REVIEW
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Diseases & Research

Artificial Intelligence in Histopathological Diagnosis: Achievements and Challenges of Digital Pathology

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Abstract: Artificial intelligence (AI) and digital pathology (DP) are transforming the landscape of diagnostic histopathology. This review provides an overview of how traditional pathology workflows-long reliant on physical slides and subjective interpretation-are being reshaped by digital slide acquisition, machine learning algorithms, and multi-omics integration. The article outlines the historical foundations of diagnostic pathology and the shift toward digitization, followed by an exploration of the practical challenges in implementing AI tools, including infrastructure needs, training requirements, and regulatory considerations. The clinical applications of AI-such as automated cancer detection, mutation prediction, and deep learning-based classification-are discussed alongside recent developments in federated learning and explainable AI (XAI). Particular attention is given to the integration of genomics and digital morphology, which allows for more accurate prognostic and predictive modeling. While the implementation of AI raises concerns regarding cost, standardization, and interpretability, the conclusion emphasizes that AI will serve as a powerful tool to support-not replace-the pathologist. By enhancing diagnostic reproducibility, reducing workload, and expanding the analytical scope of histopathology, AI has the potential to advance precision medicine and improve patient care.

Keywords: Digital pathology; Histopathology; Diagnosis; Cancer; Precision medicine; Artificial intelligence.

Introduction

For more than a century, diagnostic pathology has relied on the visual examination of stained tissue sections under a light microscope.

Tissues obtained through surgical procedures or biopsies are processed using well-established techniques, embedded in paraffin, sectioned, stained-typically with hematoxylin and eosin-and evaluated for cellular and structural features.

This workflow, though largely unchanged since the 19th century, remains cost-effective and diagnostically powerful, forming the backbone of routine pathological assessment across a wide range of diseases[1].

In the last decade, diagnostic pathology has undergone a substantial transformation driven by advances in molecular profiling (MP) and digital pathology (DP). Traditional classification systems, which are based primarily on tissue of origin and histological morphology, are increasingly being challenged by evidence of molecular heterogeneity across tumors[2]. Tumors from different anatomical sites may share common molecular features, while tumors from the same site may differ significantly in their genetic profiles. Recent evidence indicates that the use of artificial intelligence (AI) can improve the diagnostic accuracy of pathological diagnosis[3].

This shift has prompted a growing interest in classification systems rooted in genomic alterations rather than histological appearance alone. In parallel, digital pathology-characterized by the conversion of glass slides into high-resolution whole-slide images (WSIs)-has gained regulatory recognition. The FDA's approval of WSI systems in 2017 marked a pivotal moment, with subsequent studies validating their diagnostic equivalence to traditional light microscopy in more than 2,000 cases[4].

Simultaneously, the integration of artificial intelligence (AI) into digital pathology workflows has enabled significant improvements in diagnostic performance and efficiency. A recent meta-analysis involving over 150,000 WSIs demonstrated that AI-based systems achieved a mean sensitivity of 96.3% and specificity of 93.3% across various diagnostic tasks. However, the generalizability of these high-performance metrics can be influenced by the homogeneity of training data, often derived from specific institutions and scanner models, necessitating robust external validation[5]. In the context of breast cancer lymph node metastasis detection, AI-assisted workflows improved sensitivity

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from 74.5% to 93.5%, while reducing average slide review time from 129 to 58 seconds[6,7].

Beyond diagnostic accuracy, AI models have shown potential in inferring molecular subtypes and genetic alterations directly from H&E-stained slides. In lung cancer, deep learning algorithms have reached 83–97% accuracy in distinguishing adenocarcinoma from squamous cell carcinoma. Some models have also predicted gene mutation status that is not morphologically visible. Additionally, large-scale "foundation models" trained over 1.5 million WSIs across 17 cancer types have demonstrated robust performance, with specimen-level AUC values reaching 0.949[4].

Despite these promising developments, several challenges remain. The lack of standardized protocols for image acquisition and annotation, variability in staining methods, and insufficient external validation across institutions limit the generalizability of many AI solutions. Another critical concern is the limited interpretability of many AI models, often described as "black boxes". This has led to the emergence of Explainable AI (XAI), which offers visualizations such as heatmaps and attention maps to clarify which features contributed to the model's output, thereby facilitating clinical trust and adoption 7. While methods like Grad-CAM and LIME provide visual cues, translating these into robust, pathologist-understandable rationales for complex diagnoses remains an active area of research[8]. Initial clinical implementation efforts have begun in select institutions. For example, AI tools are being evaluated in prostate cancer grading and colorectal polyp classification at several academic medical centers. These early efforts suggest that, with proper validation, AI-assisted digital workflows may be gradually integrated into routine pathology practice[9].

In conclusion, the convergence of AI and DP represents a transformative moment in diagnostic medicine. With continued technical refinement, regulatory oversight, and clinical validation, AI-enhanced pathology has the potential to deliver faster, more reproducible, and more precise diagnoses, ultimately contributing to the advancement of personalized medicine[1].

Therefore, this narrative review systematically synthesizes current evidence on artificial-intelligence-driven digital pathology. We conducted a comprehensive literature search across PubMed, Scopus, and Web of Science databases using keywords such as "digital pathology", "artificial intelligence", "histopathological diagnosis", "deep learning" and "precision medicine", focusing on articles published between 2006 and 2025. Our selection prioritized peer-reviewed original research, meta-analyses, and authoritative review articles addressing diagnostic accuracy, molecular stratification, and explainability. In the sections that follow, we first delineate how routine pathology workflows evolve in the era of whole-slide imaging and cloud-based infrastructures, then examine algorithmic performance across major tumor types, discuss validation and regulatory pathways, and conclude with future research priorities.

The pathology workflows in the era of digital imaging

The adoption of digital pathology has fundamentally transformed organizational dynamics within pathology departments, affecting diagnostic routines, interprofessional communication, and laboratory infrastructure. One of the most rapidly impacted areas is the operational framework of anatomical pathology units, where manual handling of glass slides has given way to streamlined, high-throughput digital workflows powered by advanced imaging systems[10].

Once glass slides are converted into digital format using high-resolution whole-slide scanners, the resulting images are automatically uploaded to the Laboratory Information Management System (LIMS). This integration enables immediate access from any authorized workstation, allowing pathologists to review or share cases without waiting for physical slides to circulate. This paradigm shift optimizes workload distribution and reduces administrative overhead associated with slide logistics[11].

Beyond in-house accessibility, digital workflows facilitate remote diagnostics and consultation. Early pioneering work in telepathology by Weinstein et al.[12,13] laid the foundation, while modern advances by Krupinski et al. and others demonstrate improved case turnaround and interobserver agreement-especially in frozen-section analysis[14]. This capability is particularly critical for community or rural hospitals that lack specialist expertise in subspecialties such as hematopathology, neuropathology, or dermatopathology. Secure sharing of digital slides permits real-time expert review without delays and risks of physical transport[15].

A further advantage of digital pathology lies in the development of centralized case repositories. Digital images can be curated and indexed by diagnosis, staining technique, molecular profile, or patient metadata, enabling efficient retrieval and comparative review. This allows pathologists to easily revisit historical cases from the same patient or review morphologically similar cases across a patient's cohort. Such archives aid in reducing diagnostic inconsistencies and support longitudinal disease monitoring, resident education, proficiency testing, and even retrospective research studies[16].

Integration with computational image analysis tools is another major strength of digital workflows. Validated software solutions can accurately quantify histologic features including cellular morphology, mitotic activity, and immunohistochemical biomarker expression. For instance, Yan et al (2024) validated an AI algorithm for PD-L1 scoring in diffuse large B-cell lymphoma, showing high concordance with expert pathologist assessments[17]. Other studies confirm consistent quantification of Ki-67 and nuclear atypia across institutions, reducing observer variability and enhancing reproducibility[18].

By delegating repetitive quantitative tasks to software, pathologists can focus on diagnostic interpretation and contextualization, while ensuring high fidelity in measurement. This hybrid model promotes greater objectivity and minimizes subjective bias, especially in biomarker-driven oncologic decision-making[4,19].

To further illustrate the operational shift introduced by digitization, Table 1 summarizes key differences between conventional and digital pathology workflows. The comparison highlights how digital systems enhance efficiency, support remote collaboration, and enable reproducible quantitative analysis.

Collectively, digital pathology redefines the spatial and temporal dimensions of diagnostic work. Real-time access, intelligent data organization, computational augmentation, and remote collaboration create a robust, scalable diagnostic ecosystem. This environment supports standardized practices, accelerates turnaround times, and fosters interdisciplinary collaboration-key components of modern precision medicine initiatives[20].

Table 1. Comparison of Conventional vs Digital Pathology Workflows: Comparison of key workflow components between conventional and digital pathology systems.

Feature	Conventional Pathology	Digital Pathology
Slide access	Physical only, location-bound	Remote, simultaneous multi-user access
Time to review	Variable (logistics-dependent)	Immediate, via digital workstation
Subspecialty consultation	Delayed (slide shipment required)	Real-time remote consultation
Quantitative analysis	Manual, subjective	Automated, reproducible
Archive and retrieval	Physical storage, non-indexed	Digitally indexed, searchable database
Educational use	Limited storage and accessibility	Global access to annotated archives

Digital pathology enables faster, scalable, and more collaborative diagnostic processes.

Challenges for digital pathology

While digital pathology (DP) has brought substantial advancements in diagnostics, workflow efficiency, and interprofessional collaboration, several significant challenges continue to limit its full integration into routine clinical practice. These issues span technical, infrastructural, regulatory, and logistical domains.

An early misconception-analogous to the rise of molecular pathology-was that digital tools could completely replace traditional histopathology. However, this perspective overlooks a fundamental dependency: a high-quality digital image is only possible if derived from an equally high-quality physical histological slide. The pre-analytical phase remains a cornerstone of diagnostic accuracy. The technical staff must continue to apply rigorous standards in tissue processing, sectioning, and staining to ensure that digitized material meets the resolution and fidelity requirements for diagnostic interpretation[10,11].

A major unresolved barrier lies in the lack of standardized digital image formats across scanner vendors. Unlike radiology, which has widely adopted the DICOM format, pathology imaging still suffers from fragmentation. Each digital slide scanner manufacturer typically uses proprietary image formats, which complicates image sharing between institutions, particularly in multicenter studies or external consultations. This limits the interoperability of systems and hinders collaborative diagnostic workflows. Initiatives aiming to develop a unified digital pathology standard are in progress, but widespread adoption has yet to occur. Until then, inter-institutional diagnostic networks remain restricted mainly to research collaboration rather than real-time clinical deployment[14,21].

Fig. 1 illustrates a typical digital pathology workflow, from slide preparation and scanning to data archiving, AI-assisted interpretation, and report generation. This schematic emphasizes how technical and organizational bottlenecks-such as format incompatibility and storage infrastructure-can affect the implementation of digital systems across institutions.

Another constraint is related to workforce dynamics. As diagnostic demand rises-driven by an aging population, increased cancer screening, and expanding use of companion diagnostics-the volume and complexity of pathology cases continue to grow. Paradoxically, many regions are facing a decline in the number of practicing pathologists. Digital pathology offers opportunities to mitigate workload through AI assistance and remote triaging, but its successful implementation requires strategic workforce planning, training, and resource allocation[15].

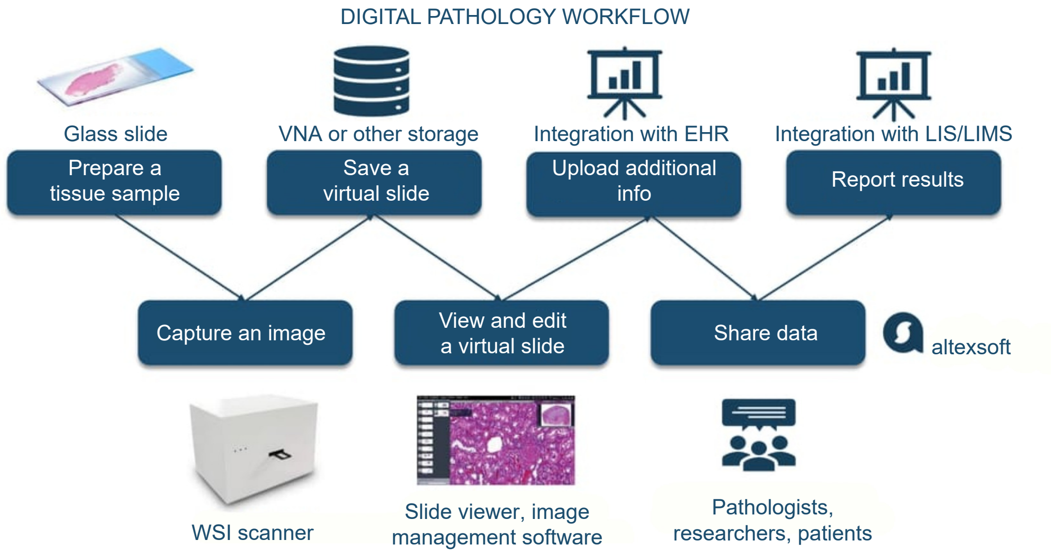

Fig. 1. Schematic representation of the digital pathology workflow, including slide scanning, LIMS integration, digital archiving, remote consultation, and computational analysis.
Adapted from open-source materials (e.g., Kvalito Consulting Group [2023]; AltexSoft [2022]) under CC license[22]).

Infrastructure and storage requirements also pose significant challenges. High-resolution whole-slide images generate enormous file sizes-ranging from hundreds of megabytes to several gigabytes per slide. For high-throughput institutions, this can amount to petabytes of data annually, necessitating robust and scalable data storage solutions. Moreover, there is ongoing debate about the legal and regulatory requirements regarding long-term retention of digital images versus physical glass slides. While some institutions maintain both formats to satisfy compliance and verification protocols, others are exploring digital-only archiving strategies. However, no universal consensus exists, and practices vary widely depending on national legislation, institutional policy, and technological capacity[16].

Additionally, concerns persist regarding long-term accessibility and digital image integrity. Institutions must ensure that images remain retrievable and diagnostically intact over extended periods, which demand regular system maintenance, software updates, and future-proof data migration strategies. These factors contribute to the total cost of ownership of digital pathology platforms, potentially hindering adoption, especially in low-resource settings[23].

Lastly, the implementation of quality control protocols, consensus criteria, and validation studies is essential to establish diagnostic reliability equivalent to or better than that of traditional light microscopy. Without regulatory frameworks and multicenter validation, the routine use of DP in primary diagnosis will continue to face institutional hesitation.

In summary, while digital pathology holds transformative potential, its widespread deployment is impeded by technological fragmentation, workforce limitations, storage burdens, and the absence of standardized practices. Addressing these challenges will be key to realizing the full promise of digital diagnostics in the era of precision medicine.

AI-driven decision support systems in digital pathology

The transformation enabled by digital pathology extends well beyond the digitization of histological slides. Once analog slides are converted into high-resolution whole-slide images (WSIs), they provide a foundation not only for remote access and archiving, but also for advanced computational analysis[4,24]. At the forefront of this transformation is the integration of AI-powered decision support systems (DSS), which leverage machine learning and deep learning algorithms to assist pathologists in diagnostic workflows[1,4,24].

These systems are designed to analyze complex tissue patterns and provide interpretive support across a growing number of pathological conditions. They differ from traditional diagnostic aids in that they can learn from vast datasets and continuously improve their predictive capabilities. While many platforms remain under clinical validation, early examples demonstrate substantial potential. For instance, commercially available systems like Paige Prostate have received FDA clearance for prostate cancer detection and grading, demonstrating high concordance with expert pathologists in routine clinical settings. Similarly, Ibex Galen™ has been successfully deployed in multiple laboratories for real-time detection of various cancer types, significantly improving diagnostic efficiency and accuracy in high-volume settings[25]. In controlled studies, some of these tools have achieved diagnostic accuracy metrics (AUC > 0.95) comparable to, or in some cases exceeding, human experts in narrow domains such as prostate or breast cancer screening[26,27].

Unlike fully autonomous AI, these tools are generally intended to function in a complementary role, augmenting pathological decision-making rather than replacing it. They can help reduce oversight errors, flag atypical regions for closer inspection, and standardize interpretation, particularly in borderline or ambiguous cases. Their utility is especially pronounced in high-volume laboratories, where workload and time pressure pose significant challenges[28].

In addition to classification and detection tasks, AI-based systems are increasingly capable of predicting molecular profiles and clinical outcomes from routine H&E images. Several recent studies have demonstrated that AI can infer the presence of specific mutations (e.g., EGFR, TP53) and even patient prognosis based on histological features alone, without requiring additional molecular testing[29,30]. These capabilities may eventually support pathology-driven treatment stratification in precision oncology.

Despite these advances, important challenges remain. Regulatory approval is limited to a small subset of applications, and many algorithms are trained on homogenous datasets, which may not generalize across different institutions, scanner types, or population groups. Moreover, transparency and explainability remain critical concerns. Without clear interpretability mechanisms-such as heatmaps or confidence scoring-clinicians may hesitate to fully trust algorithmic output.

Integration into routine workflows also requires compatibility with existing laboratory information systems (LIS) and digital slide viewers. Seamless interaction between AI tools and the digital pathology ecosystem (e.g., through DICOM standards or HL7 protocols) is essential for clinical adoption. Furthermore, ethical and legal issues regarding liability in case of AI-assisted misdiagnosis are yet to be fully addressed, particularly in jurisdictions where medical software is tightly regulated[31,32].

Nevertheless, as digital pathology becomes the standard of care, decision support systems powered by AI are poised to play an increasingly central role. When rigorously validated and properly integrated, they offer a powerful means to enhance diagnostic precision, reduce variability, and support the broader shift toward computational and personalized medicine[33].

Digital pathology and AI applications

The term "artificial intelligence" was coined by McCarthy et al. in 1956 during the Dartmouth Summer Research Project on Artificial Intelligence, marking a pivotal moment in the field's inception[34], which has since taken on multiple connotations. It refers broadly to the concept that machines can make predictions, recognize patterns, or solve problems in ways that mimic human cognitive processes. Over the past seven decades, this idea has evolved from theoretical speculation to widespread implementation across various fields[11].

And, after 70 years of predictions, AI has indeed become a reality. However, the practical application of AI techniques to diagnostic pathology remains in its early stages. Despite rapid advances in computational power, algorithmic sophistication, and digital infrastructure, the integration of AI into routine diagnostic workflows is still limited. As a result, predicting its long-term impact on diagnostic practice-and especially the timeline of its adoption-remains highly uncertain[35].

In clinical practice, histopathological diagnosis relies fundamentally on visual recognition and semi-quantitative assessment of morphological characteristics within tissue sections. The pathologist performs this complex task by observing the slide under a microscope (or digitally), recognizing and interpreting specific patterns that correspond to normal or pathological processes. These visual impressions are then contextualized with clinical, radiological, and molecular data to establish a diagnosis[9,36].

The ability to perform such tasks is not innate but the result of extensive medical training and years of experience. Through a rigorous education and specialization process, pathologists learn to recognize diagnostically relevant morphological features and to correlate them with disease classifications as defined by established criteria in scientific literature. Based on this integration, the pathologist formulates a diagnostic conclusion and conveys it through a structured histopathological report, which becomes a cornerstone of clinical decision-making[37].

Standardized diagnostic frameworks, such as the WHO tumor classification and CAP protocols, help reduce interobserver variability and promote reproducibility. However, the diagnostic process is still subject to individual perception, judgment, and cognitive bias. In fact, interobserver variability remains a documented challenge in several subspecialties of pathology, particularly in the grading of dysplasia, tumor margins, or subtle cellular atypia. Subjectivity in visual perception and cognitive fatigue can influence diagnostic outcomes even among experienced practitioners[38].

In this context, artificial intelligence offers a promising complementary tool. AI systems-particularly those based on deep learning-are trained on thousands of annotated images and can perform tasks such as classification, segmentation, and feature extraction with growing accuracy. These tools may assist in objectifying measurements (e.g., mitotic count, nuclear atypia), detecting patterns that are difficult for the human eye to quantify, or even predicting molecular alterations from H&E slides. Moreover, AI can contribute to quality control, triaging, and prescreening by highlighting regions of interest for further review[39].

Nevertheless, the current role of AI remains that of a supportive technology, augmenting but not replacing the diagnostic acumen of the pathologist. The synergy between human expertise and machine precision represents the most realistic and ethically grounded model for integrating AI into pathology[40].

AI applications in low-volume tissue diagnostics

The evolution of diagnostic techniques has led to a growing reliance on less invasive procedures for obtaining tissue samples. Minimally invasive approaches such as fine-needle aspiration, core needle biopsies, and image-guided sampling have become the standard in many clinical settings[41]. While these procedures offer clear benefits in terms of patient safety, reduced complications, and faster recovery, they present new challenges for histopathological assessment.

This shift toward smaller and more limited tissue specimens requires pathologists to extract maximal diagnostic, prognostic, and predictive information from minimal material. Often, tissue samples now consist of just a few millimeters of core biopsy or cytology smears, which must be analyzed not only for morphological features but also for immunohistochemistry and, in many cases, molecular profiling. Consequently, there is increasing pressure on histopathology services to deliver comprehensive and accurate diagnostic reports despite constrained sample volumes[42,43].

In this context, artificial intelligence tools provide a promising avenue for maintaining diagnostic accuracy in the face of limited material. AI programs, which have already received regulatory approval for diagnostic use, can assist-and in certain settings, potentially replace-pathologists in well-defined diagnostic tasks. By leveraging pattern recognition, feature quantification, and probabilistic modeling, these systems can extract subtle histologic patterns and make reproducible classifications even from small and fragmented samples[44].

Examples of this type of program, which can currently be utilized in clinical practice, include the diagnostic evaluation of prostate biopsies for the identification and grading of prostatic adenocarcinoma[14], and the detection of lymph node micrometastases in breast cancer[21]. In the case of prostate cancer, deep learning algorithms have demonstrated non-inferiority to expert pathologists in identifying malignant foci and assigning Gleason grades, particularly in standard H&E-stained core biopsies. Similarly, in breast cancer, AI systems trained on tens of thousands of annotated images have been able to reliably detect micrometastatic tumor deposits in sentinel lymph nodes, which may be overlooked during routine slide examination due to their subtle morphology and small size[26,45,46].

These applications demonstrate how AI can enhance diagnostic throughput and consistency, especially in scenarios where sample material is sparse, and precision is critical. Moreover, automated tools reduce the cognitive load on pathologists and ensure uniform interpretation across institutions, thereby contributing to diagnostic standardization and quality control[47].

Although the integration of such technologies into routine workflows is still in progress, their use in specific, narrowly defined diagnostic tasks illustrates the growing symbiosis between artificial intelligence and modern histopathology in an era of minimally invasive medicine[28].

Table 2 summarizes selected AI-based diagnostic tools currently used or validated for low-volume tissue specimens, highlighting their application areas and sample types.

Training AI models through supervised learning

Artificial intelligence in histopathology relies heavily on supervised machine learning, a paradigm that closely mirrors the cognitive training of human pathologists[48]. In this approach, algorithms are trained using large datasets composed of digital slides labeled with known diagnoses. The system learns to associate specific morphological features with diagnostic outcomes by iteratively analyzing these annotated images[49].

This training process involves multiple cycles of pattern recognition, prediction, and correction. Initially, the model evaluates a set of labeled examples, adjusting its internal parameters to minimize the difference between its predictions and the ground truth. Over time, the algorithm "learns" to classify or segment tissue structures with increasing precision, eventually achieving diagnostic performance comparable to that of expert pathologists[1]. As illustrated in Fig. 2, supervised learning in digital pathology follows a clearly defined workflow-from the initial collection of labeled data to model validation and clinical implementation[50].

Table 2. Selected examples of artificial intelligence applications in diagnostic histopathology involving small or minimally invasive tissue samples.

AI Tool / Study	Application	Sample Type	Task	Validation
Paige Prostate	Prostate cancer	Core needle biopsies	Tumor detection, Gleason grading	FDA-cleared, CE-marked
Lunit INSIGT MMG	Breast cancer	Sentinel lymph nodes	Detection of micrometastases	Multicenter validation
Ibex Galen™	Breast biopsy	Small-volume biopsies	Invasive carcinoma detection	Peer-reviewed studies
PathAI	General oncology	Multiple sample types	Triage, classification, biomarker AI	Ongoing clinical trials

Adapted from published sources[26].

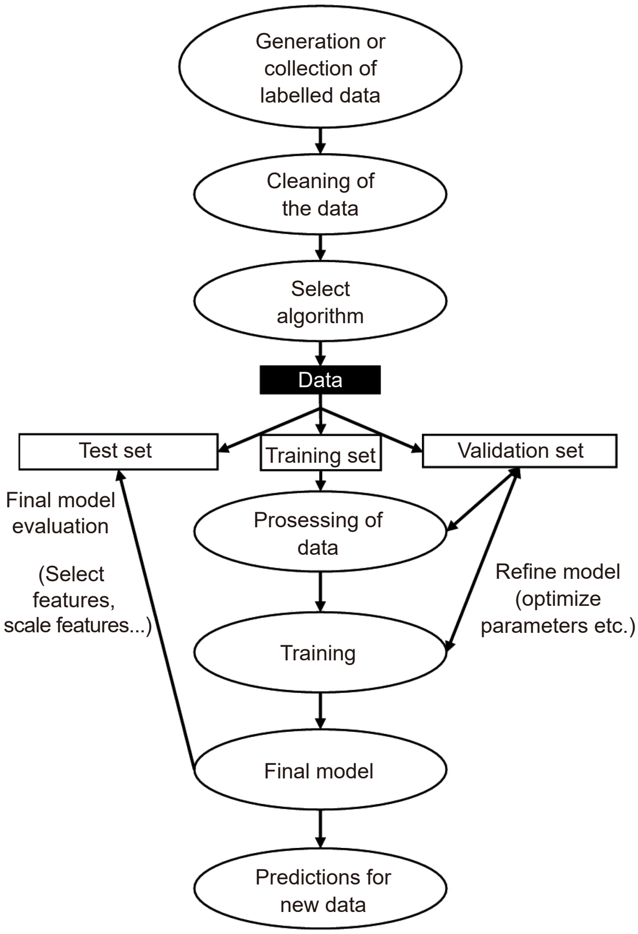

Fig. 2. Workflow of supervised machine learning: data labeling, training-validation-test split, algorithm training, and evaluation.
Adapted from Schmidt et al., under CC BY license[50].

Once trained, the algorithm must be validated using independent datasets to assess its generalizability. This validation typically measures sensitivity, specificity, and overall accuracy in replicating human-level diagnoses across diverse samples and institutions[4].

Despite promising results, these tools-many of which have recently received regulatory approval-are still not widely used in routine diagnostic workflows. However, their potential to enhance consistency, reduce interpretive variability, and support reproducible diagnostic outcomes positions them as valuable adjuncts in modern histopathology[10,51].

The federated learning network

To further explore the integration of AI into diagnostic workflows, the San Donato Institute has launched a multi-center research initiative funded by the Italian Ministry of Health. The study aims to evaluate the impact of artificial intelligence algorithms on the detection and grading of prostatic adenocarcinoma in patients undergoing core needle prostate biopsies.

In this project, the San Donato Institute serves as the coordinating center. Two additional institutions-Reggio Emilia and Trento-will contribute to the analysis through a Federated Learning network architecture. This decentralized model enables collaborative algorithm training across institutions without direct sharing of patient data, thereby ensuring data privacy and regulatory compliance.

The study will involve a combined caseload of approximately 1,200 patients. Its outcomes are expected to provide real-world insights into the clinical utility of AI-assisted diagnostic systems in prostate cancer pathology.

Deep learning in digital pathology and omics integration

While traditional supervised learning algorithms have laid the foundation for computational diagnostics, recent advances in processing power and data infrastructure have enabled the widespread development of neural networks and deep learning. These architectures represent a substantial leap in artificial intelligence, capable of analyzing massive amounts of unstructured data derived from digital pathology slides and beyond[52].

In contrast to earlier rule-based or feature-engineered models, deep neural networks are designed to learn hierarchical feature representations directly from raw input, such as whole-slide images. This capability allows them not only to detect patterns invisible to the human eye, but also to integrate complex datasets from diverse biomedical domains. The increasing availability of

GPUs and high-performance computing infrastructure has played a crucial role in making this computational complexity feasible in real-world clinical and research environments[52,53].

Deep learning systems expand our ability to extract both qualitative and quantitative information from histopathological slides. Beyond cell morphology and tissue structure, these models can capture subtle spatial variations, texture gradients, and architectural patterns that may correlate with disease behavior. Importantly, deep learning also opens the door to multimodal integration-the combination of digital pathology data with genomic, transcriptomic, proteomic, or radiomic features to build a comprehensive and predictive biological framework[21].

The conceptual framework of multimodal data integration through AI systems is illustrated in Fig. 3, highlighting the potential of deep learning to unify histological, genomic, proteomic, and radiological inputs for enhanced diagnostic and prognostic accuracy.

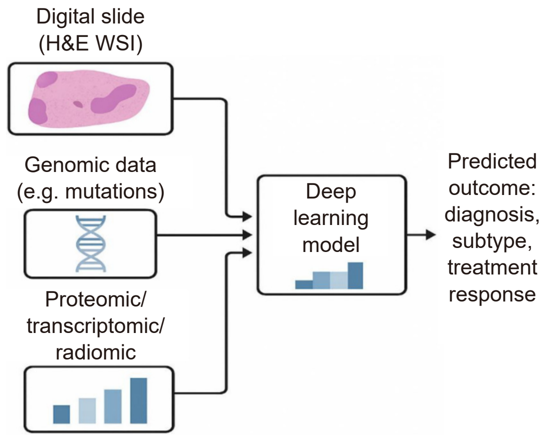

Fig. 3. Schematic representation of a deep learning pipeline integrating digital histopathology slides and multi-omics data (genomics, transcriptomics, proteomics) to predict diagnostic categories, molecular subtypes, and treatment response.
Adapted for illustrative purposes.

Indeed, the morphological phenotype observed on the slide-whether physical or digital-is the visual reflection of complex biological states driven by molecular alterations. These include driver mutations, differential gene expression, epigenetic shifts, and protein-level dysregulations[54]. By correlating these molecular profiles with image-based features, AI models can potentially predict underlying genomic events or treatment responsiveness without requiring additional molecular assays[55].

Such approaches are already being tested in several types of tumors. For example, deep learning models have been trained to infer mutation status (e.g., EGFR, KRAS, TP53) in lung and colorectal cancer directly from H&E images, promising accuracy[56]. Similar efforts are underway to predict microsatellite instability, tumor mutational burden, and even response to immunotherapy-all from routine histology[57].

In this context, neural networks do not merely automate diagnostic routines but extend the pathologist's reach into the molecular underpinnings of disease. The fusion of digital morphology with "omics" data through deep learning may ultimately transform histopathology into a truly predictive and personalized discipline[58].

Applicability of AI in digital pathology

While the integration of artificial intelligence into digital pathology presents exciting opportunities, it also introduces a range of practical challenges that may hinder widespread adoption across diagnostic laboratories. The development and deployment of AI-based tools require not only substantial financial investment but also highly specialized technical infrastructure, which may not be accessible to all healthcare institutions[59,60].

The core of AI system development lies in the expertise of computer engineers and data scientists, who are responsible for designing, training, and validating algorithmic models[59]. However, pathologists remain the primary end users of these tools and must ultimately oversee their clinical implementation[60]. Their role extends beyond passive application; it includes ensuring that the diagnostic outputs align with clinical standards and real-world variability.

To ensure effective and safe integration of AI systems into routine practice, the establishment of interdisciplinary teams is essential[61]. These teams must bring together professionals with diverse backgrounds, including software engineering, machine learning, pathology, and clinical medicine. This collaborative structure enables a shared understanding of both technical limitations and diagnostic priorities, thereby fostering the development of clinically meaningful AI solutions.

At the same time, the incorporation of AI tools into diagnostic workflows will require significant adjustments in medical education and training[33]. New educational programs in pathology and other diagnostic disciplines must be introduced to equip future specialists with the necessary digital competencies[33]. The goal is not to turn clinicians into programmers, but rather to ensure that they are able to critically evaluate AI outputs, understand model limitations, and maintain clinical oversight over automated processes.

Ultimately, the successful implementation of AI in pathology depends not only on technological innovation but also on structural and cultural readiness within healthcare institutions. A coordinated effort involving policy makers, educators, hospital administrators, and clinicians will be necessary to ensure equitable and effective adoption of this transformative technology[7].

Conclusions

Although the integration of artificial intelligence into digital pathology holds enormous promise, its widespread implementation still faces financial, technical, and regulatory challenges. Developing clinically validated AI tools requires significant investment in data acquisition, algorithm training, and quality assurance. While several commercial and academic groups have already introduced AI-powered systems into pathology workflows, cost-effectiveness and scalability remain important concerns.

Despite early fears, there is currently no realistic scenario in which AI will replace the pathologist. The interpretation of complex histological images still relies on expert knowledge, clinical reasoning, and nuanced judgment that cannot be fully replicated by algorithms. Rather than replacing the human diagnostician, AI will increasingly serve as an assistive tool-reducing workload in routine or repetitive tasks, minimizing inter-observer variability, and enhancing reproducibility across institutions.

In the short term, AI systems are expected to contribute most significantly to areas such as pre-screening, quality control, and the prediction of prognostic or therapeutic biomarkers. This may free pathologists to dedicate more attention to complex or ambiguous cases, research, and interdisciplinary collaboration. Ultimately, the convergence of digital pathology and artificial intelligence has the potential to elevate the diagnostic process to new levels of precision, consistency, and clinical utility-paving the way for a new era of personalized, data-driven medicine.

Abbreviations

AI, Artificial Intelligence; AUC, Area Under the Curve; DICOM, Digital Imaging and Communications in Medicine; DP, Digital Pathology; FDA, Food and Drug Administration; Grad-CAM, Gradient-weighted Class Activation Mapping; H&E, Hematoxylin and Eosin; Ki-67, Ki-67 Proliferation Index; LIME, Local Interpretable Model-agnostic Explanations; LIMS, Laboratory Information Management System; MP, Molecular Profiling; PD-L1, Programmed Death-Ligand 1; WSI, Whole-Slide Image; WSIs, Whole-Slide Images; XAI, Explainable Artificial Intelligence.

Conflicts of interest

The authors have no conflict of interest to disclose.

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Authors' contributions

PPP and VT: Conception and design. CI, SS, PC, GT: Data collection and analysis. PPP and GT: Supervision. PPP: Funding acquisition.

References

[1] Fatima G, Alhmadi H, Mahdi AA, et al. Transforming Diagnostics: A Comprehensive Review of Advances in Digital Pathology. Cureus, 2024, 16(10).

[2] Carbone A. Cancer Classification at the Crossroads. Cancers, 2020, 12(4): 980.

[3] Kusta O, Rift CV, Risør T, et al. Lost in digitization-A systematic review about the diagnostic test accuracy of digital pathology solutions. J Pathol Inform, 2022, 13: 100136.

[4] McGenity C, Clarke EL, Jennings C, et al. Artificial intelligence in digital pathology: a systematic review and meta-analysis of diagnostic test accuracy. Npj Digit Med, 2024, 7(1): 114.

[5] Suleman MU, Mursaleen M, Khalil U, et al. Assessing the generalizability of artificial intelligence in radiology: a systematic review of performance across different clinical settings. Ann Med Surg, 2025, 87(12): 8803-8811.

[6] Zhang DY, Venkat A, Khasawneh H, et al. Implementation of Digital Pathology and Artificial Intelligence in Routine Pathology Practice. Lab Invest, 2024, 104(9): 102111.

[7] Gaffney H, Mirza KM. Pathology in the artificial intelligence era: Guiding innovation and implementation to preserve human insight. Acad Pathol, 2025, 12(1): 100166.

[8] Mumtaz H, Riaz MH, Wajid H, et al. Current challenges and potential solutions to the use of digital health technologies in evidence generation: a narrative review. Front Digit Health, 2023, 5: 1203945.

[9] You JG, Hernandez-Boussard T, Pfeffer MA, et al. Clinical trials informed framework for real world clinical implementation and deployment of artificial intelligence applications. Npj Digit Med, 2025, 8(1): 107.

[10] Fraggetta F, L'Imperio V, Ameisen D, et al. Best Practice Recommendations for the Implementation of a Digital Pathology Workflow in the Anatomic Pathology Laboratory by the European Society of Digital and Integrative Pathology (ESDIP). Diagnostics, 2021, 11(11): 2167.

[11] McCarthy J, Minsky ML, Rochester N, et al. A Proposal for the Dartmouth Summer Research Project on Artificial Intelligence, august 31, 1955. AI Mag, 2006, 27(4): 12.

[12] Weinstein RS. Prospects for telepathology. Hum Pathol, 1986, 17(5): 433-434.

[13] Weinstein RS, Holcomb MJ, Krupinski EA. Invention and early history of telepathology (1985-2000). J Pathol Inform, 2019, 10(1): 1.

[14] Campanella G, Hanna MG, Geneslaw L, et al. Clinical-grade computational pathology using weakly supervised deep learning on whole slide images. Nat Med, 2019, 25(8): 1301-1309.

[15] Swanson K, Wu E, Zhang A, et al. From patterns to patients: Advances in clinical machine learning for cancer diagnosis, prognosis, and treatment. Cell, 2023, 186(8): 1772-1791.

[16] Reis-Filho JS, Kather JN. Overcoming the challenges to implementation of artificial intelligence in pathology. J Natl Cancer Inst, 2023, 115(6): 608-612.

[17] Yan F, Da Q, Yi H, et al. Artificial intelligence-based assessment of PD-L1 expression in diffuse large B cell lymphoma. Npj Precis Oncol, 2024, 8(1): 76.

[18] Dawe M, Shi W, Liu TY, et al. Reliability and Variability of Ki-67 Digital Image Analysis Methods for Clinical Diagnostics in Breast Cancer. Lab Invest, 2024, 104(5): 100341.

[19] Go H. Digital Pathology and Artificial Intelligence Applications in Pathology. Brain Tumor Res Treat, 2022, 10(2): 76.

[20] Kiran N, Sapna FNU, Kiran FNU, et al. Digital Pathology: Transforming Diagnosis in the Digital Age. Cureus, 2023, 15(9).

[21] van der Laak J, Litjens G, Ciompi F. Deep learning in histopathology: the path to the clinic. Nat Med, 2021, 27(5): 775-784.

[22] Eloy C, Vale J, Curado M, et al. Digital Pathology Workflow Implementation at IPATIMUP. Diagnostics, 2021, 11(11): 2111.

[23] Chemnad K, Othman A. Digital accessibility in the era of artificial intelligence-Bibliometric analysis and systematic review. Front Artif Intell, 2024, 7: 1349668.

[24] Kim I, Kang K, Song Y, et al. Application of Artificial Intelligence in Pathology: Trends and Challenges. Diagnostics, 2022, 12(11): 2794.

[25] Cheng CH, Shi SS. Artificial intelligence in cancer: applications, challenges, and future perspectives. Mol Cancer, 2025, 24(1): 274.

[26] Perincheri S, Levi AW, Celli R, et al. An independent assessment of an artificial intelligence system for prostate cancer detection shows strong diagnostic accuracy. Mod Pathol, 2021, 34(8): 1588-1595.

[27] Flach RN, van Dooijeweert C, Nguyen TQ, et al. Prospective Clinical Implementation of Paige Prostate Detect Artificial Intelligence Assistance in the Detection of Prostate Cancer in Prostate Biopsies: CONFIDENT P Trial Implementation of Artificial Intelligence Assistance in Prostate Cancer Detection. JCO Clin Cancer Inform, 2025(9): e2410093.

[28] Rashid AB, Kausik MDAK. AI revolutionizing industries worldwide: A comprehensive overview of its diverse applications. Hybrid Adv, 2024, 7: 100277.

[29] Bhinder B, Gilvary C, Madhukar NS, et al. Artificial Intelligence in Cancer Research and Precision Medicine. Cancer Discov, 2021, 11(4): 900-915.

[30] Ligero M, El Nahhas OSM, Aldea M, et al. Artificial intelligence-based biomarkers for treatment decisions in oncology. Trends Cancer, 2025, 11(3): 232-244.

[31] Vallano A, Pontes C, Agustí A. The challenges of access to innovative medicines with limited evidence in the European Union. Front Pharmacol, 2023, 14: 1215431.

[32] Alenazi SM, Bugis BA. The Role of Laboratory Information System in Improving the Delivery of Laboratory Services: A Recent Systematic Review. Comb Chem High Throughput Screen, 2023, 26(8): 1451-1460.

[33] Hanna MG, Ardon O. Digital pathology systems enabling quality patient care. Gene Chromosome Cancer, 2023, 62(11): 685-697.

[34] Russell SJ, Norvig P. Artificial Intelligence: A Modern Approach. Pearson Education: London, UK, 2010.

[35] Shao Z, Zhao R, Yuan S, et al. Tracing the evolution of AI in the past decade and forecasting the emerging trends. Expert Syst Appl, 2022, 209: 118221.

[36] Mezei T, Kolcsár M, Joó A, et al. Image Analysis in Histopathology and Cytopathology: From Early Days to Current Perspectives. J Imaging, 2024, 10(10): 252.

[37] Ghezloo F, Wang PC, Kerr KF, et al. An analysis of pathologists' viewing processes as they diagnose whole slide digital images. J Pathol Inform, 2022, 13: 100104.

[38] Uttley L, Indave BI, Hyde C, et al. Invited commentary-WHO Classification of Tumours: How should tumors be classified? Expert consensus, systematic reviews or both? Int J Cancer, 2020, 146(12): 3516.

[39] Akinnagbe OB. Human-AI Collaboration: Enhancing Productivity and Decision-Making. Int J Educ Manag Technol, 2024, 2(3): 387-417.

[40] Alon I, Haidar H, Haidar A, et al. The future of artificial intelligence: Insights from recent Delphi studies. Futures, 2025, 165: 103514.

[41] Pulumati A, Pulumati A, Dwarakanath BS, et al. Technological advancements in cancer diagnostics: Improvements and limitations. Cancer Rep, 2023, 6(2): e1764.

[42] Dexter A, Tsikritsis D, Belsey NA, et al. Next Generation Digital Pathology: Emerging Trends and Measurement Challenges for Molecular Pathology. J Mol Pathol, 2022, 3(3): 168-181.

[43] Arakaki S, Takenaka S, Sasaki K, et al. Artificial intelligence in minimally invasive surgery: current state and future challenges. JMA J, 2025, 8(1): 86-90.

[44] Aravazhi PS, Gunasekaran P, Benjamin NZY, et al. The integration of artificial intelligence into clinical medicine: Trends, challenges, and future directions. Dis Mon, 2025, 71(6): 101882.

[45] Agrawal S, Vagha S. A Comprehensive Review of Artificial Intelligence in Prostate Cancer Care: State-of-the-Art Diagnostic Tools and Future Outlook. Cureus, 2024, 16(8).

[46] André F, Rassy E, Marabelle A, et al. Forget lung, breast or prostate cancer: why tumour naming needs to change. Nature, 2024, 626(7997): 26-29.

[47] Taylor RA, Sangal RB, Smith ME, et al. Leveraging artificial intelligence to reduce diagnostic errors in emergency medicine: Challenges, opportunities, and future directions. Acad Emerg Med, 2025, 32(3): 327-339.

[48] Tiwari A, Ghose A, Hasanova M, et al. The current landscape of artificial intelligence in computational histopathology for cancer diagnosis. Discov Oncol, 2025, 16(1): 438.

[49] Rahmani AM, Azhir E, Ali S, et al. Artificial intelligence approaches and mechanisms for big data analytics: a systematic study. PeerJ Comput Sci, 2021, 7: e488.

[50] Schmidt J, Marques MRG, Botti S, et al. Recent advances and applications of machine learning in solid-state materials science. NPJ Comput Mater, 2019, 5(1): 83.

[51] Pinto-Coelho L. How Artificial Intelligence is Shaping Medical Imaging Technology: A Survey of Innovations and Applications. Bioengineering, 2023, 10(12): 1435.

[52] Mienye ID, Swart TG. A Comprehensive Review of Deep Learning: Architectures, Recent Advances, and Applications. Information, 2024, 15(12): 755.

[53] Soori M, Arezoo B, Dastres R. Artificial intelligence, machine learning and deep learning in advanced robotics, a review. Cogn Robot, 2023, 3: 54-70.

[54] Mohammadi M, Tajik E, Martinez-Maldonado R, et al. Artificial intelligence in multimodal learning analytics: A systematic literature review. Comput Educ Artif Intell, 2025, 8: 100426.

[55] Carreras-Puigvert J, Spjuth O. Artificial intelligence for high content imaging in drug discovery. Curr Opin Struct Biol, 2024, 87: 102842.

[56] Hsu CY, Pallathadka H, Jasim SA, et al. Innovations in cancer immunotherapy: A comprehensive overview of recent breakthroughs and future directions. Crit Rev Oncol Hematol, 2025, 206: 104588.

[57] Lenis AT, Ravichandran V, Brown S, et al. Microsatellite Instability, Tumor Mutational Burden, and Response to Immune Checkpoint Blockade in Patients with Prostate Cancer. Clin Cancer Res, 2024, 30(17): 3894-3903.

[58] Dixon D, Sattar H, Moros N, et al. Unveiling the Influence of AI Predictive Analytics on Patient Outcomes: A Comprehensive Narrative Review. Cureus, 2024, 16(5).

[59] Zarella MD, McClintock DS, Batra H, et al. Artificial intelligence and digital pathology: clinical promise and deployment considerations. J Med Imaging, 2023, 10(5): 051802.

[60] Chong PL, Vaigeshwari V, Mohammed Reyasudin BK, et al. Integrating artificial intelligence in healthcare: applications, challenges, and future directions. Futur Sci OA, 2025, 11(1): 2527505.

[61] Singh MP, Keche YN. Ethical Integration of Artificial Intelligence in Healthcare: Narrative Review of Global Challenges and Strategic Solutions. Cureus, 2025, 17(5): e84804.