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Review

Rediscovering neuroblastoma pathology from the perspective of digital pathology and AI: Current challenges and future implications

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Summary

Neuroblastoma is the most common extracranial solid malignancy of childhood and demonstrates marked clinical and biologic heterogeneity. Histopathologic evaluation, particularly through the International Neuroblastoma Pathology Classification system, remains central to risk stratification by integrating patient age, degree of neuroblastic differentiation, Schwannian stromal development, and the mitosis–karyorrhexis index. However, diagnostic interpretation is challenged by intratumoral heterogeneity, sampling bias, interobserver variability, and the subjective assessment of subtle morphologic thresholds. These limitations directly influence prognostic categorization and subsequent clinical management.

Digital pathology, through whole-slide imaging, provides a platform for standardized visualization and quantitative analysis of entire tumor sections. Recent computational and artificial intelligence–assisted approaches have demonstrated feasibility in tumor category classification, assessment of differentiation, automated mitosis–karyorrhexis index quantification, prognostic stratification, and prediction of molecular features such as MYCN amplification. While reported performance metrics are promising, most studies remain retrospective, single-institution studies, and limited by small pediatric datasets.

Significant barriers to clinical translation persist, including the need for multi-institutional validation, workflow standardization, quality assurance frameworks, regulatory governance, and mitigation of algorithmic bias. Current evidence supports the role of digital and artificial intelligence tools as complementary aids rather than replacements for expert pathologist interpretation. Coordinated efforts addressing validation, infrastructure readiness, and ethical considerations will be essential for responsible integration of computational methods into neuroblastoma histopathology.

Keywords: neuroblastoma, digital pathology, whole-slide imaging, artificial intelligence, computational pathology

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Introduction

Neuroblastoma (NB) is one of the most common pediatric malignancies and is characterized by a neuroectodermal origin with an immature neuroblastic phenotype. The tumor arises from the sympathoadrenal lineage of neural crest-derived cells. Neuroblastoma represents the most common cancer in infancy and the most common extracranial solid pediatric tumor, with the majority of cases diagnosed before the age of five [1,2]. Neuroblastoma is exceedingly rare in adults; more than 97% of cases are diagnosed before the age of ten years.These tumors contrib-

ute substantially to childhood cancer-related mortality and are considered among the leading causes of cancer-related death in children under five years of age [3,4]. Most neuroblastomas arise in the adrenal gland, followed by the retroperitoneum and mediastinum, typically along the sympathetic chain [1,4].For many decades, patient age at diagnosis and tumor stage have been considered key variables in the prognostication of childhood neuroblastoma. Towards the end of the last century, Shimada proposed a classification system that correlated histopathologic features of neuroblastoma with clinical behavior. Later, the Shimada classification was incorporated into the International Neuroblastoma Pathology Classification (INPC) system, which stratifies neuroblastoma into favorable and unfavorable histology based on patient age, degree of differentiation, and the mitosis–karyorrhexis index (MKI) [5,6].

The clinical behavior of neuroblastoma is highly heterogeneous, with outcomes ranging from spontaneous regression to aggressive progressive disease. When tumors are localized and surgically resectable, surgery represents the first-line treatment. However, many cases develop distant metastases. For low-risk and intermediate-risk NB, cure rates approach 90-95% with multimodal therapy, while for high-risk neuroblastoma (HR-NB), it falls to 50-60%. Neuroblastoma is a clinically and biologically heterogeneous disease, reflected in its pathogenesis, behavior, and therapeutic management [7,8].

Methodology

This narrative review evaluates the current applications and challenges of digital pathology and artificial intelligence (AI) in neuroblastoma pathology diagnosis. A literature search was conducted using PubMed, Google Scholar, and Scopus to identify relevant studies published between 2006 and the present, aiming to capture early developments while emphasizing more recent advances. The search terms included ("neuroblastoma" OR "neuroblastic tumor") AND ("digital pathology" OR "whole-slide imaging" OR "artificial intelligence" OR "deep learning"). Reference lists of relevant articles were also screened to identify additional studies.

Studies addressing neuroblastoma pathology and AI or digital pathology applications, including original research, reviews, or relevant technical papers published in English, were included. Studies focusing solely on radiology or genomics without pathology relevance, case reports, and non-English articles were excluded.

Titles and abstracts were screened for relevance, followed by full-text review of eligible studies. Data extracted from included studies comprised study design, sample size, specimen type, computational method, validation strategy, reported performance metrics, and key limitations. Findings were subsequently summarized with emphasis on clinical applicability and methodological robustness of AI-assisted approaches in neuroblastoma pathology.

The final literature search was conducted in February 2026. The search initially retrieved approximately 35 records, of which 13 studies met the inclusion criteria and were included in the final synthesis. As a narrative review, this study may be subject to selection bias.

Histopathology of neuroblastoma

The pathological classification of neuroblastoma is complex and encompasses multiple diagnostic categories with diverse morphologic patterns. Undifferentiated neuroblastoma is characterized by dense sheets of primitive small round blue cells with minimal neuropil, which may create histologic ambiguity. These tumors usually display high mitotic and karyorrhectic activity. Homer-Wright rosettes may be present. Poorly differentiated neuroblastomas retain a primitive appearance but contain more neuropil and ≤ 5% differentiating neuroblasts. In contrast, differentiating neuroblastomas exhibit an admixture of immature neuroblasts with ≥ 5% differentiating neuroblasts. Ganglionic differentiation is characterized by larger cell size, vesicular nuclei, and prominent nucleoli [9,10].

Ganglioneuroblastomas are classified into intermixed and nodular types. Both share Schwannian-rich stroma (either exclusively or in combination with stroma-poor areas) and exhibit ganglionic differentiation. In the nodular type, the presence of discrete nodular growth of neuroblasts represents a major diagnostic parameter and an important prognostic determinant [10]. The mitosis–karyorrhexis index (MKI) represents the number of nuclei displaying mitotic or karyorrhectic activity per 5,000 neuroblastic cells. Based on this parameter, all Schwannian stroma-poor neuroblastomas and the neuroblastoma components of nodular ganglioneuroblastoma are stratified into three categories: Low MKI (<100/5,000 cells), Intermediate MKI (100-200/5,000 cells), and High MKI (>200/5,000 cells), which contribute to final classification and prognostic stratification [11].

Sources of diagnostic variability in neuroblastoma histopathology

Complexity of histopathologic risk stratification

In routine pathology practice, histopathologic diagnosis of neuroblastoma may exhibit variability that directly affects subsequent prognostic stratification. A primary source of complexity arises from the multi-component nature of the diagnostic framework used for neuroblastoma and ganglioneuroblastoma classification. The International Neuroblastoma Pathology classification (INPC) integrates age-based evaluation with multiple histologic parameters-including the degree of neuroblastic differentiation, Schwannian stromal maturation, and mitosis–karyorrhexis index (MKI). In practice, the need to assess and integrate these independent features adds interpretive complexity and creates several points for diagnostic variability and inconsistency [5].

Assessment of neuroblastic differentiation, which represents a core element of neuroblastoma evaluation, depends on identifying subtle morphologic changes along a differentiation spectrum. This task is specifically challenging and time-consuming, especially in borderline cases where poorly defined thresholds may contribute to inconsistent interpretation and reporting [12].

Sampling bias

Sampling bias represents an additional challenge in neuroblastic tumors, particularly due to the presence of intratumoral heterogeneity, which is well recognized in these tumors. In routine practice, histopathologic interpretation often relies on selected "representative" microscopic regions rather than whole-slide assessment. As a result, morphologically distinct components within the same tumor may be underrepresented during routine microscopic evaluation [13].

Interobserver and intraobserver variability, workload and human factors

Diagnostic interpretation is further influenced by pathologist-dependent factors. Variations in experience level, together with additional effects of fatigue and heavy workloads, can contribute to both interobserver and intraobserver variability, particularly in evaluating complex tumors with subtle morphologic thresholds [13]. These human factors introduce additional subjectivity into assessments that already require precise recognition of delicate morphologic features across multiple slides and tumor sections. In this context, the limitations of purely visual assessment by the human eye-especially for subtle features-may further contribute to diagnostic variability [14].

Spatial heterogeneity of morphologic features

In addition to sampling related limitations, recent large-cohort digital histopathology studies have drawn attention to the marked spatial morphologic heterogeneity within neuroblastic tumors, including variation in MKI, stromal composition, and differentiation patterns across different regions of the same tumor. This degree of spatial heterogeneity highlights the limitations of relying on region-restricted assessment in routine diagnostic practice [15].

Several observations regarding the sources of diagnostic variability have been highlighted in studies applying computational analysis to neuroblastoma histopathology, as these investigations tend to define and overcome limitations and sources of subjectivity in conventional microscopic assessment. Collectively, these challenges establish a clear rationale for digital pathology-particularly whole-slide imaging-as a foundational platform for improving diagnostic standardization and reproducibility, which is addressed in the following section.

Digital pathology as an enabling platform

From glass slide to whole-slide Image (WSI)

Digital pathology is the transformation of conventional glass slide-based pathology practice into digital workflows, with the primary aim of generating high-quality whole-slide images (WSIs) suitable for diagnostic use, while preserving diagnostic accuracy, reproducibility, and reliability [16]. A recent systematic review evaluating validation studies comparing WSIs with conventional light microscopy demonstrated that diagnostic performance using digital pathology is not inferior to conventional glass slide interpretation, including diagnostic accuracy, concordance, and interobserver agreement [17]. In addition, professional guidelines have documented acceptable intraobserver diagnostic concordance between WSIs and glass slide diagnoses with applying appropriate validation protocols, including a washout period of two weeks between the two modalities [18].

Importantly, expert consensus has emphasized the need for standardized implementation of digital pathology workflows**.** Eloy et al. state that "all processes must be maximally standardized to guarantee reproducibility and reliability of pathologic diagnosis," highlighting the need to standardize laboratory workflows in the steps of whole-slide image generation, management, and use to ensure consistent digital diagnostic interpretation. Beyond diagnostic considerations, digital pathology offers practical benefits for pathology

practice, including support for remote consultations, improved workflow efficiency and flexibility, reduced physical slide handling and enhanced slide comparison and case organization [16].

Digital pathology in quantification tasks

Beyond visual interpretation, digital pathology enables quantitative assessments of histologic features through image analysis. Quantitative measurements of tissue architecture, mitotic counts, and biomarker expression can be performed in a more standardized and reproducible manner than conventional microscopy, particularly by reducing variability related to staining intensity and subjective visual estimation [19].

Digital pathology in pediatric tumors

Digital pathology has been increasingly applied in pediatric oncology, with studies describing the use of WSIs as a foundation for exploratory computational analysis in the diagnostic process. Recent reviews addressing WSIs in pediatric solid tumors-including neuroblastoma-highlight ongoing developments as well as challenges specific to pediatric pathology, including limited dataset sizes, tumor rarity and difficulties in validation [20].

Digital pathology as prerequisite for computational and AI-assisted analysis

Importantly, the application of image analysis and artificial intelligence tools in pathology practice depends on the availability of WSIs, making digital pathology a prerequisite for AI-assisted approache [16]. Through digital pathology workflows, WSIs are converted into analyzable data, allowing objective interpretation, comparison, and downstream computational analysis [19].

Collectively, these features position digital pathology as the essential platform for AI-assisted histopathologic analysis of neuroblastoma, where diagnostic variability and subtle morphologic criteria directly influence risk stratification and clinical management.

Computational and AI-assisted applications in neuroblastoma pathology

Overview of AI uses in neuroblastoma

A recent large-cohort study by Ramesh et al. [15] developed a deep learning model to evaluate the feasibility of AI-assisted diagnosis in neuroblastoma using WSIs. The model was trained and validated on WSI datasets to assess multiple diagnostic tasks, including tumor category, histologic grade, mitosis–karyorrhexis index (MKI) and MYCN amplification status, with performance compared to expert pathologist assessment. While both internal and external validation showed promising results, the study remains limited by its retrospective design and the small external validation cohort (n=25), which may restrict generalizability and clinical applicability. The multiple analytic tasks addressed in this study are discussed in the following sections.

Table I summarizes datasets, computational and AI-assisted modalities, validation strategies, and main performance metrics across key neuroblastoma computational and AI-assisted pathology studies.

Category classification of neuroblastic tumors

In Ramesh et al. [15], tumor category classification-distinguishing neuroblastoma from ganglioneuroblastoma- demonstrated the strongest performance among other evaluated tasks, supporting the suitability of AI for morphologic categorization based on whole-slide assessment.

Earlier computational studies also addressed diagnostic categorization. Gheisari et al. [14] applied scale invariant feature transform (SIFT)- based feature extraction with supervised classification (SVM) to classify neuroblastic tumor histologic images into five diagnostic categories aligned with the INPC/ Shimada system, including undifferentiated, poorly differentiated, and differentiating neuroblastoma, as well as ganglioneuroblastoma (intermixed and nodular). The study reported performance at image level classification across categories, with lower discrimination between morphologically similar subtypes (*e.g.*, poorly differentiated vs. differentiating neuroblastoma), highlighting limitations in resolving subtle morphologic differences.

Similarly, Sertel et al. [13] demonstrated that whole-slide image analysis could classify neuroblastic tumors based on Schwannian stromal development into stroma-rich and stroma-poor patterns, with relatively high overall accuracy compared with expert pathologists. However, performance was lower in stroma-poor tumors, particularly differentiating subtypes, indicating reduced reliability in more complex morphologic categories and limiting generalizability.

Collectively, these studies support the feasibility of computational and AI-assisted tools in classification tasks of neuroblastic tumors, particularly for categories with clear morphologic boundaries. However, most studies are retrospective, single-institution based, and report variable performance across closely related subtypes, highlighting the need for robust external validation before clinical implementation.

Table I. Summary of key computational and AI-assisted studies in neuroblastoma pathology, including study design, datasets, validation approaches, performance metrics, and major methodological limitations.

Study/Year	Task	Dataset (No., setting)	Modality used	Validation	Main outcome	Main limitation
Kong et al., 2009	Classification of neuroblastic differentiation (undifferentiated, poorly differentiated, differentiating)	36 cases (WSIs); 3 training, 33 testing; retrospective	Feature extraction + supervised machine learning classifier	Internal held-out test set (33 WSIs); single institution	Classification accuracy: **87.88%** (vs. expert pathologist labels)	No external validation; single-institution dataset
Sertel et al., 2009	Stromal development classification (stroma-rich vs. stroma-poor)	45 cases (WSIs); 2 training, 43 testing; retrospective	Feature extraction + supervised machine learning classifier	Internal held-out test set (43 WSIs); single institution	Overall classification accuracy: **88.4%** (stroma-rich vs. stroma-poor); reduced performance in certain subgroups	No external validation; single-institution dataset
Gheisari et al., 2018	Five-class Shimada / INPC classification	1043 cropped histologic images; 623 training, 211 validation, 209 testing; retrospective	SIFT feature extraction + feature encoding + SVM classifier	Image-level internal train/ validation/test split	Best weighted F-measure: **85.19%** (image-level classification)	Image-level analysis only; no case-level validation
Yu et al., 2022	Automated MKI quantification	16 cases (WSIs); retrospective	Digital image analysis software (QuPath)	Internal comparison with manual MKI scoring (single center)	Precision > **0.96;** Recall > **0.96;** False positive rate: **0.6-3.7%;** False negative rate: **0.6-3.8%**	Small sample size; single institution; ROI-based approach
Liu et al., 2022	Prognostic classification (FH vs. UH)	563 WSIs; 107 patients; retrospective	Nuclear segmentation + quantitative feature extraction + logistic regression classifier	Retrospective training dataset with independent validation dataset	AUC: **0.946** (train), **0.938** (test); Accuracy: **0.856** (train), **0.865** (test); MCC **0.703** (train), **0.630** (test)	Retrospective design; no external multi-institutional validation
Bhardwaj et al., 2022	Digital MKI assessment in FNAB	50 cases; retrospective	Digital image visual analysis score (DIVAS)	Compared with conventional visual MKI assessment and corresponding cell-block histology	**96%** concordance with cell-block histology; **86%** concordance with conventional visual assessment; cytology-based INPC category correlated with clinical outcome	Small sample size; single institution
Ramesh et al., 2024	Tumor category; histologic grade; MKI category; MYCN status	197 WSIs (multi-institutional); 172 training, 25 external test cohort; retrospective	Deep learning attention-based multiple instance learning model (aMIL) with feature extraction via pretrained self-supervised learning system (UNI)	Internal training cohort and independent external test cohort	External test set accuracy: tumor category **0.92;** histologic grade **0.68;** MKI category **0.78;** MYCN status **0.77**	Retrospective design; limited external cohort size (n=25)

Assessment of differentiation and risk-related morphologic features

Kong et al. [12] demonstrated that quantitative morphologic features extracted from WSIs could assist in assessing the degree of neuroblastic differentiation (undifferentiated, poorly differentiated, and differentiating), with reported accuracy against expert labels. As differentiation is a key histologic component that directly influences prognostic classification in neuroblastoma, AI-supportive tools may support this time-consuming and interobserver-dependent task**.** However, assess-

ment of differentiation remains challenging in practice due to subtle morphologic thresholds and variability between observers.

More recently, Ramesh et al. [15] evaluated AI performance in other risk-related factors, including histologic grade, mitosis–karyorrhexis index (MKI) categories and MYCN status, with variable performance reported among tasks. This variability reflects the complexity of these features, suggesting that not all prognostic parameters are equally amenable to accurate AI-based assessment.

Additional studies have explored digital quantification of specific risk-related parameters in neuroblastoma. The use of QuPath software has been investigated to support automated MKI assessment on WSIs by defining regions of interests (ROIs) followed by automated identification and counting of mitotic and karyorrhectic figures. This approach aims to provide more objective and reproducible MKI evaluation while reducing manual workload and interobserver variability, with reported accuracy comparable to manual assessment. However, the ROI-based approach and limited cohort size may restrict robustness and generalizability, particularly in heterogeneous tumors [21].

A complementary work evaluated MKI assessment in fine-needle aspiration biopsies (FNA) using digital image visual analysis score (DIVAS) [22]. Smear-based MKI assessment achieved high concordance with corresponding cell block histology and conventional visual scoring, especially in high MKI categories. Furthermore, INPC categorization based on DIVAS-scored MKI showed significant correlation with clinical outcomes. However, the cytology-based approach and limited sample size may limit broader applicability in routine practice.

Liu et al. [23] applied digital pathology methods to segment nuclei from WSIs and extract quantitative nuclear features, including size, shape, and spatial arrangement. Aggregation of these features across entire tumor sections enabled capturing of prognostic differences in morphologic patterns and nuclear intensity between favorable and unfavorable histologic groups. While this approach highlights the potential of quantitative morphologic analysis and objective support for pathologists, particularly in visually complex cases, its retrospective design, limited dataset diversity, and lack of external validation limit its readiness for routine clinical application.

Overall, the literature supports the applicability of computational and AI-assisted approaches in prognostically relevant assessment in neuroblastoma, particularly for quantifiable features such as MKI and nuclear morphology. However, features requiring subjective interpretation–such as differentiation and stromal composition-are more challenging. In addition, most studies are investigational, retrospective, and single-institution based cohorts requiring prospective and multi-institutional validation before clinical implementation.

From a pathological perspective, the feasibility of computational assessment in neuroblastoma varies depending on how clearly and objectively the morphologic feature can be defined. Quantifiable and morphologically well-defined parameters that can be detected, counted, or segmented-such as mitosis–karyorrhexis index (MKI) and nuclear morphometric features- appear more amenable to computational analysis. In contrast, features with less distinct boundaries that require contextual interpretation across tumor sections-such as differentiation status, Schwannian stromal development, stromal composition, and necrosis-remain more challenging for algorithm-based evaluation. These parameters often depend on subtle morphologic features and intermediate thresholds that require integrated interpretation by pathologists. Consequently, current computational applications in neuroblastoma pathology tend to perform better in tasks based on discrete and quantifiable features than in those requiring complex contextual evaluation.

Table II summarizes the relative feasibility of computational evaluation of key histologic features in neuroblastoma based on current evidence.

Table II. Summary of relative feasibility of computational evaluation of key histologic features in neuroblastoma based on current evidence

Morphologic feature	Current computational feasibility
Tumor category classification	Moderate to high feasibility; clearer distinction between neuroblastoma and ganglioneuroblastoma, while closely related subtypes remain difficult
Mitosis–Karyorrhexis index (MKI)	Relatively feasible; automated detection and counting approaches reported
Nuclear morphometric features	Feasible using quantitative feature extraction methods
Differentiation status	Challenging due to subtle morphologic thresholds and mixed tumor patterns
Schwannian stromal development	Partially feasible; performance better for stroma-rich vs stroma-poor distinction, while lower in stroma-poor tumors particularly differentiating subtype
Necrosis	Limited exploration in current studies

Spatial heterogeneity and region-based analysis

Several AI-based approaches in neuroblastoma histopathology apply region-based or whole-slide analysis frameworks that incorporate spatial variation across tumor sections. As previously demonstrated by Sertel et al. [13] in stromal classification, region-based image analysis can identify spatial variation in stromal patterns across entire slides, highlighting the importance of distributed morphologic assessment rather than field-restricted evaluation. Similarly, Ramesh et al. [15] applied deep learning models at patch level to analyze neuroblastic tumors across whole-slide images, capturing spatially diverse morphologic features across different tumor areas and identifying diagnostically relevant regions within heterogeneous tumors. Liu et al. [23] also aggregated automatically derived quantitative features from multiple tumor regions to generate case-level predictions that reflect whole-tumor morphology.

In addition to their primary classification objectives, these studies, by integrating information from multiple regions across whole-slide images, provide a more comprehensive representation of tumor heterogeneity and may reduce sampling bias. This is especially relevant in neuroblastic tumors, where intratumoral heterogeneity-including variability of stromal composition, differentiation patterns, and proliferative activity- can contribute to diagnostic variability. However, most current implementations remain exploratory and rely on retrospective datasets, highlighting the need for broader validation before routine clinical use. With further validation, such approaches may improve reproducibility in complex and time-consuming neuroblastoma assessment and guide more representative ROI selection.

Barriers to clinical implementation and future directions

Scope of current evidence

Despite promising results, most published computational and AI-assisted approaches in neuroblastoma pathology remain constrained by the rarity of pediatric tumors-particularly neuroblastoma-which results in small dataset sizes, and uneven distribution of diagnostic categories. As highlighted in recent reviews of pediatric pathology, these limitations restrict model development and validation [20]. Additionally, many studies have been conducted within single institutions and lack external validation, increasing the risk of model overfitting and limiting generalizability [15].

Another important limitation relates to the quality of annotations used as ground truth for model training. In neuroblastoma pathology, interpretation of features such as differentiation status, stromal composition, and MKI assessment may vary between observers, introducing inconsistencies in annotated datasets.

These challenges are particularly relevant in neuroblastoma pathology due to the intrinsic morphologic heterogeneity of neuroblastic tumors, the complexity of diagnostic system, as well as other sources of diagnostic variability discussed in Section 4. Variability in stromal development, differentiation status, and regional distribution of mitotic and karyorrhectic figures may occur within the same tumor section, making consistent annotation challenging even for expert pathologists. Consequently, assembling large and consistently annotated datasets suitable for training robust computational models remains particularly difficult in this rare pediatric tumor. These factors collectively indicate that AI-assisted neuroblastoma pathology research remains largely at an exploratory stage.

In addition, current computational and AI-assisted studies in neuroblastoma pathology predominantly focus on morphologic features and a limited set of prognostic markers, including MKI and MYCN amplification status. Other established prognostic factors, such as ALK mutations[24], tumor-infiltrating lymphocytes[25], and other genomic risk markers[26], are rarely systematically evaluated through these modalities. As a result, the feasibility of digital and AI-based methods to assess the full complexity of multifactorial neuroblastoma risk-stratification remains incompletely explored.

Evidence gaps and adoption barriers

Beyond study-level limitations, broader evidence gaps continue to hinder clinical translation. In an international study based on surveys and interviews, Swellins et al. [27] explored pathologists' perspectives on barriers for adopting computational pathology in oncology practice. Reported concerns included the quality of evidence supporting reported outcomes, uncertainty regarding clinical utility, and variability in expectations about how AI tools can be integrated within the existing diagnostic workflows. Importantly, participants demonstrated a lack of consensus on what constitutes sufficient validation, particularly with respect to local and prospective deployment of AI-supported systems. A similar concept was highlighted by Bessen et al. [28], reporting that some pathologists remain hesitant to adopt digital workflows instead of conventional microscopy.

Technical generalizability and robustness

Technical variability across digital pathology platforms represents a major challenge to the generalizability of these methods. Eloy et al. [16] provide expert recommendations for safe digital pathology implementation, emphasizing the need for workflow standardization and robust quality control across all stages from slide preparation to image output. Such measures are essential to ensure consistent generation of high-quality WSIs, which are a prerequisite for downstream digitalized or AI-assisted applications. Supporting this concern, Ardon et al. [29] reported image-quality issues including out-of-focus areas, digital artifacts, missing tissue regions and barcode detection failures observed by quality management system at a large cancer center. These findings demonstrate that image quality varies in routine scanning processes, creating a source of variability that may limit AI generalizability and reliability.

Beyond scanner level factors, insufficient expertise among pathologists, limited availability of large annotated datasets, and lack of standardization in image acquisition and analysis [30] represent other implementation challenges. Importantly, successful deployment requires multidisciplinary coordination among pathologists, laboratory staff, IT teams and institutional stakeholders for integration of these digital systems in routine practice [23].

Bessen et al. [28] addressed practical barriers to adoption, including high implementation costs, the need for dedicated teams to digitize and analyze slides, and greater coordination with laboratory information systems and electronic health records. They also noted that clinical formal guidelines including CAP can facilitate future adoption.

Regulatory, quality assurance and governance

Formal professional guidelines highlight additional requirements for the clinical implementation of digital and AI-assisted pathology systems. The updated College of American Pathologists (CAP) guidelines [18] emphasize that validation of digital pathology systems should be aligned with their intended clinical use (*e.g.*, triage, primary diagnosis, or diagnostic support), emulate real-world diagnostic workflows, and be performed locally with defined revalidation requirements when system components change. However, most published AI studies in neuroblastoma pathology remain retrospective, rely on generic performance metrics, and are conducted within single institutions, limiting their applicability in clinical practice. Furthermore, the frequent absence of structured documentation, governance frameworks, and revalidation strategies contrasts with CAP recommendations for digital systems prior to clinical deployment, highlighting a gap between current evidence and clinical implementation.

Regulatory considerations represent an additional barrier to clinical implementation. Singh et al. [31] highlighted that existing regulatory frameworks for AI-enabled medical software are challenged by the adaptive nature of machine learning systems which may evolve after deployment. The authors emphasize that requirements for managing algorithm updates, continuous performance monitoring and documentation across the entire process lifecycle remain under development. To address these challenges, the U.S. Food and Drug Administration has proposed Total Product Lifecycle (TPLC) and Good Machine Learning Practice (GMLP) approaches to support controlled updates, long-term safety monitoring, and transparency in AI-based medical systems.

Together, these professional recommendations highlight the importance of structured validation, governance, and lifecycle management prior to safe clinical deployment of AI-assisted pathology tools in practice.

Ethical considerations and bias

Ethical considerations, including algorithmic bias, represent an additional barrier to responsible AI implementation. Lin et al. [32] demonstrated that limited diversity in training datasets can result in performance disparities across demographic groups including race, gender, and age. In a large pan-cancer analysis, diagnostic performance gaps were identified in multiple tasks, highlighting the risk of bias in AI-assisted pathology systems. The study further stated that fairness-aware modeling approaches can reduce these disparities, emphasizing the need to identify and manage bias before deploying AI tools in practice.

Roadmap toward clinical integration

The reviewed evidence collectively shows meaningful progress in AI-assisted neuroblastoma histopathology, while also highlighting important requirements for future deployment. These include multi-institutional validation, standardization of digital pathology workflows, and establishment of strong quality management systems [16,18,27]. The generation of diverse and representative datasets is required to ensure fairness and generalizability across different patient demographic groups [32]. Importantly, recent implementation-focused analyses emphasize that successful translation will also depend on infrastructure readiness, cost, availability of annotated data, computational expertise, and coordinated multidisciplinary engagement of multiple stakeholders [28,30].

In practical settings, AI-assisted tools may initially

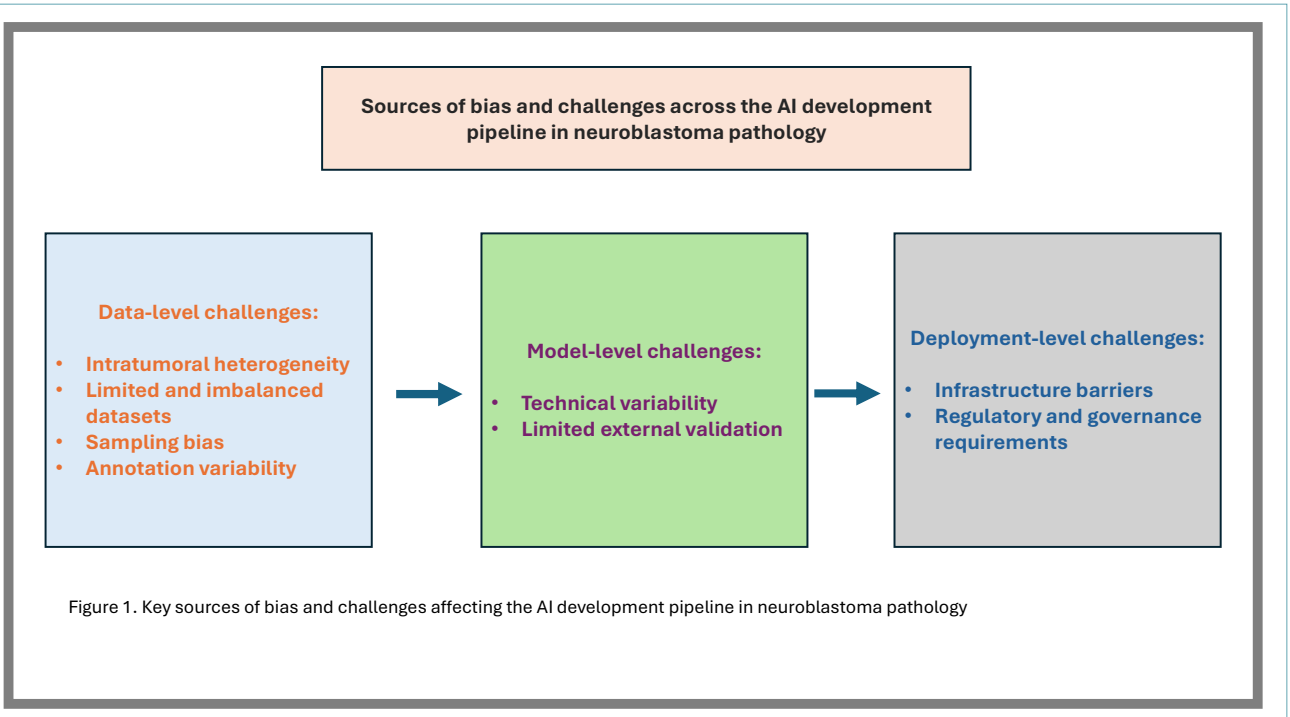


Figure 1. Summarizes the main sources of bias and challenges across the AI development pipeline in neuroblastoma pathology, including data-level, model-level, and deployment-level barriers.

function as decision-support systems integrated into digital pathology platforms. For example, algorithms could assist pathologists by highlighting regions of interest within whole-slide images, supporting automated MKI counting, or assisting in preliminary tumor categorization. Such tools may improve workflow efficiency while maintaining the central role of expert pathologist interpretation.

In parallel, AI tools should be deployed within governance frameworks that ensure transparency, controlled updates, and continuous monitoring [31]. Highlighting these priorities will require coordinated efforts and guidelines-driven implementations before these methods can be reliably integrated into the pathology diagnosis of neuroblastic tumors.

Conclusion

Neuroblastoma diagnosis is challenging and carries diagnostic subjectivity in routine pathology practice. The need for more standardized and objective assessment methods has driven interest in investigating digital pathology and AI-assisted tools in different aspects of neuroblastoma evaluation. Current evidence suggests that computational approaches are most promising for tasks involving well-defined and quantifiable morphologic features, such as tumor categorization, nuclear morphometry, and MKI assessment. In contrast, features requiring complex contextual interpretation, including differentiation patterns and stromal composition, remain more challenging for algorithm-based evaluation.

Although current studies suggest potential benefits, the available literature remains exploratory and is frequently limited by small datasets, single-institution cohorts, and limited external validation. Consequently, these approaches should currently be viewed as supportive technologies that complement, rather than replace, expert pathologist interpretation. Future progress will depend on the development of larger multi-institutional datasets, improved annotation quality, robust validation strategies, structured governance frameworks and strong quality management systems. Addressing these requirements will be critical for responsible and clinically meaningful integration of digital and AI-assisted tools into neuroblastoma histopathology.

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The authors declare that they have no conflicts of interest of a financial, personal or other nature.

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Author Contributions

Lina M. Samman: Conceptualization, writing original draft, Supervision. Osama AL-Samman: Investigation, writing original draft. Mohamed Ahmed: Writing - Review & Editing; Visualization. Riham Ibrahim: Writing - Review & Editing

References

1 Matthay KK, Maris JM, Schleiermacher G, et al. Neuroblastoma. Nat Rev Dis Primers 2016;2:16078. https://doi.org/10.1038/nrdp.2016.78

2 Pugh TJ, Morozova O, Attiyeh EF, et al. The genetic landscape of high-risk neuroblastoma. Nat Genet 2013;45:279-84. https://doi.org/10.1038/ng.2529

3 Chidiac C, McDermott KM, Ramdat C, et al. Adults and Adolescents With Neuroblastoma: An Analysis of the National Cancer Database. J Surg Oncol 2025;131:1420-30. https://doi.org/10.1002/jso.28076

4 Smith L, Minter S, O'Brien P, et al. Neuroblastoma in an adult: case presentation and literature review. Ann Clin Lab Sci 2013;43:81-4.

5 Sano H, Bonadio J, Gerbing RB, et al. International neuroblastoma pathology classification adds independent prognostic information beyond the prognostic contribution of age. Eur J Cancer 2006;42:11139. https://doi.org/10.1016/j.ejca.2005.11.031

6 Park JR, Bagatell R, London WB, et al. Children's Oncology Group's 2013 blueprint for research: neuroblastoma. Pediatr Blood Cancer 2013;60:985-93. https://doi.org/10.1002/pbc.24433

7 Pinto NR, Applebaum MA, Volchenboum SL, et al. Advances in Risk Classification and Treatment Strategies for Neuroblastoma. J Clin Oncol 2015;33:3008-17. https://doi.org/10.1200/JCO.2014.59.4648

8 Ladenstein R, Pötschger U, Valteau-Couanet D, et al. Interleukin 2 with anti-GD2 antibody ch14.18/CHO (dinutuximab beta) in patients with high-risk neuroblastoma (HR-NBL1/SIOPEN): a multicentre, randomised, phase 3 trial. Lancet Oncol 2018;1:1617-29. https://doi.org/10.1016/S1470-2045(18)30578-3

9 Meany HJ. Non-High-Risk Neuroblastoma: Classification and Achievements in Therapy. Children (Basel) 2019;6:5. https://doi.org/10.3390/children6010005

10 Centre international de recherche sur le cancer, Organisation mondiale de la santé, editors. Paediatric tumours. 5th ed. Lyon: International agency for research on cancer; 2022. (World health organization classification of tumours).

11 Teshiba R, Kawano S, Wang LL, et al. Age-dependent prognostic effect by Mitosis-Karyorrhexis Index in neuroblastoma: a report from the Children's Oncology Group. Pediatr Dev Pathol 2014;17:441-9. https://doi.org/10.2350/14-06-1505-OA

12 Kong J, Sertel O, Shimada H, et al. Computer-aided evaluation of neuroblastoma on whole-slide histology images: Classifying grade of neuroblastic differentiation. Pattern Recognition 2009;42:1080-92. https://doi.org/10.1016/j.patcog.2008.10.035

13 Sertel O, Kong J, Shimada H, et al. Computer-aided Prognosis of Neuroblastoma on Whole-slide Images: Classification of Stromal Development. Pattern Recognit 2009;42:1093-103. https://doi.org/10.1016/j.patcog.2008.08.027

14 Gheisari S, Catchpoole DR, Charlton A, et al. Computer Aided Classification of Neuroblastoma Histological Images Using Scale Invariant Feature Transform with Feature Encoding. Diagnostics (Basel) 2018;8:56. https://doi.org/10.3390/diagnostics8030056

15 Ramesh S, Dyer E, Pomaville M, Doytcheva K, et al. Artificial intelligence-based morphologic classification and molecular characterization of neuroblastic tumors from digital histopathology. NPJ Precis Oncol 2024;8:255. https://doi.org/10.1038/s41698-024-00745-0

16 Eloy C, Fraggetta F, Van Diest PJ, et al. Digital transformation of pathology - the European Society of Pathology expert opinion paper. Virchows Arch 2025;487:971-81. https://doi.org/10.1007/s00428-025-04090-w

17 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. https://doi.org/10.1016/j.jpi.2022.100136

18 Evans AJ, Brown RW, Bui MM, et al. Validating Whole Slide Imaging Systems for Diagnostic Purposes in Pathology. Arch Pathol Lab Med 2022;146:440-50. https://doi.org/10.5858/arpa.2020-0723-CP

19 Lujan G, Quigley JC, Hartman D, et al. Dissecting the Business Case for Adoption and Implementation of Digital Pathology: A White Paper from the Digital Pathology Association. J Pathol Inform 2021;12:17. https://doi.org/10.4103/jpi.jpi_67_20

20 Hutchinson JC, Picarsic J, McGenity C, et al. Whole Slide Imaging, Artificial Intelligence, and Machine Learning in Pediatric and Perinatal Pathology: Current Status and Future Directions. Pediatr Dev Pathol 2025;28:91-8. https://doi.org/10.1177/10935266241299073

21 Yu G, Yu C, Xie F, et al. Automated Tumor Count for Mitosis-Karyorrhexis Index Determination in Neuroblastoma Using Whole Slide Image and Qupath, an Image Analytic Software. Pediatr Dev Pathol 2022;2:526–3-7. https://doi.org/10.1177/10935266221093597

22 Bhardwaj N, Rohilla M, Trehan A, et al. Mitosis-Karyorrhexis Index evaluation by digital image visual analysis for application of International Neuroblastoma Pathology Classification in FNA biopsy. Cancer Cytopathology 2022;130:128-35. https://doi.org/10.1002/cncy.22520

23 Liu Y, Jia Y, Hou C, et al. Pathological prognosis classification of patients with neuroblastoma using computational pathology analysis. Comput Biol Med 2022;149:105980. https://doi.org/10.1016/j.compbiomed.2022.105980

24 Bellini A, Pötschger U, Bernard V, et al. Frequency and Prognostic Impact of *ALK* Amplifications and Mutations in the European Neuroblastoma Study Group (SIOPEN) High-Risk Neuroblastoma Trial (HR-NBL1). JCO 2021;39:3377-90. https://doi.org/10.1200/JCO.21.00086

25 Mina M, Boldrini R, Citti A, et al. Tumor-infiltrating T lymphocytes improve clinical outcome of therapy-resistant neuroblastoma. Oncoimmunology 2015;4:e1019981. https://doi.org/10.1080/2162402X.2015.1019981

26 Cheung NKV, Dyer MA. Neuroblastoma: developmental biology, cancer genomics and immunotherapy. Nat Rev Cancer 2013;13:397-411. https://doi.org/10.1038/nrc3526

27 Swillens JEM, Nagtegaal ID, Engels S, et al. Pathologists' first opinions on barriers and facilitators of computational pathology adoption in oncological pathology: an international study. Oncogene 2023;42:2816-27. https://doi.org/10.1038/s41388-023-02797-1

28 Bessen JL, Alexander M, Foroughi O, et al. Perspectives on Reducing Barriers to the Adoption of Digital and Computational Pathology Technology by Clinical Labs. Diagnostics (Basel) 2025;15:794. https://doi.org/10.3390/diagnostics15070794

[29] Ardon O, Manzo A, Spencer J, et al. Digital slide scanning at scale: Comparison of whole slide imaging devices in a clinical setting. J Pathol Inform. 2025;18:100446. https://doi.org/10.1016/j.jpi.2025.100446

[30] Del Valle AC. Leveraging digital pathology and AI to transform clinical diagnosis in developing countries. Front Med 2025;12:1657679. https://doi.org/10.3389/fmed.2025.1657679

[31] Singh V, Cheng S, Kwan AC, et al. United States Food and Drug Administration Regulation of Clinical Software in the Era of Artificial Intelligence and Machine Learning. Mayo Clin Proc: Digit Health 2025;3:100231. https://doi.org/10.1016/j.mcpdig.2025.100231

[32] Lin SY, Tsai PC, Su FY, et al. Contrastive learning enhances fairness in pathology artificial intelligence systems. Cell Reports Medicine 2025;6:102527. https://doi.org/10.1016/j.xcrm.2025.102527