**Whole Slide Imaging, Artificial Intelligence and Machine Learning in Paediatric and Perinatal Pathology: Current Status and Future Directions**

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**Abstract**

The integration of artificial intelligence (AI) into healthcare is becoming an increasingly mainstream activity. Leveraging digital technologies such as AI, especially through deep learning methodologies, has garnered significant attention among researchers, clinicians, and industry stakeholders due to its promising performance and clinical potential. Digital pathology is now a proven technology, enabling generation of high-resolution digital images from glass slides (whole slide images; WSI). WSIs has facilitated AI-based image analysis techniques to aid pathologists in diagnostic tasks, improve workflow efficiency, and address workforce shortages. Specific example applications include tumor segmentation, disease classification and detection, grading, rare object identification, and prognosis prediction. While notable advancements have been made, the integration of AI into clinical laboratories faces significant challenges, including concerns about evidence quality, regulatory adaptations, clinical evaluation, and safety considerations. Despite these barriers, the field is evolving, with ongoing research efforts addressing these challenges and generating new evidence. In paediatric and developmental histopathology, the adoption of AI could improve diagnostic efficiency, automate routine tasks, and address specific diagnostic challenges unique to the specialty, such as standardising placental pathology and developmental autopsy findings, as well as mitigating the staffing shortage in the subspeciality. Additionally, AI-based tools have the potential to mitigate medicolegal implications by enhancing reproducibility and objectivity in diagnostic evaluations. This article provides an overview of recent developments and challenges in applying AI to paediatric and developmental pathology, focusing on machine learning methods applied to WSIs of paediatric pathology specimens.

**Introduction**

Harnessing artificial intelligence (AI) for cancer diagnosis, drug discovery and prediction of adverse patient outcomes is no longer a futuristic concept, but is becoming reality.[1,2] Digital technologies are rapidly evolving within healthcare settings, impacting lives of patients and healthcare professionals globally.[3] Building on these digital technologies; the potential of AI, particularly solutions using deep learning, has gained interest of researchers, clinicians and industry in recent years with their performance and clinical potential.[4–6] Drug discovery, electronic health records (EHR), surgical procedures, screening, clinical decision making, health wearables and clinical imaging are all examples of areas of substantial AI research,[7–12] with successes and advances in this technology identified across multiple medical specialties.[6] Perhaps most notably, AI has been applied in ophthalmology to retinal images to diagnoses diseases such as diabetic retinopathy and to predict risk of systemic diseases, including myocardial infarction, stroke and Alzheimer's disease.[13–15] Example applications in radiology include deep learning for mammograms to identify breast cancer and for CT scans to identify lung nodules.[16,17] Developments have been seen in dermatology with performance comparable to a dermatologist achieved in a study using AI for skin cancer diagnosis applied to a dataset of dermoscopy images.[18] Improvements in computing power, data storage capacity and AI methods are resulting in growth of research innovations and potential clinical applications in this area.[6,19] The use of AI to analyse medical data is also impacting diagnostic histopathology, with digital pathology the technology underpinning many developments in this area.[20,21]

Digital pathology involves scanning of glass microscope slides to create high resolution digital images (whole slide images; WSIs).[21] Increasing availability of WSI has provided a medium for development of image analysis techniques to assist the pathologist with diagnostic tasks.[22] In many countries, there are concerns around maintaining provision of expert pathology and laboratory medicine services and a specialised workforce who can meet growing demand; therefore, opportunities to improve workflow and assist healthcare professionals and allow for accessable digital consultations with subspeciality experts have generated substantial interest.[23,24] AI solutions for an array of pathology tasks are described, with examples of specific applications including: outlining tumours or areas of interest, classification or detection of disease, grading and scoring diseases, identification and counting of rare or small objects and predicting prognosis or mutational status.[20,25] There have been substantial advances in cancer detection in the adult population using WSI, with specific successes in breast and prostate cancer.[26,27] CAMELYON was an early project that demonstrated the power of AI in

pathology, examining 32 algorithms used for breast cancer detection in lymph nodes, with the best algorithm achieving an area under the receiver operating curve (AUROC) of 0.994.[28] Similarly for prostate cancer, a deep learning tool developed for use on routine haematoxylin and eosin (H&E) stained images reported overall accuracy of 97-98%.[29] A tool capable of predicting tumour origins for cancers of unknown primary with a top-1 accuracy of 0.80 and top-3 accuracy of 0.93 on an external test set has also been described in adults.[30] Other general applications of AI in general digital pathology include tools for kidney transplant assessment, classification of colorectal polyp subtypes and scoring of non-alcoholic steatohepatitis disease features.[31–33] It should be noted that in addition to digital pathology, AI has also been applied to other pathology techniques, including genomic and transcriptomic techniques, free text pathology reports, fluorescence microscopy and 3D histopathology.[34–37]

Whilst there is enthusiasm and investment into AI solutions for digital pathology, examples of implementation into clinical laboratory practice remain rare, with numerous challenges to address to enable widespread AI deployment in routine workflow.[38] Concerns around the quality of evidence underpinning commercially available tools, adaptations required within existing regulatory frameworks, the need for robust evaluation within a clinical setting and gaps in evidence to address safety concerns and risks once implemented are among the barriers to routine utilisation of these tools.[39–42] However, whilst there are challenges to overcome, the pace of change is rapid, with new understanding and evidence appearing continuously within this field.[22,43]

Digital pathology is increasingly having impact across many areas of histopathological practice, with issues specific to paediatric and perinatal pathology (PPP) that should be considered. Generally, the ability of WSI and AI/ML tools to improve efficiency and speed of reporting, and to automate routine tasks such as provision of counts, have numerous applications across the speciality. However, since PPP has distinct areas of practice, in addition to general areas applicable to other histopathology disciplines, there are associated specific areas of diagnostic challenge that require specialised exprtise and experience. For example, identification of ganglion cells in biopsies for suspected Hirschsprung disease and interpretation of placental pathology and developmentally adjusted fetal autopsy findings. Furthermore, PPP is a particular shortage speciality with significance workforce issues meaning that WSI-based tools which could both allow more effective triaging of cases for referral as well as facilitation of virtual referrals to highly specialist centres are likely to have

disproportionate benefit to service provision.[44] Finally, there are significant medicolegal implications in particular areas, such as interpretation of placental pathology in cases of adverse neonatal outcome, such that reproducible objective and morphometric evaluation of cases is of major importance. At present, interpretation of many aspects of placental pathology remains subjective to the 'expert' consultants impressions. Furthermore digital WSI with AI/ML tools is likely to be associated with increased reproducibility and potential for reduced error, which would ultimately improve diagnostic accuracy. This article therefore provides an overview of developments in AI in paediatric and developmental histopathology, specifically machine learning methods applied to whole slides images of perinatal/paediatric pathology specimens.

**Rationale and areas of focus**

AI and machine learning in PPP has potential to assist paediatric pathologists in several areas currently lacking routine objective quantification, including measurements, counting, and screening for rare events. Paediatric pathology practice requires a range of measurement and counting tasks (e.g. mitosis/karyorrhexis index in neuroblastoma, eosinophil counts in eosinophilic esophagitis), screening for rare event detection (e.g. ganglion cell detection in biopsies for possible Hirschsprung disease, decidual vasculopathy in placentas, acid fast bacilli in necrotic granulomatous lymph nodes), and assessing extent of biomarker quantification (e.g. PD1/PDL1 in tumours). AI augmentation of such tasks, with oversight by a pathologist, should allow more time focused on enhancing performance in areas of interpretive diagnostic difficulty in highly specialized areas whilst reducing the burden of 'simple' tasks such as measurement/counting, and biomarker quantification; subsequent longer term developments in diagnostic support willalso lead to improved diagnostic accuracy and reduced subjective variability.

Cell counting

AI applications may augment accuracy and precision of counting for discrete events within an area of WSI, such as number of cells or number of mitoses.[45] For example, peak eosinophilic count (PEC) per high-power field is the gold standard for confirmation of eosinophilic esophagitis (EoE), but there is variability in quantification between pathologists.[46] Accurate quantification of EoE is important at initial diagnosis and for long-term follow-up and assessing effects of therapy, since these patients will undergo follow-up biopsies over the course of their disease. New drug studies, such as those sponsored by the US Food and Drug Administration (FDA), are invested in utilizing objective quantification methods for eosinophil counting in

response to different treatment protocols. Furthermore, with such tools utilized by WSI, other features, such as the density and distribution of eosinophils in the tissue can be assessed along with other global tissue features which are tediously evaluated in research settings , given their potential importance in classifying EoE subtypes[47,47] and response to therapy, but are only haphazardly collected in routine clinical practice, without standard techniques. Using a multi-label sematic segmentation approach, the PECNet algorithm uses image patches with deep convolutional neural networks (CNN) to improve efficiency and standardization in eosinophil counting that is being implemented into clinical workflow setting. The PECNet algorithm can detect intact, overlapping and degranulated eosinophils in addition to features such as basal hyperplasia and lamina propria fibrosis. Furthermore, automated triaging to areas of greatest eosinophilic density can be supported using generated heatmaps.[47] The algorithm's detection of intact eosinophils had the highest area under the curve (AUC) at 14-15 eosinophils per field, demonstrating clinical applicability in EoE.

Rare event detection with morphometric assessment

Diagnostic evaluation for rare events based on manual screening of histopathology sections is a source of potential medico-legal issues, since undetected rare events may lead to both under- and over- treatment, depending on the diagnosis, with potential lifelong consequences for a paediatric patient.[48] For example, of around 3.7 million births per year in the US, less than 20% of placentas are formally examined and of that minority, only representative sections are sampled for histopathological examination. Changes such as abnormal vasculature remodelling associate with decidual arteriopathy/vasculopathy (DV) are associated with adverse pregnancy outcomes and subsequent maternal health indications but overall detection rates remain low even in mothers with preeclampsia. This may be a consequence of intraplacental disease heterogeneity[49] but AI algorithms have the potential to augment such examination through automated vessel detection classifiers. Such ancillary tools may circumvent the reliance on expert pathologists for initial detection,[50] important given the shortages in expert trained pathologists.[23]

An archetypal disease for PPP in which rare object detection is important is Hirschsprung disease (HD), in which the diagnosis is based on the absence of ganglion cells in a biopsy specimen (in addition to ancillary features). The identification of ganglion cells, or more specifically their absence in in HD, is a task that experienced paediatric pathologists routinely perform.[51] However, such specimens may require reporting by generalist/GI pathologists who

may only see few cases per year. Medicolegal issues may arise if the pathologist fails to identify even a single ganglion cell in a tray of serial sections, since surgical resection of an apparently aganglionic rectum/bowel may be erroneously performed. While ancillary immunostains have helped improve the accuracy of a diagnosis, the complete absence of ganglion cells remains the most important diagnostic features.[51] AI algorithms trained for automated detection of ganglion cells may help both the expert and non-experts in time saving and efficiency. However, current published studies reporting performance of ML tools in this setting still remain within research/non-clinical grade application but show potential.[52–54] For example, in one study, slides from 31 specimens underwent immunostaining and WSI with machine learning using an ensemble voting classifier to achieve around 90% diagnostic accuracy on a test set for HD;[55] however, in clinical practice for HD, as near to 100% diagnostic accuracy is required, which can only currently be achieved with expert human supervision. One area that shows promise is based on hierarchical grouping analysis of similar objects together while maintaining contextual analysis in which detection is based on the regions where ganglion cells should be located (i.e. a focus within the submucosa rather than mucosa or whole slide). In this case, the algorithm performed best when associated with a pathologist having undergone training on the algorithm. Together such tools may improve accuracy in rare event detection and increase time efficiency when coupled with a pathologist for optimal rare event detection. Together such applications could have more realistic clinical useability by augmenting human pathologists through rapidly directing attention to 'high yield' areas of interest, allowing for a focused, improved diagnostic proficiency and accuracy.

Morphometric evaluation

Morphometric analysis, beyond binary detection of features such as decidual arteriopathy, would also provide quantitative data to support standardized approaches for reproducible grading of pathologies such as placental villitis and syncytial knot formation.[56] Additional areas of benefit include automatic integration of WSI measurements directly into cancer checklists (e.g. tumour size and distance to closest margin) or for automated feature and measurement of submucosal nerve hypertrophy as an additional ancillary tool in HD with integration into the lab management reporting tool. AI tools now exist for identifying micrometastasis in lymph nodes while also identifying percent fibrosis in renal and liver biopsies for more objective quantification.[57–59] Quantitative immunostaining that impacts therapy and its utilization has been reported in adult breast pathology; however, in paediatric cases, current use cases remain

more limited such as PD-L1/PD-1 staining assessment, with variable results but the underlying principle remains valid.[60]

Predicting outcomes based on histological features

Neuroblastoma is a quintessential paediatric tumour in which the histological features define the tumor subtype based on the degree of cytodifferentiation; additional factors such as markers of cellular turnover (i.e. Mitotic and karyorrhexis index per 5000 cells -MKI) and molecular changes and may provide additional prognostic information.[61] While classification of neuroblastic tumours is tractable, associated counting tasks such as MKI determination could be standardised with AI algorithms that augment manual counting and increase reproducibility.[62] Furthermore, non-specialist pathologists tasked with primary diagnosis of such paediatric tumours likely would also benefit from an automated classifier that could help identify neuroblastic differentiation and Schwannian stroma for diagnostic purposes.[63] However, there remains a paucity of clinically-driven studies focused on such algorithms for clinical deployment.

Another focus in paediatric tumours is the association of molecular drivers on specific tumour subtypes and how machine learning may help in recognizing these associations. This is particularly evident in rhabdomyosarcoma (RMS) in which fusion positive (i.e. PAX3/7-FOX01) and fusion negative RMS are associated with significantly different outcomes. Even with modern approaches, molecular result confirmation is often delayed a few days to weeks after an initial tissue diagnosis thus the potential of AI algorithms with deep learning based on convolutional neural networks (CNNs) to accurately subclassify RMS by fusion status, based only on H&E WSI with realtime fusion prediction could revolutionize the field, both for resource poor centres in which molecular testing is not possible, and even for large, academic medical centres to improve clinical workflow and treatment optimisation. Furthermore, the ability of WSI based algorithms to stratify low, intermediate- and high-risk fusion negative RMS, may be superior to the current clinical risk prediction models based on tumour size, site, stage, and patient age.[64]

**Current evidence for WSI and AI in PPP**

The potential for WSI and AI/ML applied to PPP has been described in general terms,[65] however, there is minimal published evidence to date reporting on performance of such approaches in real-world paediatric pathology clinical practice. In general, use of WSI is

feasible and effective in this setting. In a study of 60 paediatric surgical pathology cases, there was high concordance with glass slide findings (>98%)[66] and in another study of 80 surgical cases and 20 placentas, concordance was also >90%.[67] In this study identification of nucleated fetal red blood cells was reported as more challenging using WSI, suggesting that speciality specific guidance and organ specific validation may be required.[67] The use of WSI for web based learning of digital pathology has also been reported as potentially useful for subspeciality training in disease-specific pathology.[68]

There are few published studies examining real world use of AI/ML with WSI in paediatric pathology, those that exist predominantly reporting on gastrointestinal biopsies. In a study of around 70 cases of paediatric inflammatory bowel disease, which included clinical, radiological and histopathological findings, a random forest (RF) based classifer was developed which successfully clustered 58 patients into two groups, broadly representing ulcerative colitis and Crohn disease, with the RF classifier correctly labelling 97% and identifying the most important histological features.[69] Of note, however, this study did not directly apply ML techniques to WSI themselves. In another study, duodenal biopsy slides from 102 children were used to train a neural network (NN), which demonstrated 93% accuracy with only 2% false-negative rate for identification of coeliac disease. In this study feature maps and patterns were learned including microlevel features such as alterations in secretory cell populations, demonstrating the feasibility of machine learning-based histopathological analysis.[70] AI for paediatric tumour pathology remains limited. In one study of 244 neuroblastoma (NB) cases, CD3+ and CD8+ T cell density was determining using WSI and image analysis techniques to demonstrate associations with overall and event-free survival, specifically the finding that low density T cell infiltration was associated with greater risk of death even after adjusting for other factors,[71] and evidence suggests that deep learning approaches trained on manually annotated cases can achieve results similar to trained pathologists in regard to extent of immune cell infiltration in NB.[72] Automated image analysis using feature extraction and classification of NB cases using a Support Vector Machine classifier has been described in concept.[73]

Future development and research

There are significant advantages to WSI/AI based approaches from a research perspective for PPP, particularly since many disorders are rare and therefore require significant collaboration, often international. The ability of whole WSI to remove the issues involved in material transfer arrangements and other associated governance and ethical limitations significantly facilitates

such collaborative multi-institutional research, which is needed for rare pediatric tumor and disease investigation. With greater ease of sharing WSI for collaborative research there is potential benefit of improved reproducibility, objectivity and auditability of studies. The establishment of such specialist federated networks of paediatric centres not only supports collaborative research but also encourages rapid and specialist central review, for example for paediatric tumours, which has been demonstrated to have value to improve the reproducibility of diagnosis and classification.[74] In addition, one of the main challenges in paediatric tumour pathology is relating to risk stratification and prognosis prediction. For many paediatric tumours, diagnosis of tumour type may be relatively straightforward, often since these may be associated with specific and diagnostic molecular findings, but reliable risk stratification within groups to direct personalised therapy remains difficult. Given that many paediatric tumours demonstrate a poorly differentiated and mesenchymal phenotype, with minimal distinctive cytological and morphological features identifiable to the subjective human eye, the potential ability of WSI with ML techniques such as neural networks to identify as yet undescribed morphological markers which may relate to disease prognosis of treatment response represents an exciting area of future research.

Despite the opportunities, numerous challenges remain in order to achieve the benefits described. Many of these are common to all domains of histopathology, such as requirement of annotated WSI for some types of supervised methods, and challenges of weak labelling for feature identification. However, an additional significant aspect to address in placental pathology relates to difficulties in clear definitions of the 'gold standard' for supervised learning. For example, many placental pathology entities, whilst being well described, have a significant element of subjectivness and are often associated with poor reproducibility, for example evaluation of villous maturity.[75] Furthermore, the vast majority of placental pathology collections available are associated with relatively minimal clinical information and represent highly preselected populations. Without clear success or failure for 'reward' in terms of the ultimate purpose of the algorithm, machine learning approaches such as neural networks will be unable to achieve their potential. Nevertheless, the future combination of widespread WSI with evolving AI tools heralds a new and exciting era for PPP and it is essential that the specialty grasps these opportunities and supports the next generation of paediatric pathologists to work seamlessly with such technologies.

**Figures**

**Need a couple of figures for eye candy**

**Eg one WSI of placenta or tumour, one example of counting with AI etc?**

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