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REVIEW ARTICLE

GENERATIVE INTELLIGENCE IN PRECISION ONCOLOGY: PRIORITIES IN INFORMATICS ENGINEERING, PATHOLOGY AND ONCOLOGY

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ABSTRACT: Generative artificial intelligence (GAI) applied to clinical diagnostics and research is reshaping the panorama of precision oncology. Combining hematoxylin-eosin-stained whole slide images with computational algorithms opens new avenues in digital pathology. GAI allows for extracting molecular, immunological, and prognostic information based on routinely processed histological sections and removes the need for additional molecular testing.
In oncology, GAI models excelled in cancer histotyping, malignancy ranking, molecular profiling, identification of prognostic and predictive biomarkers, and inference of immune gene signatures. The latest foundational models provide additional opportunities to develop generalizable, scalable tools that can be consistently leveraged in line with pathology missions.
However, several challenges must still be addressed to optimize GAI performance and encourage its clinical application. These include data quality, algorithm bias, generalizability across institutions, and validation through robust multicenter trials. This strategy is crucial for increasing clinical confidence, ensuring reproducibility, and facilitating the routine use of AI in precision oncology.
This review focuses on the operational application of computational pathology within the broader context of precision oncology. It addresses the most significant technical innovations in biomarker assessment and critically examines the priorities to enhance the reliability, scalability, and performance of AI-driven tools in precision oncology.

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Impact statement: Generative artificial intelligence applied to digital histopathology offers novel strategies for biomarker identification and tumor classification, advancing precision oncology and diagnostic accuracy.

Key words: *precision oncology; computational pathology; deep learning; machine learning; whole slide images; generative artificial intelligence.*

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INTRODUCTION

Histology is regarded as the gold standard for diagnosing human diseases, including cancer (1). In recent years, the rapid emergence of artificial intelligence (AI)-driven models in digital and computational pathology (2) has revolutionized cancer histopathology, significantly advancing both cancer research and clinical oncology (3, 4).

The integration of AI into surgical pathology is accelerating progress across various oncological domains, including cancer subtyping (5), survival prediction (6), and detection of nodal metastasis (7). Moreover, deep learning (DL) models have shown the ability to identify clinically relevant genetic alterations, such as microsatellite instability (MSI) (8) and multiple gene mutations (9), from hematoxylin and eosin-stained (H&E) sections (10, 11). Furthermore, AI-based tools have been developed in oncology, such as grading in prostate cancer (12) and, more recently, predicting DNA methylation profiles from histology sections (13).

In this review, we describe the emerging role of artificial intelligence in oncology, with a particular focus on computational histopathology (**Figure 1**). We aim to highlight the transformative potential of AI-driven models in shaping the future of precision oncology, ultimately supporting more accurate and high-quality cancer diagnoses.

THE INTRODUCTION OF SCANNERS IN PATHOLOGY DEPARTMENTS: THE ROLE OF WHOLE-SLIDE IMAGES (WSIS) IN COMPUTATIONAL PATHOLOGY

The introduction of slide scanners for digitizing glass slides in pathology, along with the growing use of AI for research and diagnostics, signifies a pivotal shift in precision oncology. Despite the promise of AI in clinical workflows, several challenges persist (14).

Adopting new technologies often necessitates rethinking established practices. In pathology, slide scanners gradually replace the optical microscope, the pathologist's primary tool, with digital workflows. Routine slide digitization generates WSIs of cancerous tissues, serving as a crucial entry point for incorporating digital tools in diagnostics (15).

WSI technology enables the application of machine learning (ML) and dep learning (DL) algorithms to histopathological images, allowing for clinically relevant data extraction to aid in cancer diagnosis, prognosis, and treatment decisions (16-18). The broader implementation of WSI is expected to significantly influence diagnostic pathology, facilitating AI-supported precision diagnosis (19).

In oncology, DL algorithms have shown the capability to extract vital information from H&E-stained WSIs alone, such as tumor classification and treatment

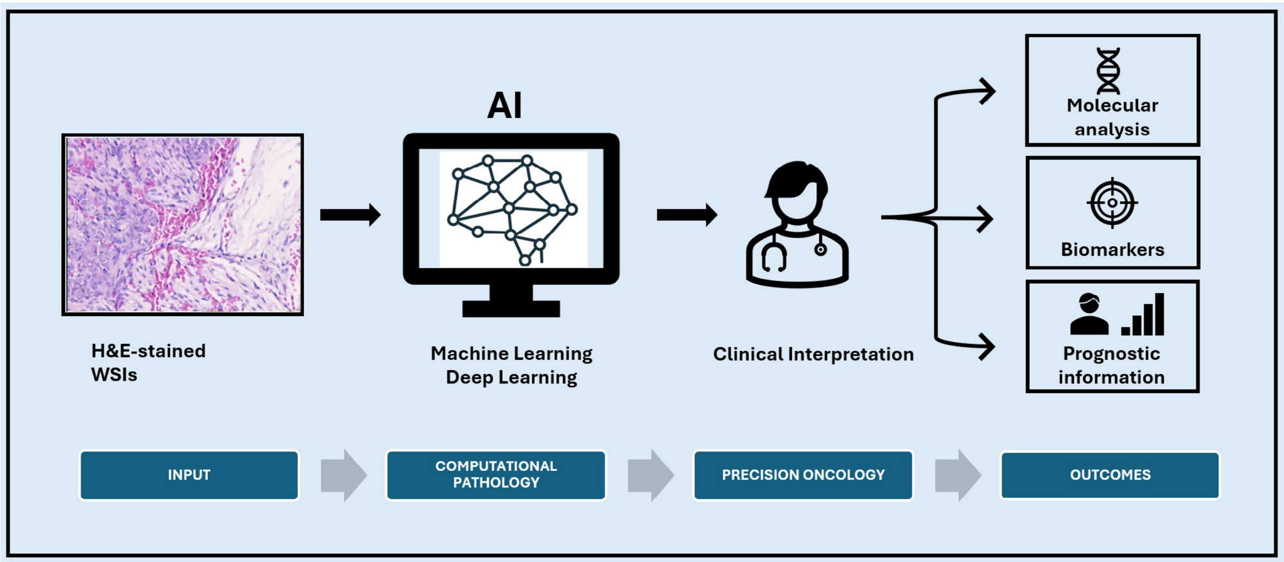

Figure 1. *Workflow of AI-Based Computational Pathology for Precision Oncology.*
Machine learning and deep learning models extract molecular and prognostic insights from H&E-stained whole slide images, supporting clinical interpretation and outcome prediction. H&E = Hematoxylin and Eosin; WSI = whole-slide images; AI = Artificial Intelligence.

selection (20), metastatic potential prediction (21), and identifying primary sites in cancers of unknown origin (22). Moreover, WSIs allow the extraction of molecular-level data, including immunohistochemical and histochemical markers, directly from H&E slides. This includes predictions of PD-L1 and PD-1 expression (23) and mutational status across cancer types (24-26). Such tools could soon offer fast, cost-effective methods to inform personalized treatments. The integration of slide scanners and routine WSI use, combined with AI-driven models, presents a significant opportunity for both healthcare institutions and research centers (27). Digital pathology through WSI technology has the potential to transform can-

Table 1. *Summary of published studies applying AI models to histopathology for biomarker prediction and clinical tasks.*

STUDY	YEAR	CANCER TYPE/TASK	AI METHODOLOGY	MAIN FINDINGS	REF.
Coudray *et al.*	2018	NSCLC – mutation classification	CNN on H&E	Predicted mutations (EGFR, STK11, TP53, etc.) and PD-L1 status	(24)
Skrede *et al.*	2020	Colorectal – outcome prediction	Deep learning on WSIs	DL model predicted prognosis with high AUC	(6)
Kather *et al.*	2020	Pan-cancer – actionable mutations	AI on H&E	Detected multiple genetic alterations from histology	(10)
Fu *et al.*	2020	Pan-cancer – mutation & composition	CNN on H&E	Inferred mutations, cell types and prognosis	(25)
Qu *et al.*	2021	Breast – pathway prediction	Deep learning on WSIs	Predicted mutations and signaling pathways	(26)
Lu *et al.*	2021	Cancer of unknown primary	AI on H&E + weak supervision	Predicted tissue of origin with high accuracy	(22)
Saldanha *et al.*	2023	Pan-cancer – mutation prediction	Self-supervised DL	Accurate prediction of genomic alterations	(11)
Shamai *et al.*	2022	Breast – PD-L1 prediction	DL on H&E	AI matched IHC PD-L1 expression	(52)
Wang *et al.*	2022	NSCLC – PD-L1 scoring	Multimodal DL	Fusion model predicted PD-L1 & survival	(55)
van Eekelen *et al.*	2024	NSCLC – PD-L1 scoring	Cell-level DL	AI showed better reproducibility *vs* pathologists	(56)
Jin *et al.*	2024	Pan-cancer (20 types) – PD-L1	Multiple instance learning	AUC 0.83 on >12k slides, mRNA correlation	(57)
Saillard *et al.*	2023	Colorectal – MSI screening	AI-based MSI detection (MSIntuit)	Validated model for MSI prediction on H&E	(36)
Arslan *et al.*	2022	Multi-cancer – multi-omic prediction	DL on H&E	Predicted mutations, expression, MSI, CNAs	(37)
McCaw *et al.*	2024	Pan-cancer – digital biomarkers	ML on histology	Predicted multiple digital biomarkers from WSIs	(38)
Nakatsuka *et al.*	2025	NASH – HCC prediction	DL on liver biopsies	Predicted HCC development years in advance	(69)
Hoang *et al.*	2024	CNS tumors – DNA methylation	DL on histology	Inferred methylation subtype from slides	(13)
Amgad *et al.*	2024	Breast – prognostic biomarker	Population-level digital pathology	Created a histological biomarker for prognosis	(75)
Chen *et al.*	2024	Pan-cancer – general model	Foundation model (UNI)	Predicted 108 cancer types from WSIs	(78)

AI = Artificial Intelligence, CNN = Convolutional Neural Network, DL = Deep Learning, H&E = Hematoxylin and Eosin, IHC = Immunohistochemistry, ML = Machine Learning, MSI = Microsatellite Instability, NSCLC = Non-Small Cell Lung Cancer, PD-L1 = Programmed Death-Ligand 1, PD-1 = Programmed Cell Death Protein 1, WSI = Whole Slide Image, CNS = Central Nervous System, NASH = Non-Alcoholic Steatohepatitis, HCC = Hepatocellular Carcinoma, CNA = Copy Number Alteration, mRNA = Messenger Ribonucleic Acid, MSI = Microsatellite Instability, UNI = Universal foundation model for computational pathology, AUC = Area Under the Curve.

cer diagnosis and research by converting conventional slides into digital data, laying the groundwork for computer-assisted diagnostics (28).

WSIs provide the foundation for fully digitized pathology workflows, backed by AI-powered decision-support systems. These tools leverage computational histopathology to enhance diagnostic accuracy and consistency (29). The ongoing digitalization of pathology departments, alongside advances in ML and DL, is poised to accelerate oncological research and foster the development of AI-assisted diagnostic tools for various malignancies (30).

ML-MODELS ALLOW THE PREDICTION OF MULTIPLE BIOMARKERS FROM WHOLE SLIDE HISTOPATHOLOGY IMAGES

One of the most intriguing aspects of AI in digital pathology is its ability to predict multiple biomarkers, including mutation status, from H&E-stained WSIs (2, 11). Recent AI-driven models can now predict diagnostic and predictive biomarkers such as immunohistochemical, genetic, epigenetic, and *in situ* hybridization markers. Traditionally, identifying these biomarkers requires manual assessment by trained pathologists, a time-consuming and costly process that can delay diagnosis and treatment.

The progressive adoption of digital pathology has been complemented by the development of an alternative approach, whereby AI models analyze routinely acquired H&E-stained WSIs to extract multiple predictive biomarkers. These include key molecular features that are instrumental in-patient stratification for targeted therapies (31-33). This paradigm shift has revealed that H&E-stained sections, long considered tools primarily for morphological assessment, contain a rich reservoir of latent molecular information.

WSIs can now support automated disease detection, histological and molecular subtyping, and tumor grading, as well as prognostic evaluation, survival prediction, and treatment planning (33). AI models trained on H&E-stained WSIs have demonstrated the ability to predict a range of molecular biomarkers across different cancer types (34-36). Additionally, emerging studies suggest that WSIs may also be used to infer other molecular alterations, such as RNA expression patterns and protein abundance (37). While initial efforts focused on models trained to predict a single biomarker in a specific cancer type, newer frameworks now predict multiple biomarkers, including copy number alterations and RNA-derived signatures, across various malignancies (38). These findings emphasize the vast, clinically relevant data embedded in standard H&E-stained slides. **Table 1** provides an overview of significant studies utilizing AI for biomarker prediction, tumor classification, and outcome forecasting across diverse cancers.

Given the widespread use of H&E-stained slides in pathology laboratories globally, digitizing these images could enable the deployment of AI-driven biomarker prediction models even in low-resource settings, potentially benefiting a broader patient population.

DL-MODELS APPLIED TO THE PREDICTION OF PD-1 AND PD-L1 EXPRESSION BASED ON H&E-STAINED SECTIONS

The immune system maintains a balance between eliminating harmful pathogens and preserving self-tolerance, regulated by immune checkpoints like PD-1 (39). PD-1, a key checkpoint receptor, modulates T-cell activity to maintain peripheral tolerance, preventing autoimmune responses (40, 41).

The identification of PD-1 and its ligand PD-L1 in tumor cells, first reported in 2002, unveiled a critical mechanism of immune evasion by which tumors exploit immune checkpoint pathways to evade immune surveillance (42). PD-L1 is predominantly expressed on the surface of tumor cells but can also be released in the tumor microenvironment via exosomes, amplifying immune suppression (43, 44). Given its role in promoting tumor immune escape, PD-L1 has become a major target in cancer immunotherapy (45-48).

Traditionally, PD-L1 expression is assessed through immunohistochemistry (IHC), which remains the standard in clinical practice (49-51). However, despite its widespread use, IHC presents several challenges: it is time-consuming, costly, and may deplete limited tissue samples, particularly in small biopsies. Furthermore, interpretation of PD-L1 staining is prone to significant variability due to differences in staining protocols, subjective interpretation of staining intensity, and interobserver variability, especially in borderline cases (52, 53). This inconsistency can critically impact clinical decision-making, potentially misclassifying patients and affecting their eligibility for immune checkpoint inhibitors.

Digital pathology and AI-driven models offer a promising alternative, providing a more standardized and reproducible assessment of PD-L1 expression by analyzing WSIs across multiple tumor regions (54). Unlike manual scoring, AI models can systematically quantify PD-L1 expression across heterogeneous tumor regions, reducing variability and enhancing diagnostic accuracy. For instance, AI algorithms applied in lung cancer demonstrated high accuracy in predicting PD-L1 status, aligning closely with pathologist assessments even in challenging cases (55, 56). A pivotal study by Jin *et al*. introduced a pan-cancer AI model capable of predicting PD-L1 expression directly from H&E-stained WSIs, analyzing over 12,000 slides from 20 tumor types and achieving a mean area under the curve (AUC) of 0.83 (57). The model's predictions were validated against conventional IHC and mRNA expression, underscoring the potential of AI to standardize biomarker assessment and minimize interobserver variability.

Table 2 summarizes selected studies comparing AI-based digital pathology approaches with conventional immunohistochemistry for PD-L1 assessment across different tumor types.

This shift toward AI-driven PD-L1 evaluation reflects the emerging paradigm of "intelligent digital pathology", where AI augments conventional diagnostics, potentially accelerating therapeutic decision-making, expanding access to precision oncology, and ensuring more consistent biomarker assessment across diverse clinical settings (32, 58, 59).

The clinical integration of this approach is particularly relevant in the context of therapeutic decision-making. By predicting multiple biomarkers, including immune checkpoint-related proteins and mutational profiles, from routine H&E-stained slides, AI-driven pathology can guide the selection of targeted therapies or immunotherapies. For instance, in advanced non-small cell lung cancer or gastric cancer, accurate prediction of PD-L1 expression or MSI status directly from histology can streamline treatment eligibility decisions and reduce dependence on costly or time-consuming molecular assays (24, 36, 52, 55, 57). Additionally, in multidisciplinary oncology settings, integrating AI-generated outputs into tumor board discussions may enhance personalized care planning, particularly when biopsy material is limited or when rapid turnaround is needed.

Table 2. *Comparison between immunohistochemistry (IHC) and AI-based digital pathology for PD-L1 assessment.*

FEATURE	IMMUNOHISTOCHEMISTRY (IHC)	AI-BASED DIGITAL PATHOLOGY (ON H&E WSIS)	REF.
Sample requirement	Requires additional antibody-based staining	Uses routine H&E-stained slides already available in pathology labs	(49-51)/ (24, 57)
Tissue consumption	Consumes precious tissue, critical in small biopsies	No additional tissue required; preserves material for other tests	(52)/ (23/37)
Cost	High costs due to antibodies, reagents, and specialized equipment	Lower long-term costs after digitization infrastructure is in place	(53)/ (24, 57)
Turnaround time	Time-consuming due to staining and manual interpretation	Faster analysis after digitization and model deployment	(52)/ (23, 55, 57)
Expertise required	Requires experienced pathologists for accurate interpretation	AI supports interpretation; reduces reliance on specialist expertise	(52, 53)/ (54, 56)
Interpretation variability	High inter- and intra-observer variability	Provides standardized, reproducible results	(53)/ (54, 56)
Accessibility	Often unavailable in peripheral or low-resource settings	H&E-based AI tools are scalable and suitable for resource-limited contexts	(52)/ (24, 57)
Multiplexing capability	Generally limited to one biomarker per slide	Potential to predict multiple biomarkers from a single H&E image	(49-51)/ (25, 26, 36-38)
Molecular correlation	Direct protein expression detection	Can predict mRNA expression, mutation status, and other molecular features	(50)/ (37, 38, 57)
Scalability and automation	Manual, slow, and hard to scale	Fully automatable and scalable across large datasets	(52)/ (23, 54, 57)

IHC = Immunohistochemistry, AI = Artificial Intelligence, H&E = Hematoxylin and Eosin, WSI = Whole Slide Image, mRNA = Messenger Ribonucleic Acid.

DEEP LEARNING APPLIED TO DIGITAL PATHOLOGY IN THE PREDICTION OF HCC

Non-alcoholic steatohepatitis (NASH), a progressive form of non-alcoholic fatty liver disease (NAFLD), is now recognized as the leading cause of chronic liver disease and a key risk factor for hepatocellular carcinoma (HCC) (60). Histologically, NASH is marked by macrovesicular steatosis, lymphocytic infiltration, hepatocellular ballooning, apoptotic bodies, and varying degrees of fibrosis (61). Traditionally, fibrosis has been considered the strongest predictor of adverse outcomes, including cirrhosis and HCC (62, 63). However, over 50% of NASH-related HCC cases arise in non-cirrhotic livers, indicating that other histological and molecular features beyond fibrosis may drive carcinogenesis (64, 65).

Recent AI-based models have been applied to the automated assessment of liver fibrosis and other NASH-related histological changes, demonstrating ML techniques' key advantage in providing objective, quantitative evaluations that reduce interobserver variability and support more consistent longitudinal disease monitoring (66, 67). DL approaches, in particular, have shown significant promise in identifying subtle histological markers associated with early carcinogenesis that may be missed in conventional assessments, extending predictive capabilities beyond fibrosis and nodular regeneration (68).

A significant study by Nakatsuka *et al.* explored a DL model to predict HCC development using only H&E-stained WSIs of liver biopsies from steatosis patients (69). The model aimed to identify individuals at higher HCC risk solely based on liver steatosis analysis, achieving an AUC of 0.80 for predicting HCC onset within seven years post-biopsy. Notably, the model identified at-risk patients without advanced fibrosis, underscoring the role of additional histological features in liver tumorigenesis.

Through saliency map analysis, the model highlighted key predictors of HCC development, including a high nuclear-to-cytoplasmic ratio, nuclear atypia, lymphocytic infiltrates, and the absence of large lipid droplets. These findings suggest that AI models can detect subtle histological changes predictive of liver cancer risk in routine biopsies, potentially without expensive molecular assays (69).

This work emphasizes two critical points: first, AI algorithms can extract complex histological signals indicative of future disease progression; second, integrating AI with digital pathology, or computational pathology (CPath), may revolutionize liver histopathology by enhancing diagnostic accuracy, aiding prognostic stratification, and supporting preventive strategies in NASH-related HCC (69).

TOWARDS A GENERAL FOUNDATION MODEL FOR COMPUTATIONAL PATHOLOGY

In routine clinical practice, pathologists are responsible for a broad spectrum of diagnostic tasks, including cancer detection, subtyping, grading, and staging. These tasks require consideration of thousands of potential differential diagnoses. To address these challenges, a wide range of AI models have been developed in recent years, particularly within the domains of digital and computational pathology (70, 71). Among the most promising innovations is the development of AI-driven models capable of multimodal data integration, which should combine clinical, genomic, epigenomic, radiomic, pathomic, and microbiological data to provide a more comprehensive view of the oncologic landscape (72). Computational pathology (CPath) has demonstrated the potential to predict molecular alterations directly from histopathological images, including microsatellite instability (MSI) (8, 73, 74), patient prognosis (75), and treatment response (76). However, most of these models are trained for a specific cancer type and are limited to predicting a narrow set of molecular or immunohistochemical features, which restricts their applicability in diverse clinical contexts. To overcome these limitations, a new class of AI tools has emerged: multi-cancer, multi-biomarker models designed to simultaneously predict a wide range of molecular alterations across various tumor types using standard H&E-stained slides (39). These systems, defined as "foundation models," are characterized by their scalability, versatility, and adaptability to multiple diagnostic tasks and cancer types (77). In this direction, a general-purpose foundation model for computational pathology, defined as *UNI*, has been recently introduced by Chen TJ and colleagues (78). Pretrained on over 100 million images, the UNI model demonstrated the capacity to classify up to 108 cancer types, marking a significant advancement toward the integration of AI into routine workflows in anatomic pathology Labs.

COMPUTATIONAL PATHOLOGY IN ONCOLOGY

Artificial intelligence has emerged as a revolutionary tool for the discovery of predictive biomarkers in human cancers. AI-based methods are redefining the landscape for researchers, pathologists, and oncologists, demonstrating the potential of well-trained algorithms to extract clinically relevant molecular information directly from routinely stained H&E sections.

When applied to clinical practice, the advantages of this paradigm shift are numerous. One of the most significant is the speed of analysis: the average computational time to generate a PD-L1 probability map has been reported at approximately 40 seconds, with a range from 7.9 to 66 seconds (79). This indicates that, with a robust and validated DL model, pathologists could provide near-instantaneous estimates of PD-L1 expression, facilitating timely and personalized therapeutic decisions for oncologists (87).

In addition to rapidity, AI-based approaches offer substantial cost-saving opportunities. The reliance on conventional immunohistochemistry, dependent on specialized reagents, equipment, and trained personnel, may be significantly reduced or even replaced. The possibility of identifying genes and immune-related biomarkers, such as PD-L1, directly from H&E sections without antibody-based detection opens intriguing transformative possibilities, particularly for decentralized and resource-limited settings.

Furthermore, AI-driven histopathological analysis enables the extraction of novel insights beyond PD-L1 expression, potentially enhancing clinical decision-making. Immune pathology, a key foundation for immune checkpoint inhibitor (ICI) therapies, remains a relatively underexplored area within diagnostic pathology. AI methodologies could facilitate the identification of novel “metabiomarkers”, complex, integrative features predictive of ICI therapy response (82). This hypothesis is supported by recent evidence showing that DL models can predict immune and inflammatory gene signatures in hepatocellular carcinoma directly from histological images (83).

Taken together, these findings underscore the potential of AI, particularly DL algorithms, to extract multiple molecular and immunological biomarkers from standard histology, enabling the discovery of novel predictive features and advancing the goals of precision oncology. Computational pathology (also referred to as pathomics) thus represents a unique opportunity: to serve as a rapid, cost-effective, and integrative diagnostic tool for clinicians, oncologists, and surgeons alike, delivering morphological, genetic, and molecular data in near real time.

Another major strength of computational pathology lies in its ability to generate large-scale datasets of digitized slides, which can be integrated with complementary clinical (real-world data), genomic, epigenomic, microbiologic, radiologic (radiomics), and laboratory information. This multimodal integration offers the potential to define novel metabiomarkers, which can outperform unimodal models in terms of predictive accuracy, as measured by improved AUC metrics (76).

Moreover, computational pathology can address a long-standing challenge in diagnostic histopathology: interobserver variability. This is particularly relevant for PD-L1 scoring, which is known to vary significantly among both expert and generalist pathologists (84-86). While DL models can provide more consistent and standardized assessments of PD-L1 expression, their capacity to directly infer molecular and transcriptomic features from histology offers a far more transformative leap than simply resolving variability issues.

For successful adoption in clinical practice, AI-based computational pathology systems must be integrated into existing digital workflows within pathology departments. This includes embedding AI models into slide viewers and laboratory information systems (LIS), allowing pathologists to access real-time predictions directly from digitized H&E slides. Additionally, the deployment of AI tools should be supported by intuitive, clinician-oriented interfaces that facilitate interpretation and integrate seamlessly into the diagnostic process. Real-world implementation also requires rigorous prospective validation studies and standardized protocols to demonstrate clinical utility. Importantly, AI-driven solutions should be designed to complement rather than replace human expertise, acting as decision-support tools that enhance diagnostic accuracy, reproducibility, and efficiency in oncology care.

NEXT CHALLENGES

Along with its unquestionable advantages, the real-world implementation of computational histology entails several major issues that need to be addressed before AI models can be safely and effectively integrated into clinical practice, particularly within the field of immuno-oncology. The major current limitations hindering clinical implementation are summarized below:

1. Data Quality and Availability: robust algorithm performance requires access to large volumes of high-quality, well-annotated data. However, oncologic datasets are often incomplete, heterogeneous, biased, and inherently complex, limiting model generalizability and reproducibility.
2. Model Selection Complexity: the proliferation of ML and DL algorithms, often promoted through marketing strategies emphasizing innovation rather than practical limitations and clinical safety, can make it challenging for researchers and clinicians to select the most appropriate model for specific applications. While advanced DL models are widely marketed as cutting-edge solutions, classical ML models may outperform them in low-data scenarios and should not be overlooked, particularly when sample sizes are limited (87).
3. Regulatory Certification: certification is a critical prerequisite for clinical adoption. At present, there is no universally accepted regulatory pathway for the validation and certification of AI-based tools in pathology. The establishment of worldwide (or at least continental-wide) standardized, harmonized processes for model certification should be encouraged to ensure safety and efficacy.
4. Lack of Guidelines and Protocols: clear protocols and guidelines for conducting rigorous, clinically meaningful studies on AI model applicability are currently lacking. This gap hinders reproducibility and delays the translation of research findings into clinical practice.
5. Lack of Trust and Interpretability: a significant barrier to clinical implementation is the skepticism among healthcare professionals, including pathologists, regarding the reliability and transparency of AI tools. Improving model interpretability is essential to foster trust. Techniques from the field of explainable artificial intelligence (XAI) may help to demystify algorithmic decision-making and reduce the “black box” effect (88, 89).
6. Insufficient External Validation: AI models that perform well on internal datasets often fail when applied to external, real-world data. To ensure clinical robustness, models should be validated using diverse, multi-institutional datasets. One proposed strategy is divergent validation, which evaluates model performance across various independent datasets to enhance generalizability and transparency (90, 91).
6. Bias and Variability: algorithmic biases can result from inconsistencies in slide staining, errors in labeling the data sets used for training, scanner calibration, or demographic imbalances in training data. These factors can significantly impair model performance and reliability. Reducing such biases is crucial to enable fair and accurate deployment of AI models in clinical settings.

Despite these several interconnected limitations, the primary obstacle hindering the widespread use of AI strategies in clinical practice is the lack of standardized and universally accepted pathways for validation and certification. Without clear regu-

Table 3. *Current challenges and proposed solutions for the clinical integration of AI in computational pathology.*

CHALLENGE	DESCRIPTION	SUGGESTED SOLUTIONS	REF.
Data Quality	Incomplete, biased, heterogeneous datasets	Centralized data curation and federated learning	(1, 92)
Model Selection	Difficult choice among ML/DL models	Model comparison guidelines, model benchmarking	(89)
Certification	Lack of standard regulatory pathways	International consensus on AI model validation	–
Trust and Interpretability	Lack of clinician trust due to black-box nature	XAI, transparent algorithms	(90–91)
Interobserver Variability	Variability in human assessment (*e.g.*, PD-L1 scoring)	Algorithmic standardization, model calibration	(86–88)
External Validation	Limited generalizability across datasets	Multi-institutional validation, divergent validation	(90-91)
Staining and demographic biases	Bias in data acquisition and population representation	Dataset balancing, domain adaptation techniques	–

ML = Machine Learning, DL = Deep Learning, AI = Artificial Intelligence, PD-L1 = Programmed Death-Ligand 1, XAI = Explainable Artificial Intelligence.

latory guidance and robust multicenter validation studies, many AI-based models remain restricted to research settings. This uncertainty, coupled with a lack of transparency in algorithmic outputs, continues to undermine clinician trust and delays the full integration of AI into routine oncologic diagnostics. The key limitations currently hindering the implementation of AI in clinical workflows, along with proposed solutions, are summarized in **Table 3**.

CONCLUSIONS

The introduction of AI-driven models has triggered a true revolution in oncology, with applications spanning from the interpretation of medical imaging to the enhancement of diagnostic and prognostic accuracy, including prediction of overall survival and response to various therapeutic strategies (92). Among these tools, convolutional neural networks (CNNs) have emerged as indispensable new tools for the recognition and classification of both histological and radiological images. CNNs can detect subtle and complex patterns that may escape even the most experienced pathologists and radiologists. A key strength of CNNs lies in their ability to autonomously learn from data, particularly when trained on large, high-quality datasets. This has enabled a shift from traditional machine learning towards deep learning in medical image analysis. CNNs have demonstrated outstanding performance in tasks such as cancer detection, histological classification, and subtype recognition.

More recently, advanced CNN-based architectures have achieved notable success in cancer diagnostics. For instance, CNNs combined with Long Short-Term Memory (LSTM) networks have shown promise in predicting cancer prognosis by capturing temporal patterns in patient data. Spatially Constrained CNNs (SC-CNNs) have proven effective for nuclei classification in colorectal cancer, enhancing precision in histopathological assessment. Moreover, the integration of CNNs with Fourier Transform Infrared (FTIR) spectroscopy has yielded promising results for accurate cancer detection in biopsy specimens. Taken together, these developments highlight the transformative role of AI in advancing precision oncology, in which context pathology assumes a pivotal role. Manual interpretation of medical images remains susceptible to human error and interobserver variability. In this context, AI-based methodologies, particularly those leveraging CNNs, offer robust solutions to improve diagnostic consistency and uncover patterns beyond human perception. These innovations pave the way for more refined, data-driven approaches to cancer detection, classification, and treatment selection, ultimately supporting the realization of a truly personalized oncology. This constellation of technological advancements fosters a more data-driven, patient-centered approach to precision oncology. It creates a new medical universe that aligns with tailored cancer care's ethical and scientific mission. Pathology plays a pivotal role in this evolving "computational" landscape, echoing the transformative impact once initiated by Virchow's microscope.

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Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Authors' contributions

GF, MR and MS collectively conceived and designed this comprehensive review. All authors contributed to the initial draft of the manuscript. GF, MR, MS, LS, MC, PZ, AP provided supervision, graphics support, editing, and finalized the manuscript. All authors actively participated in the revision of the manuscript, carefully reviewed it, and approved the final version for submission.

Availability of data and materials

The data underlying this article are available in the public domain.

Publications ethics

Plagiarism

The article provides a comprehensive review of the latest studies in the field, with accurate citations.

Data falsification and fabrication

The writing and contents of the article are entirely original and were developed entirely by the authors.

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REFERENCES

1. Fletcher CDM. Diagnostic Histopathology of tumors. 5th Edition, Elsevier, 2021.
2. Faa G, Castagnola M, Didaci L, Coghe F, Scartozzi M, Saba L, et al. The Quest for the Application of Artificial Intelligence to Whole Slide Imaging: Unique Prospective from New Advanced Tools. Algorithms. 2024;17(6):254. doi.org/10.3390/a17060254.
3. Shmatko A, Ghaffari Laleh N, Gerstung M, Kather JN. Artificial intelligence in histopathology: enhancing cancer research and clinical oncology. Nat Cancer. 2022;3(9):1026-38. doi: 10.1038/s43018-022-00436-4.
4. Song AH, Jaume G, Williamson DFK, Lu MY, Vaidya A, Miller TR, et al. Artificial intelligence for digital and computational pathology. Nat Rev Bioeng. 2023;1:930-49. doi.org/10.48550/arXiv.2401.06148.
5. Lu MY, Williamson DFK, Chen TY, Chen RJ, Barbieri M, Mahmood F. Data-efficient and weakly supervised computational pathology on whole-slide images. Nat Biomed Eng. 2021;5(6):555-70. doi: 10.1038/s41551-020-00682-w.
6. Skrede OJ, De Raedt S, Kleppe A, Hveem TS, Liestøl K, Maddison J, et al. Deep learning for prediction of colorectal cancer outcome: a discovery and validation study. Lancet. 2020;395(10221):350-60. doi: 10.1016/S0140-6736(19)32998-8.
7. Ehteshami Bejnordi B, Veta M, Johannes van Diest P, van Ginneken B, Karssemeijer N, Litjens G, et al. Diagnostic Assessment of Deep Learning Algorithms for Detection of Lymph Node Metastases in Women with Breast Cancer. JAMA. 2017;318(22):2199-210. doi: 10.1001/jama.2017.14585.
8. Faa G, Coghe F, Pretta A, Castagnola M, Van Eyken P, Saba L, et al. Artificial Intelligence Models for the Detection of Microsatellite Instability from Whole-Slide Imaging of Colorectal Cancer. Diagnostics (Basel). 2024;14(15):1605. doi: 10.3390/diagnostics14151605.
9. Guitton T, Allaume P, Rabilloud N, Rioux-Leclercq N, Henno S, Turlin B, et al. Artificial Intelligence in Predicting Microsatellite Instability and KRAS, BRAF Mutations from Whole-Slide Images in Colorectal Cancer: A Systematic Review. Diagnostics (Basel). 2023;14(1):99. doi: 10.3390/diagnostics14010099.
10. Kather JN, Heij LR, Grabsch HI, Loeffler C, Echle A, Muti HS, et al. Pan-cancer image-based detection of clinically actionable genetic alterations. Nat Cancer. 2020;1(8):789-99. doi: 10.1038/s43018-020-0087-6. Erratum in Nat Cancer. 2020;1(11):1129. doi: 10.1038/s43018-020-00149-6. 2020.
11. Saldanha OL, Loeffler CML, Niehues JM, van Treeck M, Seraphin TP, et al. Self-supervised attention-based deep learning for pan-cancer mutation prediction from histopathology. NPJ Precis Oncol. 2023;7(1):35. doi: 10.1038/s41698-023-00365-0.
12. Bulten W, Pinckaers H, van Boven H, Vink R, de Bel T, van Ginneken B, et al. Automated deep-learning system for Gleason grading of prostate cancer using biopsies: a diagnostic study. Lancet Oncol. 2020;21(2):233-41. doi: 10.1016/S1470-2045(19)30739-9.
13. Hoang DT, Shulman ED, Turakulov R, Abdullaev Z, Singh O, Campagnolo EM, et al. Prediction of DNA methylation-based tumor types from histopathology in central nervous system tumors with deep learning. Nat Med. 2024;30(7):1952-61. doi: 10.1038/s41591-024-02995-8.
14. Reis-Filho JS, Kather JN. Overcoming the challenges to implementation of artificial intelligence in pathology. J Natl Cancer Inst. 2023;115(6):608-12. doi: 10.1093/jnci/djad048.
15. Jain E, Patel A, Parwani AV, Shafi S, Brar Z, Sharma S, et al. Whole Slide Imaging Technology and Its Applications: Current and Emerging Perspectives. Int J Surg Pathol. 2024;32(3):433-48. doi: 10.1177/10668969231185089.
16. Dimitriou N, Arandjelović O, Caie PD. Deep Learning for Whole Slide Image Analysis: An Overview. Front Med (Lausanne). 2019;6:264. doi: 10.3389/fmed.2019.00264. Erratum in: Front Med (Lausanne). 2020;7:419. doi: 10.3389/fmed.2020.00419.

17. Hanna MG, Reuter VE, Hameed MR, Tan LK, Chiang S, Sigel C, et al. Whole slide imaging equivalency and efficiency study: experience at a large academic center. Mod Pathol. 2019;32(7):916-28. doi: 10.1038/s41379-019-0205-0.
18. Lee M. Recent Advancements in Deep Learning Using Whole Slide Imaging for Cancer Prognosis. Bioengineering (Basel). 2023;10(8):897. doi: 10.3390/bioengineering10080897.
19. Chang J, Hatfield B. Advancements in computer vision and pathology: Unraveling the potential of artificial intelligence for precision diagnosis and beyond. Adv Cancer Res. 2024;161:431-78. doi: 10.1016/bs.acr.2024.05.006.
20. Tran KA, Kondrashova O, Bradley A, Williams ED, Pearson JV, Waddell N. Deep learning in cancer diagnosis, prognosis and treatment selection. Genome Med. 2021;13(1):152. doi: 10.1186/s13073-021-00968-x.
21. Kim J, Lee M, Seok J. Deep learning model with L1 penalty for predicting breast cancer metastasis using gene expression data. Mach Learn Sci Technol. 2023;4:025026. doi:10.1088/2632-2153/acd987.
22. Lu MY, Chen TY, Williamson DFK, Zhao M, Shady M, Lipkova J, et al. AI-based pathology predicts origins for cancers of unknown primary. Nature. 2021;594(7861):106-110. doi: 10.1038/s41586-021-03512-4.
23. Liu Y, Chen W, Ruan R, Zhang Z, Wang Z, Guan T, et al. Deep learning based digital pathology for predicting treatment response to first-line PD-1 blockade in advanced gastric cancer. J Transl Med. 2024;22(1):438. doi: 10.1186/s12967-024-05262-z.
24. Coudray N, Ocampo PS, Sakellaropoulos T, Narula N, Snuderl M, Fenyö D, et al. Classification and mutation prediction from non-small cell lung cancer histopathology images using deep learning. Nat Med. 2018;24(10):1559-67. doi: 10.1038/s41591-018-0177-5.
25. Fu Y, Jung AW, Torne RV, Gonzalez S, Vöhringer H, Shmatko A, et al. Pan-cancer computational histopathology reveals mutations, tumor composition and prognosis. Nat Cancer. 2020;1(8):800-10. doi: 10.1038/s43018-020-0085-8.
26. Qu H, Zhou M, Yan Z, Wang H, Rustgi VK, Zhang S, et al. Genetic mutation and biological pathway prediction based on whole slide images in breast carcinoma using deep learning. NPJ Precis Oncol. 2021;5(1):87. doi: 10.1038/s41698-021-00225-9.
27. Zhang DY, Venkat A, Khasawneh H, Sali R, Zhang V, Pei Z. Implementation of Digital Pathology and Artificial Intelligence in Routine Pathology Practice. Lab Invest. 2024;104(9):102111. doi: 10.1016/j.labinv.2024.102111.
28. Omar M, Alexanderani MK, Valencia I, Loda M, Marchionni L. Applications of Digital Pathology in Cancer: A Comprehensive Review. Annu Rev Cancer Biol. 2024;8,245-68. doi:10.1146/annurev-cancerbio-062822-010523.
29. Cooper M, Ji Z, Krishnan RG. Machine learning in computational histopathology: Challenges and opportunities. Genes Chromosomes Cancer. 2023;62(9):540-56. doi: 10.1002/gcc.23177.
30. Campanella G, Hanna M, Geneslaw L, Miraflor A. Clinical-grade computational pathology using weakly supervised deep learning on whole slide images. Nat Med. 2019;25(8):1301-9. doi: 10.1038/s41591-019-0508-1.
31. Baxi V, Edwards R, Montalto M, Saha S. Digital pathology and artificial intelligence in translational medicine and clinical practice. Mod Pathol. 2022;35(1):23-32. doi: 10.1038/s41379-021-00919-2.
32. Dawson H. Digital pathology - Rising to the challenge. Front Med (Lausanne). 2022;9:888896. doi: 10.3389/fmed.2022.888896. Erratum in: Front Med (Lausanne). 2023;10:1180693. doi: 10.3389/fmed.2023.1180693.
33. Chen RJ, Ding T, Lu MY, Williamson DFK, Jaume G, Chen B, et al. A General-Purpose Self-Supervised Model for Computational Pathology. ArXiv [Preprint]. 2023:arXiv:2308.15474v1. doi: 10.48550/arXiv.2308.15474.
34. Raciti P, Sue J, Ceballos R, Godrich R, Kunz JD, Kapur S, et al. Novel artificial intelligence system increases the detection of prostate cancer in whole slide images of core needle biopsies. Mod Pathol. 2020;33(10):2058-66. doi: 10.1038/s41379-020-0551-y.
35. da Silva LM, Pereira EM, Salles PG, Godrich R, Ceballos R, Kunz JD, et al. Independent real-world application of a clinical-grade automated prostate cancer detection system. J Pathol. 2021;254(2):147-58. doi: 10.1002/path.5662.
36. Saillard C, Dubois R, Tchita O, Loiseau N, Garcia T, Adriansen A, et al. Validation of MSIntuit as an AI-based pre-screening tool for MSI detection from colorectal cancer histology slides. Nat Commun. 2023;14(1):6695. doi: 10.1038/s41467-023-42453-6.
37. Arslan S, Mehrotra D, Schmidt J, Geraldes A, Singhal S, Hence J, et al. Deep learning can predict

multi-omic biomarkers from routine pathology images: A systematic large-scale study. bioRxiv 2022.01.21.477189. doi: 10.1101/2022.01.21.477189.
38. McCaw ZR, Shcherbina A, Shah Y, Huang D, Elliott S, Szabo PM, et al. Machine learning enabled prediction of digital biomarkers from whole slide histopathology images. medRxiv 2024, 01.06.24300926. doi: 10.1101/2024.01.06.24300926.
39. Funes SC, Manrique de Lara A, Altamirano-Lagos MJ, Mackern-Oberti JP, Escobar-Vera J, Kalergis AM. Immune checkpoints and the regulation of tolerogenicity in dendritic cells: Implications for autoimmunity and immunotherapy. Autoimmun Rev. 2019;18(4):359-68. doi: 10.1016/j.autrev.2019.02.006.
40. Ishida Y. PD-1: Its Discovery, Involvement in Cancer Immunotherapy, and Beyond. Cells. 2020; 9(6):1376. doi: 10.3390/cells9061376.
41. Curran CS, Gupta S, Sanz I, Sharon E. PD-1 immunobiology in systemic lupus erythematosus. J Autoimmun. 2019;97:1-9. doi: 10.1016/j.jaut.2018.10.025.
42. Iwai Y, Ishida M, Tanaka Y, Okazaki T, Honjo T, Minato N. Involvement of PD-L1 on tumor cells in the escape from host immune system and tumor immunotherapy by PD-L1 blockade. Proc Natl Acad Sci U S A. 2002;99(19):12293-7. doi: 10.1073/pnas.192461099.
43. Sharpe AH, Pauken KE. The diverse functions of the PD1 inhibitory pathway. Nat Rev Immunol. 2018;18(3):153-67. doi: 10.1038/nri.2017.108.
44. Daassi D, Mahoney KM, Freeman GJ. The importance of exosomal PDL1 in tumour immune evasion. Nat Rev Immunol. 2020;20(4):209-15. doi: 10.1038/s41577-019-0264-y.
45. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer. 2012;12(4):252-64. doi: 10.1038/nrc3239.
46. Sharma P, Allison JP. The future of immune checkpoint therapy. Science. 2015 Apr 3;348(6230):56-61. doi: 10.1126/science.aaa8172.
47. Janjigian YY, Shitara K, Moehler M, Garrido M, Salman P, Shen L, et al. First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): a randomised, open-label, phase 3 trial. Lancet. 2021;398(10294):27-40. doi: 10.1016/S0140-6736(21)00797-2.
48. Dubois M, Liscia N, Brunetti O, Ziranu P, Lai E, Argentiero A, et al. The role of immune checkpoint inhibitors in the treatment sequence of advanced gastric or gastro-esophageal junction cancer: A systematic review and meta-analysis of randomized trials. Crit Rev Oncol Hematol. 2022;173:103674. doi: 10.1016/j.critrevonc.2022.103674.
49. Roach C, Zhang N, Corigliano E, Jansson M, Toland G, Ponto G, et al. Development of a Companion Diagnostic PD-L1 Immunohistochemistry Assay for Pembrolizumab Therapy in Non-Small-cell Lung Cancer. Appl Immunohistochem Mol Morphol. 2016;24(6):392-7. doi: 10.1097/PAI.0000000000000408.
50. Rimm DL, Han G, Taube JM, Yi ES, Bridge JA, Flieder DB, et al. A Prospective, Multi-institutional, Pathologist-Based Assessment of 4 Immunohistochemistry Assays for PD-L1 Expression in Non-Small Cell Lung Cancer. JAMA Oncol. 2017;3(8):1051-8. doi: 10.1001/jamaoncol.2017.0013.
51. Ratcliffe MJ, Sharpe A, Midha A, Barker C, Scott M, Scorer P, et al. Agreement between Programmed Cell Death Ligand-1 Diagnostic Assays across Multiple Protein Expression Cutoffs in Non-Small Cell Lung Cancer. Clin Cancer Res. 2017;23(14):3585-91. doi: 10.1158/1078-0432.CCR-16-2375.
52. Shamai G, Livne A, Polónia A, Sabo E, Cretu A, Bar-Sela G, et al. Deep learning-based image analysis predicts PD-L1 status from H&E-stained histopathology images in breast cancer. Nat Commun. 2022;13(1):6753. doi: 10.1038/s41467-022-34275-9.
53. Büttner R, Gosney JR, Skov BG, Adam J, Motoi N, Bloom KJ, et al. Programmed Death-Ligand 1 Immunohistochemistry Testing: A Review of Analytical Assays and Clinical Implementation in Non-Small-Cell Lung Cancer. J Clin Oncol. 2017;35(34):3867-76. doi: 10.1200/JCO.2017.74.7642.
54. Koelzer VH, Sirinukunwattana K, Rittscher J, Mertz KD. Precision immunoprofiling by image analysis and artificial intelligence. Virchows Arch. 2019;474(4):511-22. doi: 10.1007/s00428-018-2485-z.
55. Wang C, Ma J, Shao J, Zhang S, Li J, Yan J, et al. Non-Invasive Measurement Using Deep Learning Algorithm Based on Multi-Source Features Fusion to Predict PD-L1 Expression and Survival in NSCLC. Front Immunol. 2022;13:828560. doi: 10.3389/fimmu.2022.828560.
56. van Eekelen L, Spronck J, Looijen-Salamon M, Vos S, Munari E, Girolami I, et al. Comparing deep learning and pathologist quantification of cell-level PD-L1 expression in non-small cell lung can-

cer whole-slide images. Sci Rep. 2024;14(1):7136. doi: 10.1038/s41598-024-57067-1.
57. Jin D, Liang S, Shmatko A, Arnold A, Horst D, Grünewald TGP, et al. Teacher-student collaborated multiple instance learning for pan-cancer PDL1 expression prediction from histopathology slides. Nat Commun. 2024;15(1):3063. doi: 10.1038/s41467-024-46764-0.
58. Sulaieva O, Dudin O, Koshyk O, Panko M, Kobyliak N. Digital pathology implementation in cancer diagnostics: towards informed decision-making. Front Digit Health. 2024;6:1358305. doi: 10.3389/fdgth.2024.1358305.
59. Acs B, Rimm DL. Not Just Digital Pathology, Intelligent Digital Pathology. JAMA Oncol. 2018;4(3):403-4. doi: 10.1001/jamaoncol.2017.5449.
60. Huang DQ, Singal AG, Kono Y, Tan DJH, El-Serag HB, Loomba R. Changing global epidemiology of liver cancer from 2010 to 2019: NASH is the fastest growing cause of liver cancer. Cell Metab. 2022;34(7):969-77.e2. doi: 10.1016/j.cmet.2022.05.003.
61. Giashuddin S, Alawad M. Histopathological Diagnosis of Nonalcoholic Steatohepatitis (NASH). Methods Mol Biol. 2022;2455:1-18. doi: 10.1007/978-1-0716-2128-8_1.
62. Yasui K, Hashimoto E, Komorizono Y, Koike K, Arii S, Imai Y, et al.; Japan NASH Study Group, Ministry of Health, Labour, and Welfare of Japan. Characteristics of patients with nonalcoholic steatohepatitis who develop hepatocellular carcinoma. Clin Gastroenterol Hepatol. 2011;9(5):428-33; quiz e50. doi: 10.1016/j.cgh.2011.01.023.
63. Angulo P, Kleiner DE, Dam-Larsen S, Adams LA, Bjornsson ES, Charatcharoenwitthaya P, et al. Liver Fibrosis, but No Other Histologic Features, Is Associated With Long-term Outcomes of Patients With Nonalcoholic Fatty Liver Disease. Gastroenterology. 2015;149(2):389-97.e10. doi: 10.1053/j.gastro.2015.04.043.
64. Foerster F, Gairing SJ, Müller L, Galle PR. NAFLD-driven HCC: Safety and efficacy of current and emerging treatment options. J Hepatol. 2022;76(2):446-57. doi: 10.1016/j.jhep.2021.09.007.
65. Spanu D, Pretta A, Lai E, Persano M, Donisi C, Mariani S, et al. Hepatocellular carcinoma and microbiota: Implications for clinical management and treatment. World J Hepatol. 2022;14(7):1319-32. doi: 10.4254/wjh.v14.i7.1319.
66. Soon GST, Liu F, Leow WQ, Wee A, Wei L, Sanyal AJ. Artificial Intelligence Improves Pathologist Agreement for Fibrosis Scores in Nonalcoholic Steatohepatitis Patients. Clin Gastroenterol Hepatol. 2023;21(7):1940-2.e3. doi: 10.1016/j.cgh.2022.05.027.
67. Taylor-Weiner A, Pokkalla H, Han L, Jia C, Huss R, Chung C, et al. A Machine Learning Approach Enables Quantitative Measurement of Liver Histology and Disease Monitoring in NASH. Hepatology. 2021;74(1):133-47. doi: 10.1002/hep.31750.
68. Yamamoto Y, Tsuzuki T, Akatsuka J, Ueki M, Morikawa H, Numata Y, et al. Automated acquisition of explainable knowledge from unannotated histopathology images. Nat Commun. 2019;10(1):5642. doi: 10.1038/s41467-019-13647-8.
69. Nakatsuka T, Tateishi R, Sato M, Hashizume N, Kamada A, Nakano H, et al. Deep learning and digital pathology powers prediction of HCC development in steatotic liver disease. Hepatology. 2025;81(3):976-89. doi: 10.1097/HEP.0000000000000904.
70. Song AH, Jaume G, Williamson DFK, Lu MY, Vaidya A, Miller TR, et al. Artificial intelligence for digital and computational pathology. Nat Rev Bioeng. 2023;1,930-49. doi: 10.48550/arXiv.2401.06148.
71. Bera K, Schalper KA, Rimm DL, Velcheti V, Madabhushi A. Artificial intelligence in digital pathology - new tools for diagnosis and precision oncology. Nat Rev Clin Oncol. 2019;16(11):703-15. doi: 10.1038/s41571-019-0252-y.
72. Lipkova J, Chen RJ, Chen B, Lu MY, Barbieri M, Shao D, et al. Artificial intelligence for multimodal data integration in oncology. Cancer Cell. 2022;40(10):1095-110. doi: 10.1016/j.ccell.2022.09.012.
73. Coudray N, Ocampo PS, Sakellaropoulos T, Narula N, Snuderl M, Fenyö D, et al. Classification and mutation prediction from non-small cell lung cancer histopathology images using deep learning. Nat Med. 2018;24(10):1559-67. doi: 10.1038/s41591-018-0177-5.
74. Kather JN, Pearson AT, Halama N, Jäger D, Krause J, Loosen SH, et al. Deep learning can predict microsatellite instability directly from histology in gastrointestinal cancer. Nat Med. 2019;25(7):1054-6. doi: 10.1038/s41591-019-0462-y.
75. Amgad M, Hodge JM, Elsebaie MAT, Bodelon C, Puvanesarajah S, Gutman DA, et al. A population-level digital histologic biomarker for enhanced prognosis of invasive breast cancer. Nat Med. 2024;30(1):85-97. doi: 10.1038/s41591-023-02643-7.
76. Vanguri RS, Luo J, Aukerman AT, Egger JV, Fong CJ, Horvat N, et al. Multimodal integration of radiology, pathology and genomics for prediction of

response to PD-(L)1 blockade in patients with non-small cell lung cancer. Nat Cancer. 2022;3(10):1151-64. doi: 10.1038/s43018-022-00416-8.

77. Bommasani R, Hudson DA, Adeli E, Altman R, Arora S, von Arx S, et al. On the opportunities and risks of foundation models. Arxiv 2021. Doi.org/10.48550/arxiv.2108.07258.
78. Chen RJ, Ding T, Lu MY, Williamson DFK, Jaume G, Song AH, et al. Towards a general-purpose foundation model for computational pathology. Nat Med. 2024;30(3):850-62. doi: 10.1038/s41591-024-02857-3.
79. Sha L, Olinski BL, Ho IY, Tan TL, Willis C, , Weiss H, et al. Multi-Field-of-View Deep Learning Model Predicts Nonsmall Cell Lung Cancer Programmed Death-Ligand 1 Status from Whole-Slide Hematoxylin and Eosin Images. J Pathol Inform. 2019;10:24. doi:10.4103/jpi.jpi_24_19.
80. Davis AA, Patel VG. The role of PD-L1 expression as a predictive biomarker: an analysis of all US Food and Drug Administration (FDA) approvals of immune checkpoint inhibitors. J Immunother Cancer. 2019;7(1):278. doi: 10.1186/s40425-019-0768-9.
81. Fang Y, Xiao X, Wang J, Dasari S, Pepin D, Nephew KP, et al. Cancer associated fibroblasts serve as an ovarian cancer stem cell niche through non-canonical Wnt5a signaling. NPJ Precis Oncol. 2024;8(1):7. doi: 10.1038/s41698-023-00495-5.
82. Prelaj A, Miskovic V, Zanitti M, Trovo F, Genova C, Viscardi G, et al. Artificial intelligence for predictive biomarker discovery in immuno-oncology: a systematic review. Ann Oncol. 2024;35(1):29-65. doi: 10.1016/j.annonc.2023.10.125.
83. Zeng Q, Klein C, Caruso S, Maille P, Laleh NG, Sommacale D, et al. Artificial intelligence predicts immune and inflammatory gene signatures directly from hepatocellular carcinoma histology. J Hepatol. 2022;77(1):116-27. doi: 10.1016/j.jhep.2022.01.018.
84. Hoda RS, Brogi E, D'Alfonso TM, Grabenstetter A, Giri D, Hanna MG, et al. Interobserver Variation of PD-L1 SP142 Immunohistochemistry Interpretation in Breast Carcinoma: A Study of 79 Cases Using Whole Slide Imaging. Arch Pathol Lab Med. 2021;145(9):1132-7. doi: 10.5858/arpa.2020-0451-OA.
85. Reisenbichler ES, Han G, Bellizzi A, Bossuyt V, Brock J, Cole K, et al. Prospective multi-institutional evaluation of pathologist assessment of PD-L1 assays for patient selection in triple negative breast cancer. Mod Pathol. 2020;33(9):1746-52. doi: 10.1038/s41379-020-0544-x.
86. Wang X, Wang L, Bu H, Zhang N, Yue M, Jia Z, et al. How can artificial intelligence models assist PD-L1 expression scoring in breast cancer: results of multi-institutional ring studies. NPJ Breast Cancer. 2021;7(1):61. doi: 10.1038/s41523-021-00268-y.
87. Rudin C. Stop Explaining Black Box Machine Learning Models for High Stakes Decisions and Use Interpretable Models Instead. Nat Mach Intell. 2019;1(5):206-15. doi: 10.1038/s42256-019-0048-x.
88. Ali S, Abuhmed T, El-Sappagh S, Muhammad K, Alonso-Moral JM, Confalonieri R, et al. Explainable Artificial Intelligence (XAI): What we know and what is left to attain Trustworthy Artificial Intelligence. Information Fusion. 2023;99(101805):1566-2535. doi: 10.1016/j.inffus.2023.101805.
89. Jarrahi MH, Davoudi V, Haeri M. The key to an effective AI-powered digital pathology: Establishing a symbiotic workflow between pathologists and machine. J Pathol Inform. 2022;10;13:100156. doi: 10.1016/j.jpi.2022.100156.
90. Goh WWB, Kabir MN, Yoo S, Wong L. Ten quick tips for ensuring machine learning model validity. PLoS Comput Biol. 2024;20(9):e1012402. doi: 10.1371/journal.pcbi.1012402.
91. Ho SY, Phua K, Wong L, Bin Goh WW. Extensions of the External Validation for Checking Learned Model Interpretability and Generalizability. Patterns (N Y). 2020;1(8):100129. doi: 10.1016/j.patter.2020.100129.
92. Ejiyi CJ, Qin Z, Agbesi VK, Yi D, Atwereboannah AA, Chikwendu IA, et al. Advancing cancer diagnosis and prognostication through deep learning mastery in breast, colon, and lung histopathology with ResoMergeNet. Comput Biol Med. 2025;185:109494. doi: 10.1016/j.compbiomed.2024.109494.