr, I., Beretta, E., Diella, E., & Biffi, E. (2025). Effectiveness of treadmill-based virtual-reality biofeedback training to improve gait function in children and adolescents with congenital and acquired brain injury. *Scientific Reports*..

46. Alrashidi, M. M., Evans, J. O., Tomlinson, R. J., Williams, C. A., & Buckingham, G. (2026). Usability of a virtual reality circle drawing task to assess upper-limb motor performance in children and young people with cerebral palsy: pilot study. *BMC Pediatrics*.

47. Silva, A. B. J., Barros, W. M. A., Silva, R. F., Machado Silva, B., Souza, A. P. D. S., Silva, K. G., ... & Lopes De Souza, S. (2025). The use of virtual reality technologies in children with adverse health conditions: can it improve neuromotor function? a systematic review of randomized clinical trials. *Frontiers in Virtual Reality*, *6*, 1542804.

48. Avcil, E., Tarakci, D., Arman, N., & Tarakci, E. (2021). Upper extremity rehabilitation using video games in cerebral palsy: a randomized clinical trial. *Acta Neurologica Belgica*, *121*(4), 1053-1060.

49. Bonnechère, B., Jansen, B., Omelina, L., & Jan, S. V. S. (2016). The use of commercial video games in rehabilitation: a systematic review. *International journal of rehabilitation research*, *39*(4), 277-290.

50. Pintado-Izquierdo, S., Cano-de-la-Cuerda, R., & Ortiz-Gutiérrez, R. M. (2020). Video game-based therapy on balance and gait of patients with stroke: a systematic review. *Applied Sciences*, *10*(18), 6426.

51. Ravi, D. K., Kumar, N., & Singhi, P. (2017). Effectiveness of virtual reality rehabilitation for children and adolescents with cerebral palsy: an updated evidence-based systematic review. *Physiotherapy*, *103*(3), 245-258.

52. Wu, J., Loprinzi, P. D., & Ren, Z. (2019). The rehabilitative effects of virtual reality games on balance performance among children with cerebral palsy: a meta-analysis of randomized controlled trials. *International journal of environmental research and public health*, *16*(21), 4161.

53. Iosa, M., Verrelli, C. M., Gentile, A. E., Ruggieri, M., & Polizzi, A. (2022). Gaming technology for pediatric neurorehabilitation: A systematic review. *Frontiers in pediatrics*, *10*, 775356.

54. Vezer, M., Gresits, O., Engh, M. A., Szabo, B., Molnar, Z., Hegyi, P., & Terebessy, T. (2024). Effectiveness of Video-Game-Based Therapy to Improve Hand Function in Children with Cerebral Palsy: A Systematic Review and Meta-Analysis. *Journal of Clinical Medicine*, *13*(24), 7524.

55. Wang, L., Chen, J. L., Wong, A. M., Liang, K. C., & Tseng, K. C. (2022). Game-based virtual reality system for upper limb rehabilitation after stroke in a clinical environment: systematic review and meta-analysis. *Games for health journal*, *11*(5), 277-297.

CHAPTER 42

Artificial Intelligence in Plastic Surgery: Fundamental Concepts, Current Clinical Applications, and the Paradigm of the Future

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1. Introduction

Artificial intelligence is playing an increasingly visible role in modern medicine, gradually shifting clinical practice away from purely intuition-driven decisions toward something more data-informed and reproducible. Deep learning and neural networks, in particular, are changing how clinicians approach diagnosis and treatment planning (1,3,4). Importantly, the goal isn't to sideline clinical judgment these technologies are best understood as decision-support tools that can sharpen accuracy and bring greater consistency to complex assessments (3,6).

Of all the surgical disciplines, plastic, reconstructive, and aesthetic surgery may be among the most naturally suited to AI integration. The field depends heavily on visual evaluation, fine anatomical detail, and the kind of subtle morphological judgment that is genuinely difficult to codify. AI particularly through image-based analysis has something real to offer here (5,7).

1.1. The Synergy Between Plastic Surgery and AI

At the heart of plastic surgery lies the careful interpretation of symmetry, proportion, and form. For generations, these judgments have been shaped by the surgeon's experience and aesthetic sense. That expertise isn't going anywhere but AI brings something complementary: the ability to analyze visual data with a level of precision and consistency that is hard for any human observer to sustain (1,2).

Through computer vision, AI systems can detect patterns and anatomical details that are difficult to quantify by eye alone, enabling a more objective and reproducible evalu-

ation of clinical findings. The surgeon's perspective isn't replaced it's supported. Assessments become more standardized, and clinical decisions more consistently grounded (3-6).

2. Aims and Scope

This chapter looks at how AI is making its way into plastic surgery, focusing on four areas where its impact is most clearly felt:

(i) **Diagnostic Precision:** AI-driven tools are increasingly used to classify skin lesions, assess burn depth, and evaluate tissue viability. These applications can support earlier detection and more accurate clinical judgment (1,2).

(ii) **Surgical Planning and Optimization:** Machine learning models can support patient selection, simulate surgical approaches, and enable personalized implant design. In complex procedures such as microsurgery, AI can also contribute to preoperative mapping (3,4).

(iii) **Predictive Analytics:** AI-based simulations allow surgeons to anticipate postoperative outcomes and develop a clearer understanding of how soft tissues are likely to change over time. This improves both planning and risk management (4,5).

(iv) **Enhancing Patient Experience:** By generating realistic visual simulations, AI helps patients develop a more grounded understanding of what surgery can and cannot achieve. This strengthens the informed consent process, aligns expectations, and tends to improve overall satisfaction (6).

3. Fundamentals of Artificial Intelligence in Surgical Sciences

Artificial intelligence has become one of the main forces driving digital transformation in healthcare. By combining computational algorithms with clinical data, AI systems can assist physicians with diagnostic evaluation, treatment planning, and outcome prediction (5,6). Over the last decade, the rapid growth of healthcare datasets and major advances in computing power have accelerated this process considerably.

At the foundation of AI sits machine learning (ML) — a computational approach that allows algorithms to learn from data and improve their performance over time, without needing an explicit rule for every possible scenario (5). Rather than following a fixed script, ML systems identify statistical relationships and recurring patterns within datasets and use these to generate predictions or classifications. In healthcare, they are increasingly applied to patient stratification, risk assessment, surgical planning, and clinical decision support (4,5).

Deep learning (DL) is a more advanced branch of AI that takes things further by using multilayered artificial neural networks loosely inspired by the structure of the human brain (1). Unlike traditional ML, which often requires researchers to manually identify relevant features in the data, deep learning systems can autonomously extract complex, hierarchical representations directly from raw inputs — radiological images, pathology

slides, clinical photographs (1,3). This capacity allows DL algorithms to detect subtle imaging characteristics that human observers might miss or find inconsistent.

The clinical importance of deep learning is especially apparent in specialties that rely heavily on images. Multiple studies have shown that DL-based systems can match the diagnostic accuracy of experienced clinicians in specific imaging tasks (4). In dermatology, for example, convolutional neural networks have demonstrated performance on par with dermatologists when classifying skin cancers from clinical images (14). Similar work has been done in radiology, pathology, ophthalmology, and reconstructive surgery (2,3).

Beyond diagnosis, AI technologies are being integrated into the surgical sciences for preoperative simulation, intraoperative guidance, and outcome prediction. AI-driven systems can analyze patient-specific anatomical and clinical data to support individualized treatment strategies and improve the precision of procedural planning (6).

3.1. Computer Vision and Neural Architectures

The interpretation of medical images, a cornerstone of many surgical disciplines, is now largely driven by modern neural network architectures. Two approaches stand out for their transformative impact:

3.1.1. Convolutional Neural Networks (CNNs)

Convolutional neural networks have become the standard tool for image analysis. By applying specialized filters across images, CNNs learn to recognize spatial relationships between pixels and progressively build an understanding of increasingly complex visual structures. In surgical practice, this makes them highly effective for tasks such as image segmentation, lesion detection, and the precise identification of anatomical landmarks (1,8).

3.1.2. Generative Adversarial Networks (GANs)

Generative adversarial networks work through an ongoing competition between two models: a generator that creates synthetic data and a discriminator that evaluates how realistic those outputs are. Through this iterative back-and-forth, GANs learn to produce highly convincing results. In medicine, they are increasingly used to enhance image quality, generate synthetic training datasets, and compensate for the limited data available in rare conditions or specialized surgical contexts (9).

4. Diagnosis and Clinical Assessment

4.1. Automated Analysis of Cutaneous Lesions

Advances in deep learning — particularly through convolutional neural networks — have significantly changed how skin malignancies are identified and classified. By analyzing

high-resolution dermoscopic images, these systems can recognize complex visual patterns, such as pigment networks and vascular structures, that are difficult to detect consistently with the naked eye (10). In practice, AI-based tools support clinicians by providing standardized risk assessments for both melanoma and non-melanoma skin cancers, reducing the inter-observer variability that has long been a challenge in dermatoscopic evaluation.

4.2. Precision Assessment of Burn Severity

Accurately determining burn depth in the early stages remains one of the more persistent challenges in acute surgical care, as visual and tactile assessments can be unreliable and inconsistent. AI-supported approaches offer a more objective alternative, combining imaging technologies such as near-infrared spectroscopy (NIRS) and laser Doppler imaging (LDI) with advanced computational models (11). These systems evaluate tissue perfusion and microvascular integrity, giving clinicians a more solid basis for distinguishing between burn depths. In practice, this can meaningfully improve decisions about whether and when surgical intervention is needed particularly when differentiating deep partial-thickness from full-thickness burns.

4.3. Quantitative Monitoring of Wound Kinetics

AI is also changing how chronic and complex wounds are tracked over time. Rather than relying on subjective visual impressions at each clinic visit, AI enables precise, data-driven monitoring of the healing process. Using image segmentation, these systems can measure changes in wound size and geometry while analyzing the composition of the wound bed — for instance, identifying when necrotic tissue is giving way to healthy granulation (12). This kind of continuous, quantitative monitoring helps clinicians catch delayed healing earlier and make more informed adjustments to treatment.

5. Digital Paradigms in Preoperative Surgical Planning

Modern plastic surgery has moved well beyond the limitations of two-dimensional imaging, embracing advanced digital tools as part of routine preoperative evaluation. High-resolution three-dimensional technologies now offer a far more detailed and patient-specific understanding of anatomy — a genuine advantage in procedures where symmetry, proportion, and subtle contour differences can determine the outcome (3,4).

5.1. Three-Dimensional Morphometric Surface Analysis

Three-dimensional surface imaging provides an objective and highly precise method for anatomical assessment, with a level of detail that standard clinical photography simply cannot match (3). By capturing anatomical structures within a 3D coordinate system, these technologies allow surgeons to quantify volumetric differences, skeletal asymmetries, and

surface contours with high accuracy. Key anthropometric relationships nasofacial and mentocervical angles, for example can be calculated in a reproducible and mathematically consistent way. Surgical planning becomes less a matter of estimation and more a matter of measurement.

5.2. Virtual Surgical Simulation and Prototyping

Digital simulation platforms have become genuinely useful tools in preoperative planning, allowing surgeons to rehearse procedures virtually before entering the operating room (4). In rhinoplasty, simulation software can model how soft tissues are likely to respond to structural changes such as osteotomies or cartilage grafting. In breast surgery, virtual planning tools let surgeons visualize how different implant sizes and shapes will interact with a patient's anatomy, optimizing implant selection based on thoracic dimensions and the desired degree of projection — improving both aesthetic outcomes and surgical predictability (3).

5.3. Expectation Management and Patient Communication

Beyond technical planning, digital simulations play an important role in the conversation between surgeon and patient. By translating surgical intentions into realistic visual representations, these tools make abstract concepts accessible and understandable (2). The process helps align patient expectations with what is surgically achievable, which in turn reduces the risk of dissatisfaction. It also strengthens the informed consent process by providing a clear visual reference for what is being planned. Ultimately, this collaborative approach builds trust and contributes to more satisfying postoperative results (2,4).

6. Surgical Simulation and Outcome Prediction

The broader shift toward Surgery 4.0 has fundamentally changed how plastic surgeons approach preoperative planning and patient communication. At the center of this transformation are advanced AI techniques, particularly generative adversarial networks (GANs), which have expanded the capabilities of 3D modeling. Unlike earlier approaches, GAN-based systems can generate highly realistic "before-and-after" images that closely reflect potential postoperative outcomes while preserving the patient's individual anatomical characteristics (13).

Technically, GANs work through the interaction of two neural networks: a generator that creates images and a discriminator that evaluates their realism. Through this iterative process, the system progressively refines its outputs, producing images with a high degree of visual fidelity. In clinical practice, this means surgeons can offer patients more lifelike and personalized projections of what surgery might achieve.

Alongside simulation, predictive analytics represents another meaningful advance. By incorporating patient-specific variables tissue characteristics, healing capacity, anatomical structure AI systems can analyze large clinical datasets to estimate how tissues are likely

to respond over time (14). This allows surgeons to anticipate postoperative changes more accurately and tailor their approach accordingly, supporting better patient selection and more evidence-based outcomes (14,15).

These technologies also play an important role in communication. Advanced simulation tools provide a shared visual reference that helps bridge the gap between clinical expertise and patient expectations, making potential outcomes more concrete and the decision-making process more transparent (16). This reduces preoperative uncertainty and strengthens the relationship between patient and surgeon.

In this context, GAN-based simulations and AI-driven predictive models are no longer optional extras. They are becoming integral parts of modern plastic surgery practice — supporting technical precision while reinforcing a more patient-centered approach to care (13-16).

7. Intraoperative Digital Assistance in Surgery 4.0

Surgery 4.0 has introduced a new digital layer into the operating room, changing how surgeons perceive anatomy and carry out procedures. Rather than relying solely on direct visual and tactile feedback, modern surgical environments increasingly integrate data-driven systems that enhance precision, safety, and real-time decision-making (1,3). This evolution has effectively expanded what surgeons can see and do beyond the limits of unaided human perception.

7.1. Robotic Surgical Systems

Robotic platforms have become sophisticated intermediaries between the surgeon and the patient, translating hand movements into highly refined instrument actions. Among their most important features is tremor filtration the effective elimination of involuntary hand movement — alongside motion scaling, which converts large natural movements into extremely fine instrument adjustments, enabling microsurgical precision in even delicate anatomical regions (3). Modern robotic systems often include multi-articulated instruments that can match or exceed the range of motion of the human wrist, which is particularly valuable in confined surgical spaces where conventional instruments struggle (1).

7.2. Real-Time Tissue Recognition

Bio-spectral analysis systems including intelligent electrosurgical tools such as iKnife technologies can analyze surgical smoke in real time to differentiate between malignant and healthy tissue within seconds, offering immediate feedback during resection and supporting more accurate margin control (1,5). Fluorescence-guided surgery (FGS) has similarly become an important tool in the modern operating room. Agents such as indocyanine green (ICG) enable real-time visualization of tissue perfusion and lymphatic flow, helping surgeons assess viability and vascular integrity during reconstructive and oncologic procedures (3,5).

7.3. Surgical Navigation Systems

Surgical navigation is often described as the GPS of the operating room — it integrates preoperative imaging with real-time intraoperative anatomy, aligning CT or MRI data with the surgical field to provide a dynamic reference that enhances spatial orientation during complex procedures (4). More advanced systems incorporate augmented reality (AR), projecting 3D anatomical reconstructions directly onto the surgical site and allowing surgeons to visualize underlying structures, vessels, nerves, and tumor margins without physically exposing them (4). The result is millimetric accuracy in procedures such as osteotomies, implant placement, and reconstructive surgery, significantly reducing the risk of technical error (1,4).

8. Modern Strategies in Postoperative Surveillance

Digital transformation is reshaping postoperative care, especially in plastic and reconstructive surgery, where outcomes depend so heavily on visual and morphological assessment. Follow-up today is increasingly supported by standardized photographic documentation combined with computer vision-based analysis, allowing wound healing to be monitored in a more objective and reproducible way (12).

A key goal of modern postoperative monitoring is early detection of complications. Catching problems like infection or flap compromise early can significantly reduce morbidity and improve outcomes. Remote surveillance tools can now detect subtle warning signs — localized erythema, temperature variation, early perfusion changes — that might precede clinically obvious deterioration (1,3).

Telemedicine has grown into an important extension of surgical care, providing a continuous communication channel between patients and their surgical teams. This improves access and reduces unnecessary in-person visits while maintaining meaningful clinical oversight (2). Combined with AI and mobile health platforms, telemedicine systems can analyze patient-submitted images in real time, identify deviations from expected healing patterns, and generate automated alerts enabling earlier intervention when it's needed (2,4).

9. AI-Driven Diagnostics and Non-Invasive Burn Management

Accurately assessing burn depth remains one of the most consequential and technically challenging steps in acute surgical care, since it directly shapes treatment strategy and surgical timing. In routine clinical practice, this assessment still relies heavily on visual inspection and bedside judgment methods that introduce inter-observer variability and can leave clinicians working with genuine uncertainty. AI offers a different path: more objective, data-driven analysis of burn wounds that can support and standardize clinical decision-making (1,4).

Modern non-invasive diagnostic systems use advanced imaging modalities to evaluate tissue perfusion and structural damage at a level of detail that is simply not achievable by eye alone. By analyzing thermal patterns, vascular changes, and surface characteristics, these tools provide real-time decision support that can improve both diagnostic consistency and clinical confidence (3,5).

9.1. Burn Depth Analysis and Grafting Requirement Prediction

Recent advances in AI modeling particularly deep learning approaches using convolutional neural networks have significantly improved the ability to predict burn depth and wound progression. By integrating multispectral imaging and thermal mapping data, these systems can assess tissue viability and estimate healing potential more accurately than conventional methods, especially in the critical early post-injury period (1,4).

Evidence suggests that AI-based models may offer higher sensitivity in identifying burn progression within the first 48 hours a window that is often decisive for clinical management. This improved predictive capacity helps surgeons avoid unnecessary debridement while ensuring that areas genuinely requiring early grafting are correctly flagged. The result is more efficient treatment planning, with potential benefits for both patient outcomes and resource utilization (3,5).

9.2. AI-Powered Diagnostic Platforms and Non-Invasive Systems

Emerging platforms for automated burn assessment represent the next stage in this evolution. By combining high-resolution clinical photography with AI-driven analysis, these systems can standardize the calculation of total body surface area (TBSA), reducing the variability that has long been associated with manual estimation (2,3). Beyond basic classification, these tools can evaluate intermediate burn depths and estimate healing potential in clinically ambiguous cases. Critically, they do all this without requiring invasive biopsy procedures providing detailed information on microvascular perfusion and tissue oxygenation in a way that is safer and more comfortable for patients (3,5).

10. Benefits of AI in Surgical Practice

10.1. Impartial Evaluation and Consistency

One of AI's most meaningful contributions to clinical practice is its capacity for consistent, objective analysis. Human assessment is inevitably subject to fatigue, workload pressures, and individual interpretation. AI-based systems apply the same analytical criteria every time, regardless of circumstances. This helps standardize the interpretation of complex clinical data and reduces the inter-practitioner variability that can lead to uneven patient care (1,4).

10.2. Accelerated Data Processing

AI systems can process and analyze very large datasets in a fraction of the time it would take a human clinician. This includes structured data such as electronic health records as well as unstructured inputs like imaging and laboratory results. In time-sensitive settings — emergency medicine, urgent surgical planning — this processing speed can directly translate into faster decisions and better outcomes for patients (1,5).

10.3. Precision and Tailored Therapeutics

Healthcare is increasingly moving toward personalized medicine, and AI is a key driver of that shift. By integrating diverse data sources genetic information, anatomical characteristics, lifestyle factors AI systems can help design treatment strategies that are genuinely tailored to the individual. This allows clinicians to move beyond one-size-fits-all protocols toward approaches that better match each patient's unique profile, improving both effectiveness and safety (2,4).

10.4. Mitigation of Human Error

AI also functions as a meaningful safety mechanism within clinical workflows. Operating as a kind of automated "second reader," it can flag subtle abnormalities, inconsistencies, or potential medication interactions that might be missed when clinicians are operating under cognitive load or fatigue. In this way, AI contributes to reducing preventable errors and strengthening patient safety across a range of clinical settings (2,5).

11. Limitations and Challenges in Surgical AI

AI continues to show real promise in surgical practice, but its integration into everyday clinical workflows remains constrained by important technical, ethical, and regulatory challenges. These issues need to be taken seriously if AI systems are to be deployed safely, fairly, and in ways that are clinically trustworthy.

11.1. Data Quality and Algorithmic Bias

Perhaps the most fundamental limitation of current AI systems is their dependence on high-quality, representative training data. When the underlying datasets are incomplete or skewed, the models trained on them will reflect those imbalances a phenomenon known as algorithmic bias. This occurs when certain populations, such as specific age groups, ethnicities, or socioeconomic backgrounds, are underrepresented in the training data (2,4).

In surgical subspecialties like reconstructive and aesthetic surgery, this problem is particularly pronounced. Variations in skin type, anatomical diversity, and clinical presentation are not always well captured in existing datasets. As a result, AI tools may perform

less reliably in certain patient groups, potentially contributing to unequal clinical outcomes and limiting how broadly the technology can be applied (1,3).

11.2. The "Black Box" Problem and Explainability

A major barrier to the adoption of AI in surgery is the opacity of many advanced models, particularly deep learning systems. These models often generate accurate predictions, but the reasoning behind those outputs is not always interpretable this is what is commonly referred to as the "black box" problem (1). For clinicians, this lack of transparency can make it difficult to trust AI-generated recommendations, especially when the stakes are high. There is growing interest in the field of Explainable AI (XAI), which aims to make algorithmic decision-making more transparent and clinically legible (3,4).

11.3. Ethical and Regulatory Constraints

Beyond technical limitations, AI in surgery raises genuine ethical and legal questions. The issue of liability is particularly contested: when an AI system contributes to or influences a clinical decision, it is not always clear who bears responsibility for adverse outcomes (2). Regulatory frameworks also face the challenge of keeping pace with rapidly evolving technology, particularly when it comes to distinguishing between fixed ("locked") algorithms and adaptive systems that continue to learn after deployment (4).

The use of large volumes of sensitive patient data also raises concerns about privacy, consent, and data governance. Ensuring that patients are fully informed about how AI is contributing to their care is becoming an increasingly important aspect of contemporary informed consent practices and medical ethics (2,5).

12. Ethical and Legal Dimensions: AI in Aesthetic Surgery

Integrating AI into aesthetic and plastic surgery is not simply a technological step forward it carries with it a complex set of ethical and legal responsibilities. As these systems become more embedded in clinical workflows, questions around privacy, consent, accountability, and patient expectations become increasingly important to address in a structured and transparent way.

12.1. Digital Privacy and Data Security

AI systems in healthcare depend on large volumes of often highly sensitive data. In aesthetic surgery, this includes facial biometric mapping, high-resolution clinical photographs, and detailed morphological information. Because of how inherently identifiable these inputs are, inadequate anonymization or weak data governance can create serious risks to patient privacy (2,5). Strong cybersecurity infrastructure and strict adherence to data protection regulations such as the GDPR or equivalent national frameworks are not

optional. They are fundamental safeguards for maintaining patient trust and confidentiality in AI-assisted clinical environments (2,4).

12.2. The New Paradigm of Informed Consent

Traditional informed consent models are no longer adequate in the context of AI-assisted surgical planning. Patients today need to be informed not only about the risks and benefits of the surgical procedure itself, but also about the role AI systems are playing in the decision-making process (2). Ethically, it matters that patients understand which parts of their treatment plan reflect the clinician's own expertise and which have been shaped or supported by algorithmic tools. Where patient data is being used for algorithm training or model refinement, separate and explicit data usage consent should be obtained (2,4).

12.3. Legal Liability and Medical Malpractice

Under most current regulatory frameworks, AI tools are classified as decision-support systems rather than autonomous decision-makers. This means final responsibility typically stays with the operating surgeon, who is expected to critically evaluate and validate any AI-generated recommendations before acting on them in practice (1,2). If a clinician fails to identify or appropriately challenge an incorrect AI output, liability generally falls under existing malpractice frameworks. However, where errors stem from software design flaws or systemic defects in the algorithm, legal responsibility may extend to developers or manufacturers under product liability principles (4,5).

12.4. Simulations and Expectation Management

AI-generated surgical simulations are increasingly used to help patients visualize potential outcomes. While these tools improve communication and support shared decision-making, they also risk creating unrealistic expectations if not carefully framed (2). From an ethical standpoint, surgeons need to be clear that these simulations represent probabilistic scenarios, not guaranteed results. Real outcomes are shaped by a wide range of biological variables, healing patterns, tissue response, and individual anatomy that no simulation can fully predict. Transparency here is not only ethically important; it also serves as a practical safeguard against legal disputes arising from misrepresentation (2,4).

13. Future Perspectives in Surgical Technologies

Surgery is moving into a new era defined by digital intelligence, automation, and high-precision engineering. The days of relying solely on manual planning and intraoperative judgment are giving way to an environment where AI actively supports decision-making, optimizes workflows, and helps reduce preventable error (1,4).

13.1. Fully Automated Surgical Planning

One of the most significant developments on the horizon is AI-assisted and potentially fully automated surgical planning. By analyzing radiological imaging alongside large clinical datasets, advanced algorithms can propose optimized operative pathways tailored to individual patients. This approach reduces variability in planning, improves consistency, and may substantially decrease the human-related errors that can emerge during complex procedure preparation (1,4).

13.2. Patient-Specific Implant Design and 3D Printing

The integration of AI with additive manufacturing is another major step forward. Patient-specific implants can now be designed from high-resolution anatomical data, achieving a near-micrometric fit that was previously impossible with off-the-shelf options. This level of customization improves biomechanical compatibility and reduces complications such as implant malposition, loosening, or foreign body reactions (3,5). Combining computational modeling with 3D printing allows surgeons to produce highly individualized reconstructive solutions, particularly valuable in craniofacial and orthopedic applications where anatomical precision is critical (3).

13.3. Augmented Reality in the Operating Room

Augmented reality is reshaping intraoperative navigation by enhancing the surgeon's visual field in a fundamentally new way. By projecting preoperative imaging data directly onto the surgical site, AR systems allow critical structures — nerves, blood vessels, tumor margins — to be visualized in real time without physical exposure (3,4). This creates a kind of guided vision that improves spatial awareness during complex dissections and reconstructions, supporting more accurate navigation, particularly in anatomically dense or high-risk regions.

13.4. Digital Twins and Predictive Surgical Modeling

Perhaps the most forward-looking development in surgical planning is the concept of the digital twin: a dynamic, high-resolution virtual replica of an individual patient that integrates anatomical, physiological, and biomechanical data. Surgeons can use these models to simulate and test different procedural strategies in a risk-free digital environment before ever entering the operating room (1,4). The potential benefits are significant — improved surgical preparedness, reduced intraoperative uncertainty, and the ability to rehearse personalized procedures in ways that simply weren't possible before.

14. Conclusion

Artificial intelligence is no longer an emerging technology in plastic surgery — it is becoming part of the fabric of how the discipline operates. From advanced image analysis

to machine-learning-based decision support, these systems are helping to standardize clinical workflows and reduce variability in surgical planning (17). In both reconstructive and aesthetic procedures, AI-driven tools are increasingly relied upon to analyze complex datasets and support surgeons in tailoring interventions to individual patients, with meaningful improvements in outcomes (18).

At the same time, it is worth keeping in mind that data alone does not define good surgical practice. The core of plastic surgery remains clinical experience, aesthetic judgment, and the kind of nuanced understanding that takes years to develop. As technology becomes more deeply embedded in practice, the ethical and human dimensions of care need to remain front and center (19). Real progress depends on maintaining a thoughtful balance between algorithmic guidance and the surgeon's own expertise, intuition, and sense of responsibility.

Ultimately, AI is best understood not as a replacement for the surgeon, but as an evolving partner one that enhances precision, supports better decisions, and expands what is technically possible. Used well, it has the potential to elevate the art and science of surgical practice without redefining what makes that practice fundamentally human (20).

15. References

1. Goodfellow, I., Bengio, Y., & Courville, A. (2016). Deep learning. MIT Press.
2. World Health Organization. (2021). Ethics and governance of artificial intelligence for health. WHO.
3. Topol, E. J. (2019). High-performance medicine: The convergence of human and artificial intelligence. Nature Medicine, 25(1), 44–56. https://doi.org/10.1038/s41591-018-0300-7
4. Yu, K. H., Beam, A. L., & Kohane, I. S. (2018). Artificial intelligence in healthcare. Nature Biomedical Engineering, 2(10), 719–731. https://doi.org/10.1038/s41551-018-0305-z
5. Hashimoto, D. A., Rosman, G., Rus, D., & Meireles, O. R. (2018). Artificial intelligence in surgery: Promises and perils. Annals of Surgery, 268(1), 70–76. https://doi.org/10.1097/SLA.0000000000002693
6. Meskó, B., & Görög, M. (2020). A short guide for medical professionals in the era of artificial intelligence. NPJ Digital Medicine, 3, Article 126. https://doi.org/10.1038/s41746-020-00333-z
7. Brunton, G., Arshad, Z., Al-Azzawi, M., Ahmed, S., Ali, R., Jawad, M. A., & Kyriacou, H. (2022). Artificial intelligence and machine learning in plastic surgery: A systematic review. Aesthetic Plastic Surgery, 46(5), 2335–2347. https://doi.org/10.1007/s00266-021-02668-5
8. He, J., Baxter, S. L., Xu, J., Xu, J., Zhou, X., & Zhang, K. (2019). The practical implementation of artificial intelligence technologies in medicine. Nature Medicine, 25(1), 30–36. https://doi.org/10.1038/s41591-018-0307-0
9. Esteva, A., Robicquet, A., Ramsundar, B., Riocheau, V., DeGrave, J., Howard, K., & Dean, J. (2019). A guide to deep learning in healthcare. Nature Medicine, 25(1), 24–29. https://doi.org/10.1038/s41591-018-0316-z
10. Liu, Y., Jain, A., Eng, C., Way, D. H., Lee, K., Bui, P., & Kanada, K. (2020). A deep learning system for differential diagnosis of skin diseases. Nature Medicine, 26(6), 900–908. https://doi.org/10.1038/s41591-020-0842-3
11. El Masry, M., Rahman, M. M., Gnyawali, S. C., Smeenge, T., Xue, Y., Hartman, B. C., & Sen, C. K. (2026). Automated Non-Invasive Burn Diagnostic System for Healthcare using Artificial Intelligence: AMBUSH-AI. Annals of Surgery. Advance online publication. https://doi.org/10.1097/SLA.0000000000007029
12. Stein, M. J., & Rohrich, R. (2025). Artificial intelligence and postoperative monitoring in plastic surgery. Plastic Surgery, 33(2), 312–317. https://doi.org/10.1177/22925503231210873
13. Liu, X., Faes, L., Kale, A. U., Wagner, S. K., Fu, D. J., Bruynseels, A., Mahendiran, T., Moraes, G., Shamdas, M., Kern, C., Ledsam, J. R., Schmid, M. K., Balaskas, K., Topol, E. J., Bachmann, L. M., Keane, P. A., & Denniston, A. K. (2019). A comparison of deep learning performance against health-care professionals in detecting diseases from medical imaging: A systematic review and meta-analysis. The Lancet Digital Health, 1(6), e271–e297. https://doi.org/10.1016/S2589-7500(19)30123-2
14. Rajkomar, A., Dean, J., & Kohane, I. (2019). Machine learning in medicine. New England Journal of Medicine, 380(14), 1347–1358. https://doi.org/10.1056/NEJMra1814259
15. Esteva, A., Kuprel, B., Novoa, R. A., Ko, J., Swetter, S. M., Blau, H. M., & Thrun, S. (2017). Dermatologist-level classification of skin cancer with deep neural networks. Nature, 542(7639), 115–118. https://doi.org/10.1038/nature21056

16. Satava, R. M. (2002). Surgical robotics: The early chronicles: A personal historical perspective. Surgical Laparoscopy, Endoscopy & Percutaneous Techniques, 12(1), 6–16. https://doi.org/10.1097/00129689-200202000-00002
17. Liu, Y., Zhang, D., Cui, Y., Wang, C., & Wang, X. (2023). Deep learning-based burn wound image classification: A systematic review. Burns & Trauma, 11, tkad012. https://doi.org/10.1093/burnst/tkad012
18. Niazi, Z. B., Essex, T. J., Papini, R., Scott, D., McLean, N. R., & Black, M. J. (1993). New laser Doppler scanner, a valuable adjunct in burn depth assessment. Burns, 19(6), 485–489. https://doi.org/10.1016/0305-4179(93)90003-X
19. Jaskille, A. D., Shupp, J. W., Jordan, M. H., & Jeng, J. C. (2009). Critical review of burn depth assessment techniques: Part I. Historical review. Journal of Burn Care & Research, 30(6), 937–947. https://doi.org/10.1097/BCR.0b013e3181bfb65a
20. Jiang, F., Jiang, Y., Zhi, H., Dong, Y., Li, H., Ma, S., Wang, Y., Dong, Q., Shen, H., & Wang, Y. (2017). Artificial intelligence in healthcare: Past, present and future. Stroke and Vascular Neurology, 2(4), 230–243. https://doi.org/10.1136/svn-2017-000101

CHAPTER 43

Reimagining Dermatology Through Artificial Intelligence: Experimental Foundations, Clinical Applications, and Ethical Considerations

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1. Introduction

Artificial intelligence (AI) emerged with the development of advanced computer systems capable of performing tasks that require human intelligence. AI uses algorithms and computational models to learn from data, recognize patterns, and make decisions. The concept of AI dates back to the 1950s and was first articulated by the British mathematician Alan Turing, who posed the question, "Can machines think?" In the 1970s, AI became integrated into the life sciences and began to be applied in the healthcare sector. (1,2).

Dermatology is a medical specialty in which visual assessment plays a central role in diagnostic and therapeutic decision-making. The skin is not merely a superficial organ but a multilayered biological structure extending from the epidermis to the dermis, vascular networks and the cellular microenvironment. This complex architecture requires imaging techniques beyond naked-eye examination. The morphological features of skin lesions, their distribution patterns, color variations and temporal changes are fundamental to clinical evaluation in Dermatology. Therefore, imaging modalities are critically important for early diagnosis, differential diagnosis, and monitoring treatment response (3,4).

2. Artifical Intelligence and Dermatology

The early 2000s marked a significant period for the application of AI in Dermatology. During this time, researchers began to develop and explore machine learning algorithms for dermatologic use. Artificial neural networks (ANNs) have since been developed for various medical applications. In Dermatology, ANNs are primarily used to differentiate benign from malignant pigmented lesions in vivo (5).

Dermatologic telemedicine relies on AI-supported image recognition for diagnostic confirmation and screening. AI applications facilitate the classification of skin lesions and also play a role in Dermatopathology, medical metadata analysis, prognostic prediction and biomarker identification (6).

In recent years, Dermatologic imaging techniques have undergone substantial technical and digital advancements. High-resolution digital cameras, dermoscopy devices, confocal microscopy and optical coherence tomography have enabled increasingly detailed visualization of skin lesions. Although these developments have significantly improved clinical practice, they have also generated large volumes of visual data. This progress has created a favorable environment for the integration of AI (7).

AI particularly through machine learning and deep learning–based approaches, has emerged as a natural complement to Dermatologic imaging (8). The primary promise of AI is not to exceed the perceptual limits of the human eye, but to support, objectify, and standardize clinical decision-making. Consequently, the integration of AI into Dermatologic imaging represents not only a technological advancement but also a significant transformation in clinical reasoning (9).

Dermatology is the medical specialty concerned with diseases of the skin, hair, and nails. The use of AI aims to facilitate the diagnosis of Dermatologic conditions. With its growing popularity and widespread adoption, AI has increasingly transformed the delivery of healthcare services (10).

3. Artificial Intelligence Tools

Tibot is an AI application developed to analyze Dermatological conditions. In this and similar applications, results are obtained by uploading a photograph of the lesion and answering specific pathology-related questions. These platforms provide guidance on when to consult a physician, how to schedule hospital appointments, and offer information about medications and skin care products. They may also include online consultations with specialists, personalized treatment plans, and appointment reminders. Additionally, users can access a skin disease dictionary that covers the etiology, symptoms, and treatment options of various Dermatological conditions (10).

AI and its applications can generate and process medical images, provide interpretations, produce reports, and monitor disease progression. These capabilities offer significant support to healthcare professionals. Furthermore, AI provides academic advantages such as data integration, storage, and advanced data analysis (11).

4. Deep Learning

Deep learning is a subfield of machine learning that encompasses ANNs and representation learning techniques. Prominent deep learning architectures include recurrent neural networks (RNNs), Kohonen self-organizing neural networks (KNNs), generative ad-

versarial networks (GANs) and convolutional neural networks (CNNs). Among these, CNNs—a specialized subclass of ANNs are particularly well suited for image processing and detection tasks nda re therefore widely applied in Dermatology, Pathology, and Radiology. Within the dermatologic research community, commonly utilized CNN architectures include GoogleNet, Inception-V3, Inception-V4, ResNet, Inception-ResNet V2, and DenseNet (12).

In recent years, transfer learning has been increasingly applied to the classification of a wide range of skin lesions. Transfer learning enables a model developed for one task to be adapted and fine-tuned for a different but related task. This approach is particularly advantageous when large, well-annotated medical image datasets are unavailable. In situations where lesion images are limited, models are typically pre-trained on large-scale natural image datasets and subsequently fine-tuned using curated dermoscopic image datasets to improve diagnostic accuracy and specificity. This methodology enhances overall performance in medical image analysis. Singhal et al. demonstrated the applicability of transfer learning techniques for skin lesion detection using the ISIC 2018 dataset (13).

5. Multimodal machine learning

AI encompasses a broad spectrum of technologies that enable machines to simulate human-like intelligence, problem-solving abilities, and cognitive functions. Machine learning (ML) is a subfield of AI that generates predictions based on user-input data. ML offers an excellent opportunity to automate medical data analysis and support clinical decision-making processes. Numerous AI strategies based on ML methods have been developed. These strategies generate a final diagnosis based on a range of input features, potentially assisting domain experts in selecting the most appropriate course of action, thereby contributing to faster, more cost-effective and improved patient care (14).

Due to the lack of clarity in the process, deep learning applications have failed to inspire confidence from the outset. Consequently, there are doubts about their applicability to real-life cases . The aim is for new AI models to be more transparent and reliable. Wang S et al. incorporated interpretability modules into CNN models. This enables visual analysis and diagnosis for explanations . Multimodal ML is a new concept. It develops models and correlates information obtained from multiple modalities (15,16).

6. Advanced Imaging Technologies in Dermatology

6.1. Dermoscopy

Dermoscopy is widely regarded as one of the most significant advances in Dermatologic imaging. It is an epiluminescence microscopy technique that utilizes a magnifying optical system in conjunction with a (non-polarized) light source to visualize subsurface morphological structures of the skin, including pigmentation patterns within the epidermis

and superficial dermis. This technique has substantially enhanced diagnostic accuracy, particularly in the assessment of pigmented skin lesions and is extensively employed in the diagnosis of cutaneous malignancies (17).

Despite its considerable diagnostic value, dermoscopy has important limitations, most notably its strong dependence on operator expertise. Accurate interpretation of dermoscopic images requires formal training and substantial clinical experience. Moreover, variability in the evaluation of the same lesion among different dermatologists contributes to interobserver variability, thereby complicating clinical decision-making, especially in borderline or equivocal cases. The integration of AI into dermoscopy has emerged as a response to these challenges. Deep learning–based CNNs, trained on large datasets comprising thousands of dermoscopic images, are capable of transforming visually perceived patterns into quantitative mathematical representations. Diagnostic criteria such as asymmetry, color variegation, structural distribution, and border irregularity can be automatically analyzed by these algorithms. The primary application of AI in dermoscopy is the automated classification of dermoscopic images. These systems are predominantly developed using CNN architectures and have demonstrated high levels of diagnostic accuracy across multiple disease categories, particularly in the differentiation between benign and malignant lesions (18).

Unlike classical dermoscopic algorithms, CNN-based models do not rely on predefined rules. Instead, they automatically identify features such as color distributions, structural asymmetries, border irregularities and dermoscopic patterns through multilayered learning processes. This approach enables the detection of subtle visual cues that may be difficult for the human eye to perceive. However, the performance of CNNs relative to face-to-face evaluations by Dermatologists remains incompletely understood, as many studies report Dermatologist-level diagnostic accuracy under artificial conditions, using carefully curated image datasets and without providing the full range of clinical metadata typically available in real-world clinical and teledermatology settings. Diagnostic accuracy improves when dermatologists have access to close-up images along with limited clinical information such as age, sex, and anatomical location (8,9).

AI can be integrated into smartphone applications to capture images of skin lesions, collect relevant clinical information and generate referrals when appropriate. Many smartphones already support on-device deep learning while maintaining data privacy by retaining health information locally. With the increasing availability of clinical, dermoscopic and smartphone-based images, AI technologies are gaining greater potential to complement Dermatologists' workflows and expand access to early skin cancer detection. High pooled AUROC values indicate that AI tools can meaningfully support the early diagnosis of melanoma and other skin cancers, consistent with landmark demonstrations of deep learning performance in Dermatology (19,20).

Skin cancer represents one of the most common malignancies worldwide, with over 3.4 million cases of non-melanoma skin cancer and more than 325,000 new melanoma diagnoses annually (21). Historically, melanoma screening has relied on clinical examination using established visual assessment methods, particularly the ABCDE

criteria. These criteria focus on five key features of a mole or lesion: asymmetry, border irregularity, color variation, diameter (typically greater than 6 mm) and evolution over time. These features assist clinicians in identifying suspicious lesions that warrant further investigation (22). Although advanced diagnostic tools—including non-invasive imaging devices such as dermoscopes and confocal microscopes—have been developed to enhance melanoma detection accuracy, visual assessment methods remain widely used in patient self-examinations and in primary care settings where advanced imaging devices may not be available. The application of AI to improve the accuracy of visual assessment of pigmented skin lesions using clinical images may contribute to earlier melanoma diagnosis (23). Early detection significantly reduces morbidity and mortality; however, timely access to Dermatological evaluation is unevenly distributed. Many low- and middle-income countries face severe shortages of trained dermatologists, often with fewer than one dermatologist per 100,000 individuals. Even in high-income regions, Dermatology services exhibit substantial urban–rural disparities, leading to delayed diagnoses and excessive reliance on primary care or teledermatology consultations. These structural limitations have driven the development of scalable AI systems capable of supporting lesion assessment outside specialist settings (24).

Currently, skin biopsies and histopathological evaluation remain the gold standard for skin cancer diagnosis . However, confirming all skin lesions via biopsy is impractical due to scarring, time constraints and financial burden. Consequently, various imaging technologies are used to determine biopsy necessity (25). The use of AI in detecting melanoma and non-melanoma skin cancers appears promising for identifying suspicious lesions and complementing traditional diagnostic methods. AI-based image analysis combined with non-invasive imaging techniques such as dermoscopy and confocal microscopy provides rapid preliminary assessments that may be more accessible, particularly in resource-limited settings or telemedicine environments. By automating lesion classification and prioritization, AI can facilitate large-scale screening and help identify lesions requiring further evaluation, potentially reducing unnecessary biopsies (23).

AI applications in dermoscopy are not limited to benign–malignant differentiation. Algorithms can also successfully recognize dermoscopic patterns associated with seborrheic keratosis, dermatofibroma, vascular lesions, and inflammatory dermatoses. Some systems additionally provide quantitative malignancy risk scores, enhancing transparency in clinical decision-making. One of the most significant clinical contributions of dermoscopy–AI integration is the improvement of triage processes. In primary care or teledermatology settings, AI-assisted dermoscopic analysis can help identify high-risk lesions at an early stage. In the future, these systems are expected to extend beyond single-image analysis to include longitudinal evaluation of lesion evolution over time. Such approaches are likely to further enhance the power of dermoscopy in the early detection of melanoma. The integration of dermoscopy and artificial intelligence represents a major paradigm shift in dermatological diagnosis. AI is not intended to replace dermoscopic evaluation by dermatologists but rather to support clinical expertise and improve diagnostic accuracy. With the resolution of ethical, technical, and methodological challenges, the combined

use of dermoscopy and AI is poised to become a standard component of dermatological practice.

Over the years, various non-invasive imaging techniques have emerged with the aim of improving early diagnostic accuracy and reducing unnecessary biopsies. Microscopy-based techniques such as confocal scanning laser microscopy and multiphoton laser scanning microscopy represent some of the preferred alternatives to dermoscopy equipment (26,27).

6.2. Reflectance Confocal Microscopy (RCM)

Reflectance confocal laser scanning microscopy (RCM) is one of the most advanced non-invasive imaging modalities in Dermatology, enabling cellular-level visualization of the skin. It allows near–histopathological resolution assessment of the epidermis and superficial dermis. RCM provides significant clinical contributions, particularly in the evaluation of melanocytic lesions, basal cell carcinoma, and surgical margin delineation. RCM operates using a laser with a wavelength of 830 nm, which delivers point-focused light to the tissue surface and detects the backscattered reflected light. This technique enables the acquisition of "optical sections" within the tissue, clearly revealing cellular details. Micromorphological features such as epidermal keratinocytes, clusters of melanocytes, inflammatory cell infiltrates, and dermal papillary structures can be identified on RCM images (28). Each RCM image covers an area of approximately 500 × 500 μm and consists of grayscale data, generating a highly complex dataset that is difficult to interpret directly with the human eye. Consequently, RCM image interpretation requires expert-level training and is associated with a steep learning curve. Similar to histopathology, RCM provides a non-invasive visualization of skin architecture and individual cells down to a depth of approximately 200–250 μm from the skin surface. Although dermoscopy remains the most widely used method for skin cancer screening, RCM has demonstrated significantly higher diagnostic accuracy in various skin tumors. RCM shows sensitivity and specificity exceeding 70% in skin cancer detection and is also effective in diagnosing and monitoring inflammatory and other dermatological conditions. Furthermore, RCM has been used to map lateral excision margins prior to surgical treatment of skin tumors, increasing the likelihood of complete tumor removal and reducing recurrence rates. When used in combination with dermoscopy, RCM can reduce the number of unnecessary biopsies (29). RCM demonstrates high diagnostic accuracy in cutaneous malignancies, benign neoplasms and inflammatory disorders and has also been employed for monitoring disease progression. In particular, sensitivities and specificities of up to 96% and 88%, respectively, have been reported for melanocytic lesions. For non-melanocytic lesions, sensitivities approaching 100% have been documented (30,31). However, interpreting confocal images is extremely complex. Cellular atypia, architectural irregularities, and tumor structures require a high cognitive load. Confocal microscopy therefore has a steep learning curve and its clinical application has been limited to specialized centers. To date, applications of artificial intelligence in RCM image analysis have primarily focused on assessing mosaic

image quality, identifying the dermoepidermal junction (DEJ) and assisting in the detection and differentiation of various skin tumors. Advances in AI, particularly in deep learning, hold substantial promise for the automated analysis of RCM images. Architectures such as CNNs can model pixel-to-pixel relationships, cellular structural patterns and tissue differentiation in RCM images using mathematical representations . CNNs are trained on large labeled datasets to learn malignancy-associated features in RCM images. During this process, the algorithm creates layers that recognize patterns through pixel-level classification and can identify critical information such as malignant/benign differentiation and inflammation level. This method can automatically capture the micromorphological clues observed by human experts and reduce diagnostic uncertainty (32).

AI can play a critical role in overcoming this fundamental limitation of confocal microscopy. Deep learning algorithms can recognize cellular patterns in confocal images, automatically mark structures associated with malignancy and highlight suspicious areas. This could enable confocal microscopy to reach a wider clinical user base. Moreover, AI can analyze correlations between confocal images and histopathological outcomes, enhancing non-invasive diagnostic accuracy. This approach holds significant potential for reducing unnecessary biopsies and improving patient comfort.

In melanoma diagnosis, RCM offers near-histopathological resolution; however, interpretation difficulty remains a major barrier to routine clinical use . AI applications are actively being developed to address this challenge through automated or semi-automated diagnostic systems (33).

Xie et al. developed deep learning models capable of cell-type differentiation in RCM images, achieving high accuracy in identifying melanocytic cell clusters. Such approaches enable detection of features beyond the perceptual limits of the human eye, further enhancing melanoma diagnosis.Despite these advances, critical data-related challenges persist in the integration of AI with RCM. A major limitation is the lack of sufficiently large, well-annotated RCM datasets. Deep learning models require extensive and heterogeneous datasets to achieve high performance, yet RCM images are often derived from single centers and annotated by a limited number of experts. Additionally, variations in image contrast, inter-device differences, and imaging artifacts hinder algorithm generalizability. Therefore, standardization of RCM data, careful design of preprocessing pipelines and development of multicenter datasets are essential (33,34).

6.3. Optical Coherence Tomography (OCT)

Optical coherence tomography (OCT) is a non-invasive optical imaging technique that provides cross-sectional visualization of tissue microstructure. Initially developed for examining retinal layers in ophthalmology, OCT has recently found applications in Dermatology. OCT offers high-resolution cross-sectional images for assessing the epidermal–dermal junction, tumor invasion depth, stratum corneum thickness and scar tissue analysis .OCT captures the echo delay and intensity of reflected infrared or near-infrared light. It enables real-time imaging of the skin, penetrates to depths of 1–2 mm, and provides a

resolution ranging from 3 to 15 μm (35,36). Based on OCT principles, various advanced devices have been developed to improve accuracy and image quality, including full-field OCT (FF-OCT), vibrational optical coherence tomography (VOCT) and OCT systems combined with near-infrared Raman spectroscopy modules (23).

Traditional OCT interpretation relies on evaluating contrast differences between tissue layers and structures, a process subject to operator experience and subjective judgment. In this context, AI-based image analysis algorithms are increasingly playing a critical role in transforming OCT data into objective, reproducible and clinically meaningful outputs. OCT employs low-coherence interferometry to generate high-resolution tissue cross-sections (10–15 μm), allowing microscopic detail assessment up to millimeter depths. Dermatologic OCT images consist of large volumes of grayscale pixels, encoding structural information ranging from epidermal thickness to dermal papillary architecture (37).

Key challenges in OCT interpretation include limited contrast, noise and artifacts, and observer dependency. AI algorithms aim to address these issues through high-level feature extraction, automated segmentation and lesion classification. OCT images are often affected by speckle noise and artifacts, which can hinder direct analysis. Consequently, deep learning–based denoising techniques, such as convolutional denoising autoencoders, have been applied to effectively reduce speckle noise. This preprocessing step significantly enhances subsequent segmentation and classification performance (38,39).

Segmentation refers to the separation of epidermis, dermis and lesion regions. While traditional methods rely on simple techniques such as intensity thresholding, AI-based architectures such as U-Net can more accurately detect complex textural boundaries in OCT images (40). This segmentation is clinically critical for determining invasive tumor margins and guiding treatment planning.

For tasks such as malignant versus benign lesion classification, CNN architectures can learn high-level features from OCT data and perform accurate classification. These systems may outperform the human eye in detecting subtle textural differences within OCT images. AI-assisted OCT and high-frequency ultrasound (HFUS) imaging enable non-invasive measurement of tumor depth and margins, demonstrating strong correlations with histopathological Breslow thickness ($r = 0.88–0.94$). These approaches show promise for preoperative staging and risk assessment, extending AI applications from diagnostic to prognostic domains. Interpretation of OCT images requires experience, as with other advanced imaging methods. Artificial intelligence-assisted analyses enable the automatic determination of lesion boundaries and disease classification in OCT images. These systems support clinical decision-making processes, particularly in preoperative planning and monitoring non-invasive treatment approaches (41,42).

6.4. High-Frequency Ultrasonography (HFUS)

High-frequency ultrasonography (HFUS) is an important non-invasive imaging modality that enables cross-sectional visualization of the skin and subcutaneous tissues. Unlike

conventional ultrasound, HFUS operates at higher frequencies (10–20+ MHz), allowing higher-resolution imaging of superficial dermal layers. In dermatological practice, HFUS is used for lesion sizing, assessment of inflammatory depth, evaluation of tumor invasion, and monitoring of treatment response. However, HFUS image interpretation requires substantial expertise and is subject to operator-dependent variability. AI-based approaches have therefore emerged as powerful tools for automated HFUS analysis and clinical decision support. HFUS images consist of two-dimensional cross-sectional representations of reflected acoustic signals, encoded as grayscale pixels across tissue depth. These images contain clinically relevant information such as skin layer thickness, echogenicity differences, and tissue heterogeneity. HFUS displays varying echo levels depending on tissue acoustic properties; for instance, adipose tissue typically appears hypoechoic, whereas fibrotic or tumoral structures generate hyperechoic signals . While these differences provide basic morphological cues, speckle noise often obscures lesion boundaries (43,44).

Deep learning–based denoising autoencoder architectures have been applied to reduce speckle noise in HFUS images. CNN-based classification models can then learn high-level features to determine lesion types, such as benign versus malignant or inflammatory versus non-inflammatory conditions. In such tasks, trained CNNs have demonstrated performance comparable to that of clinical dermatologists .In superficial tumors such as basal cell carcinoma (BCC), HFUS can be used to evaluate tumor depth and width. AI-assisted segmentation models can automatically delineate BCC boundaries, improving surgical planning accuracy (37).

In inflammatory dermatoses such as psoriasis and atopic dermatitis, epidermal thickness correlates with disease activity. Automated segmentation and classification models applied to HFUS images enable quantitative assessment of epidermal and dermal changes, providing objective metrics for treatment monitoring (38). For clinical adoption, model interpretability is crucial. Visualization techniques such as Gradient-weighted Class Activation Mapping (Grad-CAM) can show which regions of the HFUS images the model uses in its decision-making process, thereby increasing the clinician's confidence in the model output (45,46).

6.5. Three-Dimensional Total Body Photography (3D TBP)

Standard clinical photography is one of the most widely used imaging methods in dermatology, serving as a fundamental tool for documenting lesion appearance, monitoring disease progression, and evaluating treatment response. However, factors such as lighting, angle, resolution and device variability can affect image quality. AI-based image standardization and automated quality control algorithms help mitigate these limitations. 3D TBP systems typically utilize multiple high-resolution cameras operating simultaneously to capture the entire body surface as a digital model (47). Specialized software integrates these images into a comprehensive digital skin map that stores spatial and morphological information on pigmented lesions, benign nevi, and potentially malignant findings. A major advantage of 3D TBP is the ability to track changes in the same lesion over time

at a pixel-by-pixel level, which is particularly valuable for rapidly evolving lesions such as melanoma. The system can integrate serial whole-body images to generate computable longitudinal follow-up reports. Deep learning algorithms, particularly CNNs, have strong potential for automated lesion detection and classification using 3D TBP data (45). CNNs can identify patterns not explicitly defined by humans, enabling recognition and labeling of lesions as benign or suspicious. In multicenter clinical datasets, CNN models have demonstrated high sensitivity (>90%) and specificity in detecting anomalies among thousands of nevi , with optimization strategies reducing false-positive rates to enhance clinical reliability (48).

AI models are trained on large sets of annotated images, learning parameters such as lesion location, shape, color distribution, and texture. As a result, new 3D TBP datasets can be automatically analyzed for lesion detection and classification. In some studies, AI-based classifiers have achieved accuracy comparable to experienced dermatologists (8).

The primary clinical strength of 3D TBP lies in longitudinal comparison. AI automates this process by quantifying changes in lesion size, color, and shape over time and performing trend analysis. This enables early detection of rapidly evolving lesions, particularly melanoma (47). Early diagnosis is critical in melanoma management, significantly improving survival rates. Integration of 3D TBP with AI allows continuous monitoring of millions of skin points, facilitating early detection of subtle morphological changes. Automated identification of the "E" (evolution) criterion enhances clinical decision-making . In high-risk populations—such as individuals with a family history of melanoma or numerous dysplastic nevi—AI-assisted 3D TBP provides substantial advantages by automating longitudinal evaluation of thousands of lesions, minimizing human error, and enabling early intervention (23).

6.6. Hyperspectral Imaging (HSI)

Hyperspectral imaging (HSI) is an optical imaging technique that extends beyond conventional RGB imaging by converting each pixel into spectral data across numerous narrow wavelength bands. By measuring light reflectance across hundreds of spectral bands (e.g., 490–1600 nm), HSI enables characterization of tissue chemistry and structure, allowing not only morphological but also biochemical differentiation (49).

In Dermatology, HSI captures spectral signatures that extend beyond surface appearance, enabling more precise differentiation of pigmentation, inflammatory changes, malignant tumors and benign lesions. Parameters such as pigmentation, microvascularization, tissue oxygenation, and other molecular features can be assessed using HSI. HSI has recently emerged as one of the most promising complementary techniques for early melanoma detection. Studies demonstrate that combining HSI with machine learning significantly improves discrimination between melanoma and benign lesions. Both traditional machine learning classifiers and deep learning approaches applied to hyperspectral signatures have achieved high diagnostic performance across multiple skin cancer subtypes (50).

7. Ethical, Methodological, and Technical Limitations

The ethical conditions regarding the use of AI in Dermatology are still being debated in the literature. Practical concerns about AI require concrete examples. The issue of patient privacy breaches is paramount. In 2021, a teledermatology application in the United Kingdom caused a stir by sharing case image data without sufficient user consent. This case was investigated by the Information Commissioner's Office (ICO). The application was suspended for several months, significantly restricting patients' remote access to dermatological consultations (51). Despite the substantial advantages offered by AI in dermatologic imaging, important challenges remain, including data bias, lack of algorithmic transparency, and legal accountability. Datasets that inadequately represent diverse skin types increase the risk of diagnostic inequities. Therefore, ethical principles, regulatory frameworks, and clinician oversight are indispensable for the safe integration of AI systems into clinical practice.

8. Future Perspectives

In the future, deeper integration of imaging modalities and AI in Dermatology is anticipated. Explainable AI models, real-time clinical decision support systems, and longitudinal patient monitoring will constitute the core development axes of this field. These advances have the potential to significantly enhance diagnostic accuracy, efficiency, and personalization in dermatologic care.

9. References

1. Rundle, C. W., Hollingsworth, P., Dellavalle, R. P. (2021). Artificial intelligence in dermatology. Clinics in Dermatology, 39(4), 657–666. doi:10.1016/j.clindermatol.2021.05.007
2. Buchanan, B. G., Shortliffe, E. H. (1984). Rule-based expert systems: The MYCIN experiments of the Stanford heuristic programming project. Boston, MA: Addison-Wesley.
3. Proksch, E., Brandner, J.M., Jensen, J.M. (2008). The skin: an indispensable barrier. Exp Dermatol, 17(12), 1063–1072. doi: 10.1111/j.1600-0625.2008.00786.x
4. Marghoob, A. A., Braun, R. P., Kopf, A. W. (2013). Atlas of dermoscopy (2nd ed.). London: Informa Healthcare.
5. Renders, J. M., Simonart, T. (2009). Role of artificial neural networks in dermatology. Dermatology, 219, 102–104. doi:10.1159/000228328
6. Li, Z., Koban, K. C., Schenck, T. L., Giunta, R. E., Li, Q., & Sun, Y. (2022). Artificial intelligence in dermatology image analysis: Current developments and future trends. Journal of Clinical Medicine, 11(22), 6826. doi:10.3390/jcm11226826
7. Marchetti, M.A., Wang, S.Q., Dusza, S.W. (2020). Total body photography and digital dermoscopy in the early detection of melanoma. JAMA Dermatol, 156(2), 135–143. doi: 10.1001/jamadermatol.2019.3334
8. Esteva, A., Kuprel, B., Novoa, R.A. (2017). Dermatologist-level classification of skin cancer with deep neural networks. Nature, 542(7639), 115–118. doi:10.1038/nature21056
9. Haenssle, H.A., Fink, C., Schneiderbauer, R., (2018). Man against machine: diagnostic performance of a deep learning convolutional neural network for dermoscopic melanoma recognition. Ann Oncol, 29(8), 1836–1842. doi: 10.1093/annonc/mdy166
10. Aggarwal, P. (2019). Data augmentation in dermatology image recognition using machine learning. Skin Research and Technology, 25, 815–820. doi:10.1111/srt.12735
11. Jakhar, D., Kaur, I. (2019). Artificial intelligence, machine learning and deep learning: Definitions and differences. Clinical and Experimental Dermatology, 45, 131–132. doi:10.1111/ced.14029
12. Alzubaidi, L., Zhang, J., Humaidi, A. J., Al-Dujaili, A., Duan, Y., Al-Shamma, O., …Farhan, L. (2021). Review of deep learning: Concepts, CNN architectures, challenges, applications, future directions (Vol. 8). Cham, Switzerland: Springer International Publishing.

13. Singhal, A., Shukla, R., Kankar, P. K., Dubey, S., Singh, S., Pachori, R. B. (2020). Comparing the capabilities of transfer learning models to detect skin lesion in humans. Proceedings of the Institution of Mechanical Engineers Part H: Journal of Engineering in Medicine, 234, 1083–1093. doi:10.1177/0954411920944216
14. Hogarty, D.T., Su, J.C., Phan, K., Attia, M., Hossny, M., Nahavandi, S., …Yazdabadi, A. (2020). Artificial Intelligence in Dermatology-Where We Are and the Way to theFuture: A Review. Am J Clin Dermatol, 21, 41–47. doi: 10.1007/s40257-019-00462-6
15. von Eschenbach WJ. (2021). Transparency and the black box problem: why we do not trust AI. Philos Technol, 34(4), 1607–22. doi: 10.1007/s13347-021 00477-0
16. Wang ST, Yin YQ, Wang DJ, Wang YZ, Jin YC. (2022). Interpretability-based multimodal convolutional neural networks for skin lesion diagnosis. IEEE Trans Cybern, 52(12):12623–37. doi: 10.1109/TCYB.2021.3069920
17. Vestergaard, M.E., Macaskill, P., Holt, P.E., Menzies, S.W. (2008). Dermoscopy compared with naked eye examination for the diagnosis of primary melanoma: A meta-analysis of studies performed in a clinical setting. BMJ, 336(7641), 874–877. doi: 10.1136/bmj.39537.632650.25
18. Rosendahl, C., Tschandl, P., Cameron, A., Kittler, H. (2011). Diagnostic accuracy of dermatoscopy for melanocytic and non-melanocytic pigmented lesions. British Journal of Dermatology, 165(6), 1251–1259. doi: 10.1111/j.1365-2133.2011.10542.x
19. Freeman, K., Dinnes, J., Chuchu, N., Takwoingi, Y., Bayliss, S.E., Matin, R.N. (2020) Algorithm based smartphone apps to assess risk of skin cancer inadults: systematic review of diagnostic accuracy studies. BMJ, 368, 127. doi: 10.1136/bmj.m127
20. Zbrzezny, A.M., Krzywicki, T. (2025). Artificial intelligence in dermatology: A review of methods, clinical applications, and perspectives. Appl Sci, 15:7856. doi: 10.3390/app15147856.
21. Daneshjou, R., Vodrahalli, K., Novoa, R.A., Jenkins, M., Liang, W., Rotemberg, V., …Gevaert O., (2022). Disparities in dermatology AI performance on a diverse, curated clinical image set. Sci Adv, 8, 6147. doi: 10.1126/sciadv.abq6147.
22. Duarte, A.F., Sousa-Pinto, B., Azevedo, L.F., Barros, A.M., Puig, S., Malvehy, J., …, Correia, O. (2021). Clinical ABCDE rule for early melanoma detection. Eur J Dermatol, 31:771–778. doi: 10.1684/ejd.2021.4171.
23. Mendi, İ.B., Köse, K., Fleshner, L., Adam, R., Safai, B., Farabi, B., Atak, M.F. (2024). Melanomun İnvaziv Olmayan Yöntemlerle Tespitinde Yapay Zeka. Basel, 14(12):1602. doi: 10.3390/life14121602.
24. Adamson, A.S., Smith, A. (2018). Machine learning and health care disparities in dermatology. JAMA Dermatol, 154, 1247–1248. doi:10.1001/jamadermatol.2018.2348.
25. Jones, S., Henry, V., Strong, E., Sheriff, S.A., Wanat, K., Kasprzak, J., …Stadler M. (2023) Clinical Impact and Accuracy of Shave Biopsy for InitialDiagnosis of Cutaneous Melanoma. J Surg Res, 286, 35–40. doi:10.1016/j.jss.2022.12.042
26. Tschandl, P., Codella, N., Akay, B.N., Argenziano, G., Braun, R.P., Cabo, H. (2019). Comparison of the accuracy of human readers versus machine-learning algorithms for pigmented skin lesion classification: An open, web-based, international, diagnostic study. The Lancet Oncology, 20(7), 938-947. doi: 10.1016/S1470-2045(19)30333-X
27. Finnane, A., Janda, M., Soyer, H.P. (2017). Teledermatology for the diagnosis and management of skin cancer: A systematic review. British Journal of Dermatology, 176(4), 904–913. doi:10.1001/jamadermatol.2016.4361
28. Rajadhyaksha, M., González, S., Zavislan, J.M., Anderson, R.R., Webb, R.H. (1999) In vivo confocal scanning laser microscopy of human skin II: advances in instrumentation and comparison with histology. J Invest Dermatol, 113(3), 293–303. doi: 10.1046/j.1523-1747.1999.00728.x
29. Mazzoni, L., Donati, M., Gori, A. (2018). Reflectance confocal microscopy learning curve in dermatology. Dermatol Pract Concept, 8(3), 145–150. doi: 10.5826/dpc.0803a05
30. Levine, A., Markowitz, O. (2018). Introduction to reflectance confocal microscopy and its usein clinical practice. JAAD Case Rep, 4, 1014–1023. doi: 10.1016/j.jdcr.2018.09.019.
31. Mehrabi, J.N., Baugh, E.G., Fast, A., Lentsch, G., Balu, M., Lee, B.A. (2021). A clinicalperspective on the automated analysis of reflectance confocal microscopy in dermatology. Lasers Surg Med, 53,1011–1019. doi: 10.1002/lsm.23376.
32. Malciu, A.M., Lupu, M., Voiculescu, V.M. (2022). Artificial Intelligence-Based Approaches to Reflectance Confocal Microscopy Image Analysis in Dermatology J Clin Med, 11(2), 429. doi: 10.3390/jcm11020429
33. Xie, F., Fan, H., Li, Y. (2019). Deep learning-based cell classification in reflectance confocal microscopy images. Med Image Anal, 57, 1–12. doi:10.1016/j.media.2019.06.007
34. Garcia-Garcia, B., Pedraza, A., Perez-Sala, X. (2021) Automated analysis of reflectance confocal microscopy images using deep learning. IEEE Trans Med Imaging, 40(4), 1038–1047. doi:10.1109/TMI.2020.3047073
35. Gambichler, T., Jaedicke, V., Terras, S. (2011). Optical coherence tomography in dermatology: Technical and clinical aspects. Arch Dermatol Res, 303, 457–473. doi:10.1007/s00403-011-1152-x.
36. Sattler, E., Kästle, R., Welzel, J. (2013). Optical coherence tomography in dermatology. J Biomed Opt, 18, 061224. doi: 10.1117/1.JBO.18.6.061224.
37. Farrokhi, F., Soroushmehr, S.M.R., Najarian, K. (2020). Automated skin lesion analysis in optical coherence tomography using deep learning. IEEE Access, 8, 199030–199042. doi: 10.1109/ACCESS.2020.3035206
38. Zhang, J., Song, H., Ma, X. (2021). Deep learning-based automatic analysis of skin optical coherence tomography images. Medical Physics, 48(7), 3968–3980. doi:10.1002/mp.14943
39. Yin, X., Zhang, J., Wang, Y. (2019). Speckle noise reduction in optical coherence tomography images using deep autoencoder networks. IEEE Transactions on Medical Imaging, 38(9), 1–12. doi:10.1109/TMI.2019.2899837
40. Ronneberger, O., Fischer, P., Brox, T. (2015). U-Net: Convolutional networks for biomedical image segmentation. In: Proceedings of the International Conference on Medical Image Computing and Computer-Assiste Intervention (MICCAI). Munich, Germany; p. 234–241. doi:10.1007/978-3-319-24574-4_28

41. Karim, M.A.M., Rahman, T., Ghazali, A. (2020). Automated analysis of optical coherence tomography images using deep learning for skin cancer detection. Computerized Medical Imaging and Graphics, 80, 101675. doi:10.1016/j.compmedimag.2019.101675
42. Górecki, S., Tatka, A., Brusey, J. (2025). Melanom Tanısında Yapay Zeka ve Yeni Teknolojiler: Anlatısal Bir İnceleme. Basel, 17(24), 3896. doi: 10.3390/cancers17243896
43. Wortsman, X. (2012). Atlas of High-Frequency Ultrasound of Dermatologic Lesions. Springer.
44. Park, S.H., Kim, K.S., Ko, K.H. (2017). High-frequency ultrasonography in dermatology: Basic principles and clinical applications. Clinics in Dermatology, 35(5), 1–10.
45. Liu, Y., Pan, Z., Tan, J. (2020). Deep learning models for high-frequency ultrasound dermatological image classification. Medical Image Analysis, 64, 101741. doi:10.1016/j.media.2020.101741
46. Selvaraju, R.R., Cogswell, M., Das, A. (2017) Grad-CAM: Visual explanations from deep networks via gradient-based localization. In: Proceedings of the IEEE International Conference on Computer Vision (ICCV), 618–626. doi:10.1109/ICCV.2017.74
47. Bafounta, M.L., Beauchet, A., Grangé, F. (2019). Three-dimensional total-body photography in dermatology: accuracy and clinical utility. J Eur Acad Dermatol Venereol, 33(7), 1231–1238. doi:10.1111/jdv.15500
48. Wilding, C.P., Menzies, S.W., Swetter, S.M. (2019). Machine learning algorithms for melanoma risk prediction and diagnosis. Lancet Digit Health, 1(5), 245–254. doi:10.1016/S2589-7500(19)30083-3
49. Krzysztof, W., Agnieszka, W. (2025).Hyperspectral Imaging System Applications in Healthcare. Electronics, 14 (23), 4575. doi: 10.3390/electronics14234575
50. Lin, T.L., Mukundan, A., Karmakar, R., Avala, P., Chang, W.Y., Wang, H.C. (2025) Hyperspectralimaging for enhanced skin cancer classification using machine learning. Bioengineering, 12, 755. doi: 10.3390/bioengineering12070755.
51. Powles, J., & Hodson, H. (2017). Google DeepMind and healthcare in an age of algorithms. Health and Technology, 7, 351–367. doi:10.1007/s12553-017-0179-1

CHAPTER 44

AI-Assisted Ultrasonography in Adnexal Masses: Clinical Prediction of Preoperative Malignancy Risk

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1. Introduction

A 40-year-old woman presents with an incidental unilateral cystic adnexal mass measuring 8 cm in its longest axis. The lesion demonstrates irregular contours, four papillary projections, multiple septations, and mildly increased Doppler vascular flow. No ascites is detected. Serum CA125 is 60 U/mL. She is asymptomatic.

The estimated malignancy risk is likely below 10%. Yet the management decision remains complex. Surgical intervention may result in overtreatment and unnecessary morbidity. Surveillance may expose the patient to anxiety related to delayed diagnosis. In daily clinical practice, clinicians internalize probabilistic reasoning derived from cumulative experience. However, such reasoning is rarely translated into transparent, reproducible, and quantitatively structured risk communication. Subtle variations in language may unintentionally influence patient perception and subsequent management decisions. This highlights the need for objective, reproducible, and workflow-integrated tools for estimating malignancy risk.

Artificial intelligence (AI)–assisted ultrasonography represents a potential evolution in adnexal mass assessment, not as a replacement for clinical judgment, but as a structured probabilistic support system embedded within routine imaging practice.

2. Clinical Uncertainty In Adnexal Mass Evaluation

Adnexal mass assessment is inherently probabilistic. The principal objective is to differentiate benign from malignant pathology while minimizing both overtreatment and delayed oncologic referral. Overcalling may lead to unnecessary surgery and a healthcare burden.

Undertriage may delay appropriate oncologic management. These opposing risks are influenced by operator experience, cognitive bias, and heuristic reasoning.

Although experienced clinicians often approximate statistical likelihood intuitively, intuition does not equate to reproducible risk modeling. Interobserver variability in the description of adnexal morphology, including papillary projections, septal thickness, and vascularity, has been well documented (1,2). Even structured systems do not eliminate variability entirely.

3. Established Risk Models And Their Structural Limitations

3.1 Risk Of Malignancy Index (RMI)

The Risk of Malignancy Index integrates ultrasound features, menopausal status, and CA125 levels (3). While widely implemented, its sensitivity declines in early-stage disease and in premenopausal populations.

3.2 ADNEX Model (IOTA Group)

The ADNEX model introduced multiclass risk prediction, differentiating benign, borderline, early invasive, advanced invasive, and metastatic tumors (4). External validation demonstrates strong discrimination, yet application requires structured data entry and computational support.

3.3 O-RADS Ultrasound Risk Stratification

O-RADS provides standardized terminology and risk-based management recommendations (5). It is imaging-dominant and workflow-compatible. However, operator-dependent variability in acquisition and interpretation persists (6,7).

3.4 Multivariate Biomarker Panels (OVA1 And Overa)

Multivariate index assays such as OVA1 and its second-generation iteration Overa (OVA2) combine CA125 with additional serum biomarkers to generate algorithm-based malignancy risk scores. Unlike morphology-based systems, these assays represent biologically driven stratification tools primarily designed to optimize referral to gynecologic oncology services.

While demonstrating high sensitivity, they are dependent on proprietary platforms and operate independently of real-time imaging acquisition. Their existence introduces an important conceptual question: Should AI-assisted adnexal mass evaluation remain imaging-dominant, or evolve into multimodal systems integrating serum biomarkers and clinical variables? This question remains unresolved and represents a central design consideration for future AI architectures.

4. Operator Dependency In Ultrasonography

Ultrasonography remains intrinsically operator-dependent. Morphologic assessment, Doppler grading, lesion segmentation, and even acquisition plane selection vary between examiners (6,7).Interobserver agreement in identifying papillary projections and grading vascularity is moderate rather than absolute (6). Consequently, malignancy risk categorization may differ even among experienced clinicians evaluating identical lesions. Standardized lexicons structure interpretation; however, acquisition heterogeneity remains a critical limitation.

5. Artificial Intelligence In Medical Imaging: Translational Lessons From Radiology

AI integration in radiology has progressed rapidly. Deep learning systems have demonstrated performance comparable to expert radiologists in mammography screening and chest radiograph interpretation (8,9). Importantly, these systems function as decision-support tools rather than autonomous diagnostic authorities. FDA-cleared AI systems are embedded within clinical workflows to enhance sensitivity, reduce variability, and improve documentation standardization (10).

Three translational lessons emerge:
1. Workflow integration determines adoption.
2. AI augments rather than replaces clinician expertise.
3. Acquisition quality control is as important as interpretive enhancement.

These principles are directly applicable to gynecologic ultrasonography.

6. AI-Assisted Ultrasonography In Adnexal Masses

AI integration should be conceptualized across two domains: acquisition augmentation and interpretation augmentation.

6.1 AI-Augmented Image Acquisition

An instructive parallel exists in intraoral digital scanners widely used in dentistry. During scanning, clinicians move a handheld device across dental surfaces while embedded software simultaneously evaluates data completeness. Missing regions are highlighted in real time, geometric inconsistencies are detected, and users are prompted to correct incomplete acquisition. The final dataset is standardized before further analysis.

In transvaginal ultrasonography, AI-embedded systems could similarly:
- Verify that mandatory imaging planes are captured
- Automatically segment lesion boundaries

- Quantify papillary projections objectively
- Measure Doppler vascular density quantitatively
- Classify overall image adequacy before reporting

For example, the distinction between three and four papillary projections may alter risk categorization. Automated segmentation reduces subjective variability in such assessments.

These capabilities parallel acquisition-quality AI tools already implemented in mammography and thoracic imaging (8,10).

6.2. AI-Augmented Interpretation And Probabilistic Modeling

Deep learning systems, typically based on convolutional neural networks, analyze imaging patterns hierarchically. They extract complex features related to edge irregularity, internal heterogeneity, textural complexity, and vascular distribution.

Unlike rule-based systems, these models learn latent representations from large annotated datasets linked to histopathological outcomes (11,15,17).

AI systems produce probabilistic outputs rather than binary decisions, including:

- Estimated malignancy probability
- Model confidence metrics
- Cross-referenced O-RADS or IOTA category mapping

This probabilistic transparency aligns with the inherently probabilistic nature of clinical decision-making.

6.3. Imaging-Dominant Versus Multimodal AI Architectures

Current clinical practice remains imaging-dominant. Even without AI, morphological systems guide most preoperative decisions (4,5). If AI successfully standardizes acquisition and interpretation, the relative strength of imaging-based frameworks may become even more pronounced.

Multimodal AI systems integrating imaging features, Doppler metrics, serum biomarkers (e.g., CA125 and OVA1-related proteins), and clinical variables remain theoretically attractive. However, they introduce structured data integration complexity and validation challenges.

At present, imaging-dominant AI represents the most pragmatic and scalable pathway. The ultimate architectural trajectory will be determined by prospective outcome-based validation rather than theoretical preference.

7. Ethical And Medicolegal Considerations

Clinical communication often relies on authority rather than explicit probability disclosure. AI-generated probabilistic outputs strengthen transparency and shared decision-

making. Structured documentation of malignancy probability enhances traceability. AI does not eliminate clinician responsibility; it clarifies it. Concerns regarding algorithmic bias and dataset representativeness remain valid. However, radiologic AI experience demonstrates that decision-support integration improves consistency without diminishing professional autonomy (8,16).

AI in adnexal mass evaluation should therefore be viewed as a standardization instrument, not an autonomous authority.

8. Implementation Models

Three models are foreseeable:

1. Stand-alone AI platforms
2. Embedded AI within ultrasound devices
3. Multimodal integrated platforms

Embedded systems offer optimal workflow compatibility.

9. Future Directions

Future research will likely focus on:

- Radiomics-based feature extraction (18)
- Multimodal integration
- Real-time 3D volumetric modeling
- Federated multicenter learning networks

10. Conclusion

Adnexal mass assessment remains characterized by probabilistic uncertainty and operator dependency. Structured risk models have improved standardization but not eliminated variability. AI-assisted ultrasonography offers a realistic pathway toward transparent, reproducible, workflow-integrated malignancy risk estimation. The future lies not in clinician replacement, but in clinician augmentation.

11. References

1. Andreotti, R. F., Timmerman, D., Strachowski, L. M., Froyman, W., Benacerraf, B. R., Bennett, G. L., … Reinhold, C. (2020). O-RADS US risk stratification and management system: A consensus guideline from the ACR Ovarian-Adnexal Reporting and Data System Committee. *Radiology, 294*(1), 168–185. https://doi.org/10.1148/radiol.2019191150
2. Christiansen, F., Epstein, E., Smedberg, E., Åkerlund, M., & Valentin, L. (2021). Ultrasound image analysis using deep neural networks for ovarian tumor classification. *Ultrasound in Obstetrics & Gynecology, 57*(3), 476–484. https://doi.org/10.1002/uog.22145

3. Coleman, R. L., Herzog, T. J., Chan, D. W., Munroe, D. G., Pappas, T. C., Smith, A., … Zhang, Z. (2016). Validation of a second-generation multivariate index assay for malignancy risk of adnexal masses. *Gynecologic Oncology, 141*(1), 35–39. https://doi.org/10.1016/j.ygyno.2016.01.005
4. Esteva, A., Robicquet, A., Ramsundar, B., Kuleshov, V., DePristo, M., Chou, K., … Dean, J. (2019). A guide to deep learning in healthcare. *Nature Medicine, 25*(1), 24–29. https://doi.org/10.1038/s41591-018-0316-z
5. Guerriero, S., Alcázar, J. L., Pascual, M. A., Ajossa, S., Olartecoechea, B., Hereter, L., … Valentin, L. (2018). Transvaginal ultrasound interobserver variability in the diagnosis of adnexal masses. *Ultrasound in Obstetrics & Gynecology, 52*(1), 83–88. https://doi.org/10.1002/uog.19052
6. Jacobs, I., Oram, D., Fairbanks, J., Turner, J., Frost, C., & Grudzinskas, J. G. (1990). A risk of malignancy index incorporating CA125, ultrasound and menopausal status for the accurate preoperative diagnosis of ovarian cancer. *British Journal of Obstetrics and Gynaecology, 97*(10), 922–929. https://doi.org/10.1111/j.1471-0528.1990.tb02448.x
7. Liu, X., Faes, L., Kale, A. U., Wagner, S. K., Fu, D. J., Bruynseels, A., … Denniston, A. K. (2019). A comparison of deep learning performance against health-care professionals in disease detection from medical imaging: A systematic review and meta-analysis. *The Lancet Digital Health, 1*(6), e271–e297. https://doi.org/10.1016/S2589-7500(19)30123-2
8. McKinney, S. M., Sieniek, M., Godbole, V., Godwin, J., Antropova, N., Ashrafian, H., … Shetty, S. (2020). International evaluation of an artificial intelligence system for breast cancer screening. *Nature, 577*(7788), 89–94. https://doi.org/10.1038/s41586-019-1799-6
9. Rizzo, S., Botta, F., Raimondi, S., Origgi, D., Fanciullo, C., Morganti, A. G., & Bellomi, M. (2018). Radiomics: The facts and the challenges of image analysis. *European Radiology Experimental, 2*, 36. https://doi.org/10.1186/s41747-018-0068-z
10. Song, S., Wu, Y., Li, X., Liu, Y., Zhao, Y., & Yang, J. (2022). Radiomics analysis for ovarian tumor differentiation using ultrasound imaging. *European Radiology, 32*(8), 5563–5574. https://doi.org/10.1007/s00330-022-08540-7
11. Timmerman, D., Testa, A. C., Bourne, T., Ferrazzi, E., Ameye, L., Konstantinovic, M. L., … Valentin, L. (2008). Simple ultrasound-based rules for the diagnosis of ovarian cancer. *Ultrasound in Obstetrics & Gynecology, 31*(6), 681–690. https://doi.org/10.1002/uog.5365
12. Topol, E. (2019). High-performance medicine: The convergence of human and artificial intelligence. *Nature Medicine, 25*(1), 44–56. https://doi.org/10.1038/s41591-018-0300-7
13. Ueland, F. R., Desimone, C. P., Seamon, L. G., Miller, R. A., Goodrich, S., Podzielinski, I., … Zhang, Z. (2011). Effectiveness of a multivariate index assay in the preoperative assessment of ovarian tumors. *Obstetrics & Gynecology, 117*(6), 1289–1297. https://doi.org/10.1097/AOG.0b013e31821b5118
14. U.S. Food and Drug Administration. (2023). Artificial intelligence and machine learning in medical devices. https://www.fda.gov
15. Van Calster, B., Van Hoorde, K., Valentin, L., Testa, A. C., Fischerova, D., Van Holsbeke, C., … Timmerman, D. (2014). Evaluating the risk of ovarian cancer before surgery using the ADNEX model. *BMJ, 349*, g5920. https://doi.org/10.1136/bmj.g5920
16. Valentin, L., Ameye, L., Savelli, L., Franchi, D., Leone, F. P. G., Czekierdowski, A., … Timmerman, D. (2011). Interobserver agreement in describing adnexal masses using standardized ultrasound terminology. *Ultrasound in Obstetrics & Gynecology, 37*(4), 476–482. https://doi.org/10.1002/uog.8878
17. Van Holsbeke, C., Daemen, A., Yazbek, J., Holland, T. K., Bourne, T., Mesens, T., … Timmerman, D. (2009). Ultrasound experience and adnexal mass diagnosis. *Ultrasound in Obstetrics & Gynecology, 34*(4), 454–461. https://doi.org/10.1002/uog.6437
18. Zhang, K., Liu, X., Shen, J., Li, Z., Sang, Y., Wu, X., … Zhang, Y. (2021). Deep learning models for ovarian tumor classification using ultrasound images. *Computers in Biology and Medicine, 134*, 104504. https://doi.org/10.1016/j.compbiomed.2021.104504

CHAPTER 45

Beyond Symptoms: Artificial Intelligence and Digital Phenotypes in Psychiatric Diagnosis

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1. Introduction

Unlike most other medical fields, psychiatry chiefly depends on the patient's report and the clinician's clinical observation when making a diagnosis. When we reflect on the contribution of objective measures such as the electrocardiogram in cardiology, glycated hemoglobin (HbA1c) in endocrinology, or laboratory biomarkers in infectious diseases to diagnostic support, we see that psychiatry has a relatively low count of widely accepted biomarkers. Current psychiatric diagnostic systems often use the categorical classification of clusters of clinical symptoms for this reason. However, this approach has important limitations when coping with the temporal variability of mental disorders, individual variations, and their complex associations with environmental contexts (1).

Historically, the foundation of psychiatric assessment has evolved. However, psychiatric symptoms often follow a fluctuating course and may not be fully apparent during clinical interviews. Most clinical assessments rely heavily on retrospective reports from patients. In such circumstances, diagnostic evaluation may be compromised by recall bias, a phenomenon documented in the literature in which an individual's recollection of past experiences is shaped by their current mood state (2). In addition, clinical interviews tend to take place in a time-limited context; therefore, there is limited sampling of the individual's everyday behavior.

With advances in digital technologies and data analysis methods, humans can now be continuously monitored in their daily lives. To overcome these limitations, digital phenotyping has emerged as a method for quantifying human behavior in the wild. This chapter details the theory and algorithm underlying this approach. As a result, the assessment where the psychiatrists can see beyond the examination limits the patient presentation there, but also his behavioral patterns as they occur in everyday life. Digital phenotyping

is not viewed as a replacement for clinical judgment but as a decision-support tool that enriches the clinician's assessment with multi-source data collected over time (2, 3). In this way, a more systematic relationship can be established between clinical observation and real-world data, enabling psychiatric assessment to be considered within a broader behavioral context. As such, a more systematic relationship can be established between clinical observation and real data so that psychiatric assessment can be considered in a broader behavioral context.

Nevertheless, digital phenotyping and its clinical implementation are still in the early stages of investigation. The behavioral data collected from people in different scenarios require processing and transformation to create clinically relevant indicators. This raises several methodological and ethical issues. Despite these challenges, empirical evidence from existing studies indicates that digital behavioral patterns are useful for monitoring changes in mental states and predicting clinical trajectories (4, 5). This chapter touches upon the theoretical grounds of digital phenotyping in psychiatry diagnostics to algorithm-based approaches, focusing on passive sensor data analyzed with the help of artificial intelligence methods.

2. From Symptoms to Data: The Theoretical Framework of Digital Phenotyping

The DSM and ICD classifications, the basis for psychiatric diagnostics, have helped clinicians speak a common language and contributed to the greater reliability of diagnosis. Nonetheless, owing to the phenomenological nature of the legacy system, it is still unable to represent the biological/behavioral process. The comorbidity and overlap of diagnostic categories and the heterogeneity of clinical presentation under the same diagnostic label show the limits of the present nosology (6).

Recent research indicates that psychiatric disorders should not be viewed as sharply separated categories but as a multi-dimensional continuum between normality and pathology. According to Perspective 2, mental disorders are best assessed in terms of the cognitive, behavioral, and neurobiological processes underlying the associated symptoms rather than just the lists. In this context, the Research Domain Criteria (RDoC) framework was developed in the U.S. An example of this paradigm can be found at the National Institute of Mental Health (NIMH). The Research Domain Criteria (RDoC) project seeks to reconceive mental disorders as being represented not merely by diagnostic categories but rather by neurobiological circuits, cognitive functions, and observable behaviors that span a wide range of levels from genetics to self-report (6). The theoretical framework facilitates the interpretation of mental disorders in a more process-oriented and dimensional way. Building on the RDoC framework, digital phenotyping operationalizes these behavioral dimensions by shifting measurements from controlled environments to real-world contexts. This transition allows for a dynamic data structure that captures longitudinal fluctuations in mental states.

Historical approaches to psychiatric assessments (clinical interviews, self-report scales) depend on the subject's memory, insight, and capabilities of expressing symptoms in line with the current emotional state. For example, cognitive slowing associated with depression, loss of insight in mania, and impaired reality testing in psychotic processes can greatly limit these strategies. A person suffering from severe depression may inaccurately or incompletely report their social withdrawal or psychomotor retardation over the past week because of "recall bias." Information gained at a clinical interview is therefore not a report of the experience itself but rather the portion that has traversed the patient's current psychological filter and is subsequently "remembered."

The objective data of digital phenotyping will precisely fill the gaps in the subjective narrative. With the help of smartphone sensors and wearable technologies, monitoring important domains such as mobility, sleep quality, social interaction frequency, and daily circadian rhythms is possible in the natural setting of everyday life (i.e., ecological momentary assessment). Clinical evaluation may thus rest not on measures taken at particular or fixed points in time but on a stream of data that reflects the ebb and flow of behavior over time.

One of the most critical components of this methodology is the combined use of active and passive data. Active data refer to data types that require direct user action, such as completing questionnaires or participating in ecological momentary assessment (EMA) processes, thereby transferring the patient's subjective experience into the digital environment. In contrast, passive data consist of information that is automatically collected through device sensors and usage metadata without requiring additional intervention or awareness from the user (7). The passive data collection approach increases ecological validity by reducing the influence of individuals' awareness of being monitored on their behavior (Hawthorne effect).

Digital phenotyping is not merely a new tool for data collection; it also represents an epistemological shift in our understanding of mental health. In what some researchers describe as "dynamic phenotyping" (8), individuals' movement patterns, sleep–wake cycles, keyboard micro-interactions, and physiological parameters are integrated to generate personalized "digital signatures."

Thus, methodological problems should not be neglected. Data streams generated from real-world scenarios are typically unstructured, noisy, and incomplete. In addition, the same score (e.g., less smartphone use) might reflect one person's clinical deterioration and another's healthy digital detox. Therefore, the transformation of raw data into clinically meaningful indicators is not only a technical process whereby data are processed, but also a conceptual process involving the integration of artificial intelligence and machine learning algorithms with the clinical context (5).

In conclusion, digital phenotyping represents a shift from a symptom-based, cross-sectional, and reactive model to the continuous, contextual, and proactive measurement of behavior. This approach moves psychiatric diagnosis and monitoring beyond subjective narratives, placing them within a more comprehensive, personalized, and objective framework supported by data-driven indicators.

3. Algorithmic Observation: Passive Sensor Data and Behavioral Pattern Analysis

To create clinically useful outcomes from digital phenotyping, raw data generated from sensors should be translated into behavioral and clinically meaningful indicators. A large share of these transformations is achieved using artificial intelligence and machine learning methods. As data generated by smartphones and wearable devices are high-volume, multidimensional ,and temporally dynamic, traditional statistical methods often have limited application for analyzing these data. The stream of data can be processed using artificial intelligence algorithms to model an individual's behavioral patterns, detect alterations over time, and translate these patterns into clinically meaningful indicators (4). The stages of data collection, data cleaning, signal processing, feature extraction, and pattern recognition are usually included in this approach. For instance, raw motion signals from accelerometers can be processed to generate higher-level clinical markers, such as psychomotor slowing, sleep disturbances, or even impending mood changes (4, 5).

The clinical utility of passive sensing lies in its ability to bridge the gap between the clinical visits. By integrating data from the sources outlined in Table 1, AI models can detect subtle behavioral signatures that are often inaccessible during standard psychiatric interviews.

Feature extraction is essential for raw data to be clinically meaningful. The signals produced by accelerometers only represent motion, but features derived from these signals may be clinically useful, including total activity level, activity variability, and rhythmic regularity. Likewise, GPS data capture location information and reveal the extent of life space, flexibility in routines, and degree of environmental engagement. Phone usage data may provide indirect information about social functioning and behavioral engagement via measures such as screen interaction, application usage frequency, and response delay (5, 9).

Table 1. Main data sources in digital phenotyping and the domains they measure

Data Source	Example Indicators	Clinically Related Phenotypes
Smartphone Sensors	GPS, accelerometer, ambient light sensor, application usage metadata	Mobility, life-space range, circadian rhythm, estimation of sleep architecture
Wearable Devices	Step count, heart rate (HR), heart rate variability (HRV), electrodermal activity (EDA)	Physical activity level, autonomic nervous system response, stress regulation, panic attack monitoring
Social Media and Communication	Language use (NLP), posting frequency, emoji usage, messaging speed	Mood valence, cognitive distortions, social isolation or disinhibition
Keyboard and Micro-Interactions	Keystroke speed (flight time), latency, frequency of error correction	Cognitive processing speed, motor coordination, attentional variability, executive functions
Digital Games and VR	Reaction time, strategy-switching speed, form of social interaction	Cognitive flexibility, motivational state (monitoring anhedonia), decision-making processes

Mobility and circadian rhythm patterns are among the most extensively studied areas of digital phenotyping. Changes in psychomotor activity are of central importance in mood disorders. Increased motor activity and rhythm irregularities are prominent in mania and hypomania, whereas reduced activity, constricted movement patterns, and circadian rhythm disruption may be more evident in depression. It has been shown that features derived from accelerometer data—such as activity level, variation, and rhythmic regularity—can support this differentiation (10, 11). The use of artificial intelligence for modeling is vital for converting behavioral data into clinically relevant information. Using time-series analyses and machine learning algorithms, it is possible to examine an individual's mobility and daily rhythm data, model changes over time, and anticipate approaching episodes at an early stage of the disease. Studies have shown that hypomanic episodes can be predicted in advance using accelerometer-based features (12). The idea of "predictive psychiatry" has gained popularity in psychiatry and is believed to be an essential aspect of the process. In particular, episodic disorders such as bipolar disorder and schizophrenia, changes in behavioral patterns may be one of the earliest signs of clinical deterioration (13).

Data on location and mobility are also important behavioral windows for psychiatry. The diversity of locations visited, time spent outside the home, and extent of the daily range of movement are all indicators that may reflect the narrowing of life space and lack of social participation associated with depressive symptoms. Consequently, GPS-based information shows not only where a person is but also how flexible they are and what they do every day (9).

Keyboard dynamics and other microinteraction patterns are another noteworthy area of digital phenotyping. Keyboard dynamics investigate not what a person is writing, but how they are writing it. Indicators such as key hold time, transition time between keystrokes, typing speed, and rhythmic variability are potentially useful parameters that may indirectly provide information about motor speed, attention, and processing capacity. According to reports, such data may exhibit significant correlations with neuropsychological tests and may aid in monitoring processes such as cognitive impairment and cognitive slowing in mood disorders (2, 14, 15).

Another important clinical dimension of digital phenotyping is the quantification of patterns of social interaction. Logs of calls, metadata of the messages sent and received, and details of applications used can provide indirect clues to a person's social engagement. The data can put situations, such as social withdrawal, which is frequently subjectively expressed in clinical interviews, on a more objective basis. Changes in an individual's standard social behavior may reflect an imminent clinical decline (16, 17, 18).

Research on schizophrenia has shown that this has interesting clinical uses. According to studies, mobility and sociability are behavioral variables that can differ significantly during the pre-relapse period. A study conducted by Barnett et al. showed that deviations in digital behavior increased considerably approximately two weeks prior to relapse (19). The research shows that digital phenotyping can not only act as an instrument for monitoring symptoms but can also operate as an early warning signal. Mobility, social rhythm, sleep,

and physiological parameters of mood disorders can also be passively tracked using digital sensors. Reduced mobility and speaking less often are reported in depression, whereas an increase in activity and speaking more often are experienced in mania. Some models have also been reported to predict future mood variations based on passive data (9, 11).

Another important facet of digital phenotyping is sleep and physiological data. As many psychiatric disorders manifest sleep disturbances, clinical insights may be gleaned through smartphone and wearable device-quantified sleep parameters. Indicators such as total sleep duration, sleep onset latency, nighttime awakenings, and circadian rhythm regularity have been reported to be associated with depressive and anxiety symptoms (9, 7).

A wide variety of machine learning models have been used to extract clinically usable values. Digital phenotyping studies often employ a variety of methodological techniques, including Random Forest, Gradient Boosting Machine, XGBoost, Support Vector Machines, and logistic regression. Furthermore, deep learning-based models are increasingly being utilized. These algorithms are useful for analyzing high-dimensional and heterogeneous data structures, integrating multiple data sources within a common model, and analyzing behaviors that vary over time. Artificial intelligence techniques, especially those employed in time-series analysis, can help recognize changes in an individual's behavioral patterns and assist with the early detection of possible clinical risks. Despite the expected clinical importance of the accuracy of model performance, in practice, model interpretation or the ability to learn which behavioral variables are associated with increased risk is also important for clinicians (4, 18, 20). Table 2 compiles the principal digital markers utilized in various psychiatric disorders and the performance of the algorithmic modeling.

As these studies show, digital phenotyping is a multivariable approach that does not depend on a single type of data. In this regard, the combined use of mobility, social, sleep, and physiological rhythm data will result in stronger outcome measures for assessing clinical conditions or predicting future symptom changes (5, 9).

The prospect of digital phenotyping suggests a way for psychiatric evaluation to depart from exclusively cross-sectional information obtained in a clinical interview to observe

Table 2. Digital markers and algorithmic model performance according to psychiatric conditions

Diagnosis / Condition	Core Digital Markers	AI Model	Prediction Accuracy / AUROC	Source
Depression	Step count, GPS variability, sleep latency	Random Forest / GBM	83–87% accuracy	(Choudhary et al., 2022)
Mania (Bipolar)	Accelerometer activity, typing speed, call frequency	Random Forest / XGBoost	0.88–0.98 AUROC	(Wu et al., 2025)
Schizophrenia relapse	Mobility radius, indicators of social isolation	Anomaly detection	Low error rate	(Barnett et al., 2018; Wu et al., 2025)
Mild cognitive impairment	Keyboard latency (flight time), hold time	Logistic regression	High sensitivity	(Park, 2024)

the ongoing behavior of subjects in a real-world environment. Using analytical techniques aided by artificial intelligence, these data can be transformed into clinical patterns and allow for the earlier detection of potential clinical risks. According to McGinnis et al. (2024) and Torous et al. (2025), such developments may lead psychiatric care to evolve from one that reacts only after symptoms are evident to one that uses a predictive, personalized model drawing on individual behaviors (4, 13).

4. Predictive Intervention: Early Warning Systems and Relapse Prevention

The goal of early symptom detection systems in psychiatry is to identify individuals with an increasing risk before deterioration is clinically evident to allow intervention. This helps to detect events such as relapse, self-harm, suicide attempts, agitation, and aggression, as well as the occurrence of unfavorable events within psychiatric services (21). The use of scales, interviewing clients, and observing in-clinic are traditional assessment methods for determining severity and impairment. However, because psychiatric symptoms can fluctuate, clinical deterioration may become apparent over a relatively short period (22). Consequently, we are witnessing the emergence of artificial intelligence–based early warning systems not just as tools that describe the current state but rather as systems that anticipate the deterioration to come.

These systems usually assess data from multiple sources systm. Electronic health records provide a basic data set composed of diagnoses, medication use, emergency department visits, hospital admission and co-morbidity. The passive data from smartphone and wearable devices (i.e. the behavioural traces created by people without additional effort) can also enter the model (23). Concerning clinical deterioration digital indicators include mobility patterns, smartphone screen usage, sleep routines, call and messaging patterns, speech frequency, location changes, and disruptions in daily routines. At this stage, the multimodal artificial intelligence approach is particularly useful given that psychiatric deterioration generally does not occur due to a single symptom, rather simultaneous changes in multiple biological, behavioural and clinical signals.

The various stages of functioning of early warning systems can be summarised. The initial step consists of collecting and cleaning data. The information extracted from multiple sources are standardized, missing data are checked, and the data-set is built for analysis. During the second phase, clinically important features are extracted from the data. Features of the model could be a decline in the duration of sleep, severe increase or decrease in the duration of activity, decrease in the frequency of social events, and increase in healthcare consumption. In the third phase, machine learning methods are used to learn the relationship between the identified characteristics and future risk. According to the past literature, the final stage involves the generation of a risk score for a given patient. When the subject score exceeds a predefined threshold, the system triggers an alert and suggests further clinical intervention (24). In some models, this process is continuously updated, and risk estimates are recalculated as new data become available.

One of the most concrete examples of this approach comes from research on psychotic relapse. Only using the passive sensor data of smartphones, Adler and colleagues tried to identify changes in behavior that occur in the pre-relapse period of schizophrenia spectrum disorders. In this investigation, accelerometer data, phone usage data, call and message data, speech duration, location data, screen use data and sleep-related data were utilized. The model showed an increase in behavioral anomalies during the 30 days before an episode. The study highlighted the fact that relapse does not happen in the same way for everyone. Each person may have their own "relapse signature" indicating that early warning systems in psychiatry should not be built on fixed and uniform alarm mechanisms but rather individual thresholds and patterns (22).

The literature includes another significant application in this area, which is the early warning system for suicide attempts designed by Zheng et al. using EHRs. Researchers used large-scale longitudinal data obtained from 3 hospitals to construct a deep learning-based model and defined the objective of the model as predicting patients at high-risk for suicide attempts in the next year (23). One of the strengths of the study was that the concept of an early warning system was not just seen as a 'risk prediction model' but rather as a three-stage implementation framework which necessitated the establishment of data infrastructure, stratification of risk levels and timely planning of clinical management on risk stratification. Another way of saying this, the system does not merely respond to the question 'Who is at risk?but also specifies the patient groups that should be intervened when the alert threshold is breached The thought process and analytical perspective possessed by the AI and natural intelligence was analysed separately and the spirit of willingness to learn was observed.

Studies regarding warning or alarm systems in psychiatric services draw apparently similar conclusions. In their scoping review, Velasquez et al. note that there are few early warning systems developed specifically for psychiatric settings, although machine learning–based models can demonstrate performance that ranges from moderate to good. The assessment indicated that the best validated model was a random forest–based system with an AUC value of 0.87, a sensitivity of 74% and specificity of 88%. Most of these tools were developed in certain centres and external validation across different patient populations is limited. As a result, these early warning systems in psychiatry hold great potential, but they are still undergoing a development phase regarding their generalizability and assimilation into established clinical practice (21).

The most significant clinical contribution of such systems is that they facilitate a shift from an approach based on "intervening after a crisis occurs" to one based on "intervening while risk is increasing. One example is b when high risk is detected by a model, it may be possible to establish earlier contact with the patient, review medication adherence, inform family members or caregivers, plan closer monitoring, activate crisis plans, or face-to-face clinical evaluation (24). Some studies report that early warnings are initiated, some process manually in case of high risk and not only in the electronic warning system. Hence, artificial intelligence in psychiatry should not be construed to replace the physician but as an aide that saves a doctor's time as well as the timeliness of intervention (25).

Nevertheless, the limitations of early warning systems should not be overlooked. Because psychiatric events occur relatively infrequently, class imbalance is a common problem in datasets. In addition, false positive alerts may lead to unnecessary interventions, while false negative results may result in missed genuine risks (26). Although some models report high levels of accuracy, these findings may be based on limited sample sizes, single-center datasets, or study designs that have not been sufficiently externally validated. Furthermore, models functioning as "black boxes" may have limited clinical interpretability. For this reason, an effective early warning system should be evaluated not only by its performance but also by its explainability, clinical applicability, capacity for continuous updating, and patient safety (24).

To conclude, in psychiatry, artificial intelligence enables us to detect the first symptoms and prevent relapses. Electronic health records, passive sensor information, behavioral patterns, and multiple other sources could contribute to improving visibility of early signals of clinical deterioration. Although they are able to measure risk, the real value of these systems is that they can appropriately transform risk into clinical interventions that are meaningful and timely. It is therefore suggested not only to further develop the algorithms in the future but also to implement the algorithms into existing natural workflows of clinical care safely, in an explainable manner and ethically.

5. Ethical Boundaries and Privacy

The opportunities offered by artificial intelligence in psychiatry spans several areas which include diagnosis, risk prediction, patient monitoring, and decision support. Nevertheless, the application of these technologies in mental health raises more sensitive ethical issues than in any other area of medicine. The principal reason lies within the fact that psychiatric data is often possibility contains stigma, subjective experiences, and is strongly linked to social, cultural, and interpersonal context of the individual. Consequently, in evaluating the artificial intelligence in psychiatry it is crucial to think not only of technical success but also of patient rights, privacy, justice and the preserving of clinical relationship (27).

The first stage of ethical discussions relates to data privacy and confidentiality. Large datasets typically power artificial intelligence systems. The collected data could include electronic health records, clinical notes, sensor data, digital phenotyping data, patterns of speech, or traces of behavior (28). Mental health data aren't just health information. They often include highly sensitive information such as family details, trauma history, thought content, suicide risk, substance abuse and social functioning. Consequently, data de-identification is sometimes not adequate alone. Use of Multiple Data-Demographic Sources May Heighten Re-Identification Risks Especially in cases using monitoring or surveillance-based techniques, the sensation of always being watched may enhance the loss of the patient's privacy. According to Putica et al. (2025), the monitoring of the psychiatric patient with camera- or sensor-based systems may be a cause of stress, distrust, and aggravation of symptoms in some patients (27).

The other major problem is informed consent. In the field of psychiatry, the process of consent is often not as straightforward or simple as it is in medicine. Consent is complicated by the fact that decision-making capacity may be intermittently impaired. Further some patients are under conditions of involuntary hospitalization. Finally, patients may find it difficult to understand the risks that are related to technology. This difficulty becomes even greater when artificial intelligence is added. Patients should know which and what data are collected, how those data are processed, with what model these data are used and what the limits of the system are. It is, however, not straight forward to explain such an approach in particular for complex "black box" models (29). Furthermore, when a system is changed over time and starts producing recommendations that deviate from the initially defined recommendations, the scope of the consent obtained at the outset becomes questionable too. This could mean that some authors feel that a dynamic consent could be more flexible and updatable as compared to one-off consent. The patient's ability to allow some types of use and refuse others, or to simply opt out of the system should he wish to, is especially salient in mental health (30).

Another important issue is algorithmic bias and justice. Although artificial intelligence systems may appear neutral, they can reproduce the inequalities present in the datasets on which they are trained. If a model has been trained on data that do not adequately represent certain age, sex, ethnic, or cultural groups, it may perform with lower accuracy in those groups (31). The significance of this issue is heightened in the field of psychiatry, as the manifestation of symptoms may differ based on cultural, linguistic, gender, and environmental contexts. Models that have been developed using homogeneous datasets may therefore misclassify patients, overestimate risk, or inadequately recommend interventions in other groups. The technical problem is, however, also an ethical issue in terms of access to healthcare and the provision of equitable care. New ethical frameworks are concerned about justice and equity not only as it relates to model performance but also regarding who is in the dataset, who is out, and who is exposed to an increased risk of harm (27).

Also, explainability and transparency are issues that concern clinical ethics. The decisions made in psychiatry should not only be valid but also intelligible and discussable. If it is unclear what data the risk score or treatment recommendation is based on, the clinician may be uncertain how much to trust that output. The patient's perspective might be that not understanding how a decision about them was made may lead to a distrust. In high-impact areas like involuntary treatment, hospitalization, suicide risk, and psychotic relapse, there is an increased importance for explainability. Yet, getting clear how machine learning models work is not an easy task. Some machine learning models are not interpretable in any way – even the people who built them do not know how the decisions were reached. Moreover, providing explanations and privacy-protecting efforts may occasionally come into tension with each other. Nonetheless, the use of the model cannot be unethical if its purpose of use, its limitations and the probabilities of error, and its use in the particular clinical context are clear (28).

In psychiatry, ethical questions surrounding artificial intelligence are not only about data and models; they also involve the therapeutic relationship. At the heart of psychiatric

care is taking the patient's experience seriously, listening to their story and conducting clinical operations within the relationship. When the output of an artificial intelligence takes precedence over the judgment of a clinician and the account of the patient becomes subordinate to the algorithm's prediction, autonomy and therapeutic trust may be undermined. Certain authors refer to this risk as the AI becoming "epistemically privileged" that is, the clinician considers the algorithmic output more objective and superior, thus sidelining the patient's experiential knowledge (32). In psychiatry, however, a patient's report is not just data but a part of the provision of care. In terms of ethics, the right way to position artificial intelligence is not as a voice that represses that of the patient, but rather as an adjuvant to the clinical judgement.

At this point, the conversation shifts to the issue of professional accountability and responsibility. When artificial intelligence supports a wrong recommendation or there's harm to a patient, it's not easy to determine responsibility (32). Is it the company that developed the system, the institution that utilizes it or the clinician? Also, that the recommendation may be too specific and incorrect is not the end of the problem. Harm can also arise when the doctor accepts the recommendation without thinking twice or, on the other hand, totally disregarding an important warning. Many ethical approaches highlight that AI must remain a decision-support system instead of being the final decision-maker (28). Clinical responsibility cannot be transferred. The output of artificial intelligence must be interpreted by the doctor by including the context of the patient, social circumstances, cultural characteristics, and subjective experience. Thus, the technical correctness alone without professional training and institutional guidelines and regular oversight will not suffice for safe use.

In recent times, various ethical frameworks have been developed to systematically address these problems. The IEACP claims that the ethical evaluation is a five-stage process: identification, analysis, judgement, implementation, and evaluation of the problems involved. This process will run on core values such as beneficence, non-maleficence, autonomy, justice, privacy, transparency, and scientific integrity (27). A framework with this purpose supports that ethical issues are not a checklist added at the end but rather part of the decision making from the very beginning of design and implementation. Specifically, within the domain of psychiatry, genuine conflicts arise between the efficacy of technical interventions and the advancement of patient self-governance practices. Consequently, ethical decisions should not be reduced to a singular principle but made in a context-sensitive and multi-stakeholder manner.

To conclude, artificial intelligence in psychiatry raises ethical questions that are far more complex than asking whether it should or should not be used. The actual question concerns the purpose of the technologies and their application, how they will be regulated, and for whose gain. The safety and ethical use of AI in medicine will require protecting patient privacy, strengthening consent processes, reducing bias, improving models' explainability, and preserving the human-centered architecture of clinical decision-making. While artificial intelligence may be useful in psychiatry, it is not truly useful unless a mode of use is developed that does not overshadow the patient experience, the therapeutic relationship and clinical responsibility.

6. References

1. Dalal, P. K., & Sivakumar, T. (2009). Moving towards ICD-11 and DSM-V: Concept and evolution of psychiatric classification. *Indian Journal of Psychiatry, 51*(4), 310–319.
2. Insel, T. R. (2018). Digital phenotyping: A global tool for psychiatry. *World Psychiatry, 17*(3), 276.
3. Ortiz, A., & Mulsant, B. H. (2024). Beyond step count: Are we ready to use digital phenotyping to make actionable individual predictions in psychiatry? *Journal of Medical Internet Research, 26*, e59826.
4. McGinnis, E. W., Cherian, J., & McGinnis, R. S. (2024). The state of digital biomarkers in mental health. *Digital Biomarkers, 8*(1), 210–217.
5. Mohr, D. C., Zhang, M., & Schueller, S. M. (2017). Personal sensing: Understanding mental health using ubiquitous sensors and machine learning. *Annual Review of Clinical Psychology, 13*, 23–47.
6. Hengartner, M. P., & Lehmann, S. N. (2017). Why psychiatric research must abandon traditional diagnostic classification and adopt a fully dimensional scope: Two solutions to a persistent problem. *Frontiers in Psychiatry, 8*, 101.
7. Williamson, S. (2023). Digital phenotyping in psychiatry. *BJPsych Advances, 29*(6), 428–429.
8. Onnela, J. P., & Rauch, S. L. (2016). Harnessing smartphone-based digital phenotyping to enhance behavioral and mental health. *Neuropsychopharmacology, 41*(7), 1691–1696.
9. Maatoug, R., Oudin, A., Adrien, V., Saudreau, B., Bonnot, O., & Millet, B. (2022). Digital phenotype of mood disorders: A conceptual and critical review. *Frontiers in Psychiatry, 13*, 895860.
10. Bufano, P., Laurino, M., Said, S., Tognetti, A., & Menicucci, D. (2023). Digital phenotyping for monitoring mental disorders: Systematic review. *Journal of Medical Internet Research, 25*, e46778.
11. Jakobsen, P., Stautland, A., Riegler, M. A., Côté-Allard, U., Sepasdar, Z., Nordgreen, T., et al. (2022). Complexity and variability analyses of motor activity distinguish mood states in bipolar disorder. *PLoS ONE, 17*(1), e0262232.
12. Wu, C. T., Hsieh, M. H., Chen, I. M., Jhao, L. Y., Liu, D. S., Wang, S. M., et al. (2025). Using wearable device and machine learning to predict mood symptoms in bipolar disorder: Development and usability study. *JMIR Medical Informatics, 13*(1), e66277.
13. Torous, J., Linardon, J., Goldberg, S. B., Sun, S., Bell, I., Nicholas, J., et al. (2025). The evolving field of digital mental health: Current evidence and implementation issues for smartphone apps, generative artificial intelligence, and virtual reality. *World Psychiatry, 24*(2), 156–174.
14. Ning, E., Estabrook, R., Tulabandhula, T., Zulueta, J., Ross, M. K., Kabir, S., et al. (2025). Predicting cognitive functioning in mood disorders through smartphone typing dynamics. *Journal of Psychopathology and Clinical Science*.
15. Park, J. H. (2024). Discriminant power of smartphone-derived keystroke dynamics for mild cognitive impairment compared to a neuropsychological screening test: Cross-sectional study. *Journal of Medical Internet Research, 26*, e59247.
16. Adler, D. A., Wang, F., Mohr, D. C., & Choudhury, T. (2022). Machine learning for passive mental health symptom prediction: Generalization across different longitudinal mobile sensing studies. *PLoS ONE, 17*(4), e0266516.
17. Busshart, L., Petrovic, M., Amin, R., & Hegerl, U. (2026). Distinguishing common digital phenotyping and self-report parameters for monitoring and predicting depression: Scoping review. *JMIR mHealth and uHealth, 14*, e70840.
18. Choudhary, S., Thomas, N., Ellenberger, J., Srinivasan, G., & Cohen, R. (2022). A machine learning approach for detecting digital behavioral patterns of depression using nonintrusive smartphone data: Prospective observational study. *JMIR Formative Research, 6*(5), e37736.
19. Barnett, I., Torous, J., Staples, P., Sandoval, L., Keshavan, M., & Onnela, J. P. (2018). Relapse prediction in schizophrenia through digital phenotyping: A pilot study. *Neuropsychopharmacology, 43*(8), 1660–1666.
20. Suárez, M., Torres, A. M., Blasco-Segura, P., & Mateo, J. (2025). Application of the random forest algorithm for accurate bipolar disorder classification. *Life, 15*(3), 394.
21. Velasquez, V. T., Chang, J., & Waddell, A. (2024). The development of early warning scores or alerting systems for the prediction of adverse events in psychiatric patients: A scoping review. *BMC Psychiatry, 24*(1), 742.
22. Adler, D. A., Ben-Zeev, D., Tseng, V. W., Kane, J. M., Brian, R., Campbell, A. T., et al. (2020). Predicting early warning signs of psychotic relapse from passive sensing data: An approach using encoder-decoder neural networks. *JMIR mHealth and uHealth, 8*(8), e19962.
23. Zheng, L., Wang, O., Hao, S., Ye, C., Liu, M., Xia, M., et al. (2020). Development of an early-warning system for high-risk patients for suicide attempt using deep learning and electronic health records. *Translational Psychiatry, 10*(1), 72.
24. Deng, C. (2025). Data recognition, monitoring and early warning of mental health signs based on artificial intelligence. In *Proceedings of the 3rd International Conference on Data Science and Information System (ICDSIS)*.
25. Ray, A., Bhardwaj, A., Malik, Y. K., Singh, S., & Gupta, R. (2022). Artificial intelligence and psychiatry: An overview. *Asian Journal of Psychiatry, 70*, 103021.
26. Mikaeili, N., Naeim, M., & Narimani, M. (2025). Reimagining mental health with artificial intelligence: Early detection, personalized care, and a preventive ecosystem. *Journal of Multidisciplinary Healthcare*, 7355–7373.
27. Putica, A., Khanna, R., Bosl, W., Saraf, S., & Edgcomb, J. (2025). Ethical decision-making for AI in mental health: The integrated ethical approach for computational psychiatry (IEACP) framework. *Psychological Medicine, 55*, e213.
28. Dawoodbhoy, F. M., Delaney, J., Cecula, P., Yu, J., Peacock, I., Tan, J., et al. (2021). AI in patient flow: Applications of artificial intelligence to improve patient flow in NHS acute mental health inpatient units. *Heliyon, 7*(5).

29. Poudel, U., Jakhar, S., Mohan, P., & Nepal, A. (2025). AI in mental health: A review of technological advancements and ethical issues in psychiatry. *Issues in Mental Health Nursing, 46*(7), 693–701.
30. Gupta, D., & Gandhi, T. (2025). AI and ethics in mental health: Personal reflections on the future of psychiatry. *International Review of Psychiatry*, 1–4.
31. Mukta, K. J., & Islam, M. A. (2025). Artificial intelligence in psychiatric inpatient care: Advancing diagnostics, personalized treatment, and ethical integration. *Journal of Psychology and Behavioral Studies, 5*(3), 1–15.
32. McCradden, M., Hui, K., & Buchman, D. Z. (2023). Evidence, ethics and the promise of artificial intelligence in psychiatry. *Journal of Medical Ethics, 49*(8), 573–579.

CHAPTER 46

Artificial Intelligence in Obesity Management: New Approaches from Diagnosis to Treatment

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1. Introduction

Obesity is a global health problem (1,2). It is a cause of serious economic losses (3,4). According to the World Health Organization, more than 30% of the world's population is obese or overweight (5,6). The most commonly used method for detecting obesity is the body mass index (BMI).

The factors associated with obesity are very broad, including behavioral types, diet, cultural differences, psychological background, and lifestyle choices (7,8). Nutritional deficiencies and lack of exercise are predisposing factors for obesity (9).

Obesity affects the entire body and organs. Obesity, especially around the abdomen, is the cause of numerous diseases, primarily cancer and heart disease (10–12).

Artificial intelligence (AI) is used in many scientific fields, including medicine. Machine learning (ML) and deep learning (DL) are used in every area of medicine, from diagnosis to treatment. Artificial intelligence helps in every field of medicine by processing the factors that cause diseases and their data (13,14).

With the development of technology, applications used in smartphones and wearable technologies have developed. With the data obtained from these devices, the mental states of patients during the obesity process can be examined more easily (15,16). The biggest risk related to artificial intelligence is data security and monitoring the accuracy of diagnosis and treatment. Although artificial intelligence is effectively used in obesity, it has a long way to go.

2. Diagnosis and Categorization of Obesity

The most well-known method for detecting and categorizing obesity is the Body Mass Index (BMI), which is the ratio of weight to the square of height in meters. Obesity is divided into 3 categories:

1. Category 1 if BMI < 34.9 kg/m2
2. Category 2 if BMI < 39.9 kg/m2
3. Category 3 if BMI > 40.0 kg/m2

As the obesity category increases, so do the associated diseases (17,18). There are two types of obesity: visceral obesity and peripheral obesity.

Visceral obesity is apple-shaped; also known as android obesity. Adipose tissue is located in the abdominal region. Organ fat accumulation is common. Visceral fat accumulation increases the risk of diabetes, heart disease, and cancer (19,20).

Environmental obesity resembles a pear shape; it is also known as gynecoid obesity. Fat tissue is located under the skin in the gluteal region.

Mixed type (central and peripheral) obesity occurs when two types are present together. Complications of obesity are more frequent in this type than in other types (19,21).

3. Artificial Intelligence

Artificial intelligence refers to computer programs that can behave like human intelligence. Once programmed, these programs can learn and operate without needing to be reprogrammed. Machine learning (ML) is a type of artificial intelligence that enhances the functionality of a machine by processing the data it receives. ML can provide optimal efficiency in the diagnosis and treatment of diseases with high efficiency (22).

ML/DL systems were first developed in the 1950s, but they could not be used effectively for many years (23). The development of artificial intelligence can be divided into two stages. Older forms of artificial intelligence were incapable of processing anything other than the data given to them. This form had to act according to the rules given to it. It could evaluate clearly defined data. The advantage of this system was that the results were traceable and open to interpretation. Because it was an old system, it struggled with complex tasks such as foreign language translation. Thanks to advances in computation, ML and DL have attracted more attention compared to the old type of artificial intelligence (23).

Machine learning can process large amounts of data and make predictions. ML can be trained with a training dataset. ML tests itself with the test dataset. With these datasets, the predictive power of ML increases. ML is particularly more powerful than old-style ML in processing irregular data (24,25).

4. Using Artificial Intelligence in Predicting Obesity and Related Risks

Predicting obesity in its early stages is a crucial element in preventing obesity. Researchers process vast amounts of data from electronic medical records, insurance data, and mobile

phones. The analysis of this data is important for stopping and preventing obesity (26,27). Healthcare professionals and researchers use various approaches in diagnosis, treatment, and predicting clinical course with the help of ML or DL (28,29).

Artificial intelligence models have been used in the literature for obesity prediction. In this study, six models were used: random tree, random forest, Iterative Binary Classifier 3 (ID3), J48, Naive Bayes, and Bayesian network (28,30). Three of the six models were accurate in predicting obesity. This study enables critical interventions during the development of a growing child..

In another study, they investigated the effect of environmental factors on the development of obesity (31). The primary results of this study found that obesity was more prevalent in areas with lower levels of education. This analysis also showed that obesity was less common in areas with lower incomes.

In the literature, artificial intelligence has been used to predict and prevent obesity. They found that the accuracy rate was higher as the education rates increased at different education and testing rates (32).

Furthermore, many studies have used artificial intelligence to predict genetic differences in obesity. One example of these studies investigated the effect of single nucleotide polymorphism on obesity (33).

5. Obesity Management and Artificial Intelligence

Obesity treatment requires comprehensive approaches. There are several key aspects, including lifestyle changes, psychiatric support, behavioral therapy, pharmacotherapy, and bariatric surgery. Healthcare professionals combine all these processes to help people achieve and maintain a healthy weight (34,35). In this context, artificial intelligence (AI) offers an accessible tool that facilitates patient care, real-time monitoring, and accurately predicts surgical outcomes (36,37). These are applications that improve patient compliance with postoperative bariatric follow-up, facilitate patient education, and improve long-term outcomes (38).

Artificial intelligence algorithms are used by healthcare personnel to make decisions and form thought systems (38,39). These systems process large amounts of data to provide personalized treatment regimens. AI-assisted solutions facilitate patient monitoring. Patients can be monitored without coming to the hospital with the help of a mobile phone. This method is both efficient and cost-effective (16).

Artificial intelligence can be dynamically adjusted. It can make recommendations according to the patients' choices. With these recommendations, consistency in weight loss can be ensured (40).

In bariatric surgery patient care, artificial intelligence plays an effective role, especially in patient education. Data specific to each patient is processed, and AI enables the development of customized education and nutrition plans based on patient preferences and available options. These interventions address individual challenges in treatment adherence, increasing patient participation and long-term compliance (37, 38).

For example, AI programs can help patients choose the right foods. An AI program that analyzes a patient's vital data motivates them to eat the most suitable food. In doing so, it makes it easier for patients to resist the urge to eat the wrong food.

The artificial intelligence application collects and processes information about patients' physical activity plans and conditions. Then it plans the optimal treatment and follow-up. In this way, patient satisfaction is increased (41).

In artificial intelligence, proper data storage, the risk of incorrect algorithms, and the control of medical recommendations given are very important issues (42).

6. The Use of Artificial Intelligence in Anti-Obesity Pharmacotherapy

The body produces numerous molecules to control obesity. For example, ghrelin is secreted from the gastric fundus and stimulates hunger. Glucagon-like peptide-1 (GLP-1) is secreted postprandially and stimulates satiety. Insulin and leptin suppress appetite. Orlistat reduces the absorption of fatty acids by acting on the digestive system (43). Phenformin is a molecule that reduces hunger by acting via the adrenergic system (44),

Fenformin-topiramate reduces appetite by activating dopamine.

Naltrexone-bupropion inhibits appetite. Bupropion suppresses the reuptake of dopamine and norepinephrine,

While liraglutide is a GLP-1 agonist, semaglutide is a GLP-1 receptor agonist, thus they suppress appetite (45).

Obesity treatment is a three-pronged approach involving patient actions, physician actions, and medication. Patients have to change their accustomed routines. Physicians play a role in patient treatment planning using surgical or medical treatments. Patients may struggle to fulfill their responsibilities. Patients may fear and avoid surgical treatment. At this point, medication becomes a way out for patients. For this reason, medication is frequently preferred by patients due to its ease of access and lack of effort. Although artificial intelligence provides physicians and doctors with a broad perspective and imagination in obesity treatment, it raises doubts about the complexity and accuracy of the services it provides. For this reason, it will take time to become routinely used. Despite all its negative aspects, we believe that machine learning will be more effective in regulating drug treatment.

7. Bariatric Surgery and Artificial Intelligence

Bariatric surgery is the branch of general surgery that describes and performs surgical treatment of obesity. These procedures may be restrictive techniques, malabsorptive techniques, or a combination of both. The best-known examples of bariatric surgery include gastric bypass, sleeve gastrectomy, adjustable gastric band, duodenal switch, and biliopancreatic diversion (46). However, because obesity presents many problems, it may require other surgical procedures. These surgical procedures may involve various surgical branches such as orthopedic cardiovascular, plastic and reconstructive surgery, and head

and neck surgery. The fact that these surgeries are performed on obese patients does not mean they are part of bariatric surgery. Because the aim of these surgeries is not to cause weight loss, but to eliminate the problems caused by excess weight.

Artificial intelligence is used in many preoperative, peroperative, and postoperative aspects of bariatric surgery (38). Preoperative risk analysis and the prediction and prevention of postoperative complications are areas where artificial intelligence is effective. The literature demonstrates the effectiveness of artificial intelligence in this field. An example of this was an AI model used to predict difficult intubation in obese patients showing over 80% accuracy and reaching 100% sensitivity (47).

Obstructive sleep apnea syndrome (OSAS) is a highly morbid disease characterized by airway obstruction during sleep followed by the resumption of breathing. Polysomnography (PSG) is an important diagnostic method in the diagnosis of OSAS (48). Treatment includes weight loss and positive airway pressure (CPAP) devices used at night (49). In addition to CPAP devices, mandibular advancement devices are also used (48,49). Bariatric surgery can be used in suitable patients as it provides weight loss in OSAS patients. Preoperative evaluation should keep in mind that obese patients may have lung problems. In one study in the literature, it was seen that spirometry devices connected to mobile phones provided information as comprehensive as that of trained personnel (50).

Artificial intelligence is known to be used in the field of anesthesia, especially in the intraoperative part of bariatric surgery. These include processes such as estimating the duration of surgery, investigating propofol distribution kinetics, and predicting the steps of sleeve gastrectomy through the analysis of surgical videos (51–53)

Postoperative follow-up of patients with adherence to the given diet and recommendations is an area where artificial intelligence can be effectively used. Patients who do not adhere to dietary recommendations or who experience a loss of motivation can be reached via mobile devices. Therefore, deviation from treatment can be prevented (36,38,54).

Complications after bariatric surgery are seen in a wide range. These can include bleeding, ileus, atelectasis, pneumonia, deep vein thrombosis, and pulmonary embolism. In the literature, artificial intelligence applications have been designed to predict late complications by examining patients' personal data, sociodemographic data, and intraoperative complications. At the end of the study, it was shown that the artificial intelligence application was effective in predicting late complications (55). In the literature, ANN and XGB methods have been used to predict the risk of deep vein thrombosis after bariatric surgery. The results showed that these analysis methods performed better than logistic regression in predicting venous thromboembolism (56).

8. Recent Developments in Artificial Intelligence Applications Related to Obesity

Deep learning applications in the diagnosis and treatment of obesity are developing at a high pace. Deep learning can be used in radiological image analysis, especially for investigating the distribution of adipose tissue and obesity-related comorbidities (57, 58). Fur-

thermore, the examination and evaluation of patient data, and the processing of this data with deep learning, can lead to the development of early diagnoses and interventions (59, 60). By integrating this data processing with deep learning into mobile devices, patient follow-up in the postoperative period can be individualized (61–64).

Digital twin technology creates a digital twin of the patient, simulating interventions to be performed on the individual and measuring the patient's response to these interventions. This facilitates the provision of personalized recommendations to the patient (65).

9. Current Limitations, Future Trends, and Recommendations

Artificial intelligence and machine learning (ML) require high-quality and high-quantity data. The lack of this data in current technologies reduces the accuracy and generalizability of AI and machine learning (14, 66). Providing high-quality and high-quantity data requires powerful computing systems. For countries with limited resources, establishing these systems creates additional economic burdens.

Complete collection of patient information, combining data collected from different sources and institutions, can increase the amount of data, thus improving the accuracy of AI (67, 68). Making AI more understandable and providing training on it can increase trust in AI and help healthcare providers use AI more effectively (69).

Establishing and clarifying ethical rules in the use of AI will increase trust in AI. This will facilitate the easier use of AI in the treatment of patients.

10. Conclusion

This book chapter attempts to explain how artificial intelligence (AI) is used in the process of obesity, from diagnosis to treatment. It is clear that AI can be effective at every stage of obesity surgery. This effectiveness is promising.

While AI provides powerful tools in the fight against obesity, it has shortcomings in important areas such as improving data quality and protecting privacy. Further research is needed to address these shortcomings.

11. References

1. Camacho S, Ruppel A.(2017) Is the calorie concept a real solution to the obesity epidemic? Glob Health Action. 2017;10(1):1289650. doi:10.1080/16549716.2017.1289650 PubMed PMID: 28485680; PubMed Central PMCID: PMC5496172.
2. Ibrahim S, Akram Z, Noreen A, Baig MT, Sheikh S, Huma A, et al. (2021)Overweight and Obesity Prevalence and Predictors in People Living in Karachi. Journal of Pharmaceutical Research International. 2021 Jun 15;194–202. doi:10.9734/jpri/2021/v33i31B31708
3. GBD 2019 Risk Factors Collaborators (2020). Global burden of 87 risk factors in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet (London, England)*, *396*(10258), 1223–1249. https://doi.org/10.1016/S0140-6736(20)30752-2

4. Cauchi, D., Glonti, K., Petticrew, M., & Knai, C. (2016). Environmental components of childhood obesity prevention interventions: an overview of systematic reviews. *Obesity reviews : an official journal of the International Association for the Study of Obesity*, *17*(11), 1116–1130. https://doi.org/10.1111/obr.12441
5. Safaei, M., Sundararajan, E. A., Driss, M., Boulila, W., & Shapi'i, A. (2021). A systematic literature review on obesity: Understanding the causes & consequences of obesity and reviewing various machine learning approaches used to predict obesity. *Computers in biology and medicine*, *136*, 104754. https://doi.org/10.1016/j.compbiomed.2021.104754
6. Kelly, T., Yang, W., Chen, C. S., Reynolds, K., & He, J. (2008). Global burden of obesity in 2005 and projections to 2030. *International journal of obesity (2005)*, *32*(9), 1431–1437. https://doi.org/10.1038/ijo.2008.102
7. Williams, E. P., Mesidor, M., Winters, K., Dubbert, P. M., & Wyatt, S. B. (2015). Overweight and Obesity: Prevalence, Consequences, and Causes of a Growing Public Health Problem. *Current obesity reports*, *4*(3), 363–370. https://doi.org/10.1007/s13679-015-0169-4
8. Shaharir, S. S., Gafor, A. H., Said, M. S., & Kong, N. C. (2015). Steroid-induced diabetes mellitus in systemic lupus erythematosus patients: analysis from a Malaysian multi-ethnic lupus cohort. *International journal of rheumatic diseases*, *18*(5), 541–547. https://doi.org/10.1111/1756-185X.12474
9. Hu, L., Huang, X., You, C., Li, J., Hong, K., Li, P., Wu, Y., Wu, Q., Wang, Z., Gao, R., Bao, H., & Cheng, X. (2017). Prevalence of overweight, obesity, abdominal obesity and obesity-related risk factors in southern China. *PloS one*, *12*(9), e0183934. https://doi.org/10.1371/journal.pone.0183934
10. Althumiri, N. A., Basyouni, M. H., AlMousa, N., AlJuwaysim, M. F., Almubark, R. A., BinDhim, N. F., Alkhamaali, Z., & Alqahtani, S. A. (2021). Obesity in Saudi Arabia in 2020: Prevalence, Distribution, and Its Current Association with Various Health Conditions. *Healthcare (Basel, Switzerland)*, *9*(3), 311. https://doi.org/10.3390/healthcare9030311
11. Puhl, R. M., & Heuer, C. A. (2010). Obesity stigma: important considerations for public health. *American journal of public health*, *100*(6), 1019–1028. https://doi.org/10.2105/AJPH.2009.159491
12. Listyoko, A. S., Okazaki, R., Harada, T., Inui, G., & Yamasaki, A. (2024). Impact of obesity on airway remodeling in asthma: pathophysiological insights and clinical implications. *Frontiers in allergy*, *5*, 1365801. https://doi.org/10.3389/falgy.2024.1365801
13. Khera, R., Butte, A. J., Berkwits, M., Hswen, Y., Flanagin, A., Park, H., Curfman, G., & Bibbins-Domingo, K. (2023). AI in Medicine-JAMA's Focus on Clinical Outcomes, Patient-Centered Care, Quality, and Equity. *JAMA*, *330*(9), 818–820. https://doi.org/10.1001/jama.2023.15481
14. Bajwa, J., Munir, U., Nori, A., & Williams, B. (2021). Artificial intelligence in healthcare: transforming the practice of medicine. *Future healthcare journal*, *8*(2), e188–e194. https://doi.org/10.7861/fhj.2021-0095
15. Wang, X., Zhao, J., Marostica, E., Yuan, W., Jin, J., Zhang, J., Li, R., Tang, H., Wang, K., Li, Y., Wang, F., Peng, Y., Zhu, J., Zhang, J., Jackson, C. R., Zhang, J., Dillon, D., Lin, N. U., Sholl, L., Denize, T., … Yu, K. H. (2024). A pathology foundation model for cancer diagnosis and prognosis prediction. *Nature*, *634*(8035), 970–978. https://doi.org/10.1038/s41586-024-07894-z
16. Bays, H. E., Fitch, A., Cuda, S., Gonsahn-Bollie, S., Rickey, E., Hablutzel, J., Coy, R., & Censani, M. (2023). Artificial intelligence and obesity management: An Obesity Medicine Association (OMA) Clinical Practice Statement (CPS) 2023. *Obesity pillars*, *6*, 100065. https://doi.org/10.1016/j.obpill.2023.100065
17. Guh, D. P., Zhang, W., Bansback, N., Amarsi, Z., Birmingham, C. L., & Anis, A. H. (2009). The incidence of co-morbidities related to obesity and overweight: a systematic review and meta-analysis. *BMC public health*, *9*, 88. https://doi.org/10.1186/1471-2458-9-88
18. Romero-Corral, A., Montori, V. M., Somers, V. K., Korinek, J., Thomas, R. J., Allison, T. G., Mookadam, F., & Lopez-Jimenez, F. (2006). Association of bodyweight with total mortality and with cardiovascular events in coronary artery disease: a systematic review of cohort studies. *Lancet (London, England)*, *368*(9536), 666–678. https://doi.org/10.1016/S0140-6736(06)69251-9
19. Garvey, W. T., Mechanick, J. I., Brett, E. M., Garber, A. J., Hurley, D. L., Jastreboff, A. M., Nadolsky, K., Pessah-Pollack, R., Plodkowski, R., & Reviewers of the AACE/ACE Obesity Clinical Practice Guidelines (2016). Amerıcan assocıatıon of clınıcal endocrınologısts and amerıcan college of endocrınology comprehensıve clınıcal practıce guıdelınes for medıcal care of patıents wıth obesıty. *Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists*, *22 Suppl 3*, 1–203. https://doi.org/10.4158/EP161365.GL
20. Després, J. P., Lemieux, I., & Prud'homme, D. (2001). Treatment of obesity: need to focus on high risk abdominally obese patients. *BMJ (Clinical research ed.)*, *322*(7288), 716–720. https://doi.org/10.1136/bmj.322.7288.716.
21. Snijder, M. B., Zimmet, P. Z., Visser, M., Dekker, J. M., Seidell, J. C., & Shaw, J. E. (2004). Independent and opposite associations of waist and hip circumferences with diabetes, hypertension and dyslipidemia: the AusDiab Study. *International journal of obesity and related metabolic disorders : journal of the International Association for the Study of Obesity*, *28*(3), 402–409. https://doi.org/10.1038/sj.ijo.0802567
22. Haug, C. J., & Drazen, J. M. (2023). Artificial Intelligence and Machine Learning in Clinical Medicine, 2023. *The New England journal of medicine*, *388*(13), 1201–1208. https://doi.org/10.1056/NEJMra2302038
23. Haenlein M, Kaplan A. (2019)A Brief History of Artificial Intelligence: On the Past, Present, and Future of Artificial Intelligence. California Management Review. 2019 Aug;61(4):5–14. doi:10.1177/0008125619864925
24. Cerulli, G(2023). Fundamentals of Supervised Machine Learning: With Applications in Python, R, and Stata; Springer Nature: Heidelberg, Germany, 2023.

25. Ngiam, K. Y., & Khor, I. W. (2019). Big data and machine learning algorithms for health-care delivery. *The Lancet. Oncology*, *20*(5), e262–e273. https://doi.org/10.1016/S1470-2045(19)30149-4
26. DeGregory, K. W., Kuiper, P., DeSilvio, T., Pleuss, J. D., Miller, R., Roginski, J. W., Fisher, C. B., Harness, D., Viswanath, S., Heymsfield, S. B., Dungan, I., & Thomas, D. M. (2018). A review of machine learning in obesity. *Obesity reviews : an official journal of the International Association for the Study of Obesity*, *19*(5), 668–685. https://doi.org/10.1111/obr.12667
27. Dwyer-Lindgren, L., Freedman, G., Engell, R. E., Fleming, T. D., Lim, S. S., Murray, C. J., & Mokdad, A. H. (2013). Prevalence of physical activity and obesity in US counties, 2001-2011: a road map for action. *Population health metrics*, *11*, 7. https://doi.org/10.1186/1478-7954-11-7
28. Dugan, T. M., Mukhopadhyay, S., Carroll, A., & Downs, S. (2015). Machine Learning Techniques for Prediction of Early Childhood Obesity. *Applied clinical informatics*, *6*(3), 506–520. https://doi.org/10.4338/ACI-2015-03-RA-0036
29. Maharana, A., & Nsoesie, E. O. (2018). Use of Deep Learning to Examine the Association of the Built Environment With Prevalence of Neighborhood Adult Obesity. *JAMA network open*, *1*(4), e181535. https://doi.org/10.1001/jamanetworkopen.2018.1535
30. Anand, V., Biondich, P. G., Liu, G., Rosenman, M., & Downs, S. M. (2004). Child Health Improvement through Computer Automation: the CHICA system. *Studies in health technology and informatics*, *107*(Pt 1), 187–191.
31. Allen, B., Lane, M., Steeves, E. A., & Raynor, H. (2022). Using Explainable Artificial Intelligence to Discover Interactions in an Ecological Model for Obesity. *International journal of environmental research and public health*, *19*(15), 9447. https://doi.org/10.3390/ijerph19159447
32. Kaur R, Kumar R, Gupta M. (2022) Predicting risk of obesity and meal planning to reduce the obese in adulthood using artificial intelligence. Endocrine. 2022 Dec 1;78(3):458–69. doi:10.1007/s12020-022-03215-4
33. Wang, H. Y., Chang, S. C., Lin, W. Y., Chen, C. H., Chiang, S. H., Huang, K. Y., Chu, B. Y., Lu, J. J., & Lee, T. Y. (2018). Machine Learning-Based Method for Obesity Risk Evaluation Using Single-Nucleotide Polymorphisms Derived from Next-Generation Sequencing. *Journal of computational biology : a journal of computational molecular cell biology*, *25*(12), 1347–1360. https://doi.org/10.1089/cmb.2018.0002
34. Perdomo, C. M., Cohen, R. V., Sumithran, P., Clément, K., & Frühbeck, G. (2023). Contemporary medical, device, and surgical therapies for obesity in adults. *Lancet (London, England)*, *401*(10382), 1116–1130. https://doi.org/10.1016/S0140-6736(22)02403-5
35. Durrer Schutz, D., Busetto, L., Dicker, D., Farpour-Lambert, N., Pryke, R., Toplak, H., Widmer, D., Yumuk, V., & Schutz, Y. (2019). European Practical and Patient-Centred Guidelines for Adult Obesity Management in Primary Care. *Obesity Facts*, *12*(1), 40–66. https://doi.org/10.1159/000496183
37. Lee, Y., Shin, T., Tessier, L., Javidan, A., Jung, J., Hong, D., Strong, A. T., McKechnie, T., Malone, S., Jin, D., Kroh, M., Dang, J. T., & ASMBS Artificial Intelligence and Digital Surgery Task Force (2024). Harnessing artificial intelligence in bariatric surgery: comparative analysis of ChatGPT-4, Bing, and Bard in generating clinician-level bariatric surgery recommendations. *Surgery for obesity and related diseases : official journal of the American Society for Bariatric Surgery*, *20*(7), 603–608. https://doi.org/10.1016/j.soard.2024.03.011
38. Bellini, V., Valente, M., Turetti, M., Del Rio, P., Saturno, F., Maffezzoni, M., & Bignami, E. (2022). Current Applications of Artificial Intelligence in Bariatric Surgery. *Obesity surgery*, *32*(8), 2717–2733. https://doi.org/10.1007/s11695-022-06100-1
39. Nashwan, A. J., Abdi Hassan, M., & AlBarakat, M. M. (2024). Rethinking BMI and Obesity Management: The Transformative Role of Artificial Intelligence. *Cureus*, *16*(2), e54995. https://doi.org/10.7759/cureus.54995
40. Ray, A., Bhardwaj, A., Malik, Y. K., Singh, S., & Gupta, R. (2022). Artificial intelligence and Psychiatry: An overview. *Asian journal of psychiatry*, *70*, 103021. https://doi.org/10.1016/j.ajp.2022.103021
41. Roy D, Dutta M. (2022) A systematic review and research perspective on recommender systems. J Big Data. 2022 May 3;9(1):59. doi:10.1186/s40537-022-00592-5
42. Fiske, A., Henningsen, P., & Buyx, A. (2019). Your Robot Therapist Will See You Now: Ethical Implications of Embodied Artificial Intelligence in Psychiatry, Psychology, and Psychotherapy. *Journal of medical Internet research*, *21*(5), e13216. https://doi.org/10.2196/13216
43. Seo, M. H., Lee, W. Y., Kim, S. S., Kang, J. H., Kang, J. H., Kim, K. K., Kim, B. Y., Kim, Y. H., Kim, W. J., Kim, E. M., Kim, H. S., Shin, Y. A., Shin, H. J., Lee, K. R., Lee, K. Y., Lee, S. Y., Lee, S. K., Lee, J. H., Lee, C. B., Chung, S., … Committee of Clinical Practice Guidelines, Korean Society for the Study of Obesity (KSSO) (2019). 2018 Korean Society for the Study of Obesity Guideline for the Management of Obesity in Korea. *Journal of obesity & metabolic syndrome*, *28*(1), 40–45. https://doi.org/10.7570/jomes.2019.28.1.40
44. Kang, J. G., Park, C. Y., Kang, J. H., Park, Y. W., & Park, S. W. (2010). Randomized controlled trial to investigate the effects of a newly developed formulation of phentermine diffuse-controlled release for obesity. *Diabetes, obesity & metabolism*, *12*(10), 876–882. https://doi.org/10.1111/j.1463-1326.2010.01242.x
45. Knudsen, L. B., & Lau, J. (2019). The Discovery and Development of Liraglutide and Semaglutide. *Frontiers in endocrinology*, *10*, 155. https://doi.org/10.3389/fendo.2019.00155
46. Baptista, V., & Wassef, W. (2013). Bariatric procedures: an update on techniques, outcomes and complications. *Current opinion in gastroenterology*, *29*(6), 684–693. https://doi.org/10.1097/MOG.0b013e3283651af2
47. Zhou, C. M., Xue, Q., Ye, H. T., Wang, Y., Tong, J., Ji, M. H., & Yang, J. J. (2021). Constructing a prediction model for difficult intubation of obese patients based on machine learning. *Journal of clinical anesthesia*, *72*, 110278. https://doi.org/10.1016/j.jclinane.2021.110278

48. Mencar, C., Gallo, C., Mantero, M., Tarsia, P., Carpagnano, G. E., Foschino Barbaro, M. P., & Lacedonia, D. (2020). Application of machine learning to predict obstructive sleep apnea syndrome severity. *Health informatics journal*, *26*(1), 298–317. https://doi.org/10.1177/1460458218824725
49. Pépin, J. L., Letesson, C., Le-Dong, N. N., Dedave, A., Denison, S., Cuthbert, V., Martinot, J. B., & Gozal, D. (2020). Assessment of Mandibular Movement Monitoring With Machine Learning Analysis for the Diagnosis of Obstructive Sleep Apnea. *JAMA network open*, *3*(1), e1919657. https://doi.org/10.1001/jamanetworkopen.2019.19657
50. Viswanath, V., Garrison, J., & Patel, S. (2018). SpiroConfidence: Determining the Validity of Smartphone Based Spirometry Using Machine Learning. *Annual International Conference of the IEEE Engineering in Medicine and Biology Society. IEEE Engineering in Medicine and Biology Society. Annual International Conference*, *2018*, 5499–5502. https://doi.org/10.1109/EMBC.2018.8513516
51. Ingrande, J., Gabriel, R. A., McAuley, J., Krasinska, K., Chien, A., & Lemmens, H. J. M. (2020). The Performance of an Artificial Neural Network Model in Predicting the Early Distribution Kinetics of Propofol in Morbidly Obese and Lean Subjects. *Anesthesia and analgesia*, *131*(5), 1500–1509. https://doi.org/10.1213/ANE.0000000000004897
52. Twinanda, A. P., Yengera, G., Mutter, D., Marescaux, J., & Padoy, N. (2019). RSDNet: Learning to Predict Remaining Surgery Duration from Laparoscopic Videos Without Manual Annotations. *IEEE transactions on medical imaging*, *38*(4), 1069–1078. https://doi.org/10.1109/TMI.2018.2878055
53. Hashimoto, D. A., Rosman, G., Witkowski, E. R., Stafford, C., Navarette-Welton, A. J., Rattner, D. W., Lillemoe, K. D., Rus, D. L., & Meireles, O. R. (2019). Computer Vision Analysis of Intraoperative Video: Automated Recognition of Operative Steps in Laparoscopic Sleeve Gastrectomy. *Annals of surgery*, *270*(3), 414–421. https://doi.org/10.1097/SLA.0000000000003460
54. Hany, M., Abdou, M. E., Abokhozima, A., & Zidan, M. H. (2025). Bridging Generations in Metabolic and Bariatric Surgery: Honoring Legacy and Embracing Technology in The Age of Artificial Intelligence. *Obesity surgery*, *35*(2), 376–378. https://doi.org/10.1007/s11695-024-07655-x
55. Sheikhtaheri, A., Orooji, A., Pazouki, A., & Beitollahi, M. (2019). A Clinical Decision Support System for Predicting the Early Complications of One-Anastomosis Gastric Bypass Surgery. *Obesity surgery*, *29*(7), 2276–2286. https://doi.org/10.1007/s11695-019-03849-w
56. Nudel, J., Bishara, A. M., de Geus, S. W. L., Patil, P., Srinivasan, J., Hess, D. T., & Woodson, J. (2021). Development and validation of machine learning models to predict gastrointestinal leak and venous thromboembolism after weight loss surgery: an analysis of the MBSAQIP database. *Surgical endoscopy*, *35*(1), 182–191. https://doi.org/10.1007/s00464-020-07378-x
57. Yaqub, M., Jinchao, F., Arshid, K., Ahmed, S., Zhang, W., Nawaz, M. Z., & Mahmood, T. (2022). Deep Learning-Based Image Reconstruction for Different Medical Imaging Modalities. *Computational and mathematical methods in medicine*, *2022*, 8750648. https://doi.org/10.1155/2022/8750648
58. Currie, G., Hawk, K. E., Rohren, E., Vial, A., & Klein, R. (2019). Machine Learning and Deep Learning in Medical Imaging: Intelligent Imaging. *Journal of medical imaging and radiation sciences*, *50*(4), 477–487. https://doi.org/10.1016/j.jmir.2019.09.005
59. Heydari, S. T., Ayatollahi, S. M., & Zare, N. (2012). Comparison of artificial neural networks with logistic regression for detection of obesity. *Journal of medical systems*, *36*(4), 2449–2454. https://doi.org/10.1007/s10916-011-9711-4
60. Gerl, M. J., Klose, C., Surma, M. A., Fernandez, C., Melander, O., Männistö, S., Borodulin, K., Havulinna, A. S., Salomaa, V., Ikonen, E., Cannistraci, C. V., & Simons, K. (2019). Machine learning of human plasma lipidomes for obesity estimation in a large population cohort. *PLoS biology*, *17*(10), e3000443. https://doi.org/10.1371/journal.pbio.3000443
61. Zhai, B., Elder, G. J., & Godfrey, A. (2024). Challenges and opportunities of deep learning for wearable-based objective sleep assessment. *NPJ digital medicine*, *7*(1), 85. https://doi.org/10.1038/s41746-024-01086-9
62. Karako K. (2024). Integration of wearable devices and deep learning: New possibilities for health management and disease prevention. *Bioscience trends*, *18*(3), 201–205. https://doi.org/10.5582/bst.2024.01170
63. Singer, P., Robinson, E., & Raphaeli, O. (2024). The future of artificial intelligence in clinical nutrition. *Current opinion in clinical nutrition and metabolic care*, *27*(2), 200–206. https://doi.org/10.1097/MCO.0000000000000977
64. Forte, P., Encarnação, S., Monteiro, A. M., Teixeira, J. E., Hattabi, S., Sortwell, A., Branquinho, L., Amaro, B., Sampaio, T., Flores, P., Silva-Santos, S., Ribeiro, J., Batista, A., Ferraz, R., & Rodrigues, F. (2023). A Deep Learning Neural Network to Classify Obesity Risk in Portuguese Adolescents Based on Physical Fitness Levels and Body Mass Index Percentiles: Insights for National Health Policies. *Behavioral sciences (Basel, Switzerland)*, *13*(7), 522. https://doi.org/10.3390/bs13070522
65. Sun, T., He, X., & Li, Z. (2023). Digital twin in healthcare: Recent updates and challenges. *Digital health*, *9*, 20552076221149651. https://doi.org/10.1177/20552076221149651
66. Schwalbe, N., & Wahl, B. (2020). Artificial intelligence and the future of global health. *Lancet (London, England)*, *395*(10236), 1579–1586. https://doi.org/10.1016/S0140-6736(20)30226-9
67. Batterham, M., Tapsell, L., Charlton, K., O'Shea, J., & Thorne, R. (2017). Using data mining to predict success in a weight loss trial. *Journal of human nutrition and dietetics : the official journal of the British Dietetic Association*, *30*(4), 471–478. https://doi.org/10.1111/jhn.12448
68. Ogrizović M, Drašković D, Bojić D.(2024) Quality assurance strategies for machine learning applications in big data analytics: an overview. J Big Data. 2024 Oct 30;11(1):156. doi:10.1186/s40537-024-01028-y
69. Alkhalaf M, Yu P, Shen J, Deng C. (2022)A review of the application of machine learning in adult obesity studies. ACI. 2022;2(1):32–48. doi:10.3934/aci.2022002

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