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When it comes to diagnosis of many conditions, histopathology has long been the gold standard. The assessment of tissue architecture and cellular morphology under a microscope remains a cornerstone of clinical medicine, particularly in fields like oncology, where the histopathologist plays a central role in the Multi-Disciplinary Team, with their report often being one of the most decisive factors guiding diagnosis and subsequent treatment decisions.

Histopathology has always evolved as new technologies and techniques emerged. In the 1800s, the invention of the microtome revolutionised tissue processing in histopathology. More recently, it was the popularisation of immunohistochemistry that reshaped it. In the last decade however, especially in the last few years, the field of histopathology has undergone its most profound technological transformation to date. A key milestone came in 2017, when the US Food & Drug Administration (FDA) authorised a Whole Slide Imaging (WSI) platform, the Philips IntelliSite Pathology Solution, for primary digital diagnosis after proving diagnoses made based on digital images from the platform were comparable to those made using glass slides [1]. This allowed for the large-scale digitisation of histopathology. No longer were histopathologists bound to their microscopes; they could assess the images anywhere, even share slides instantly with expert colleagues around the world for a second opinion.

But the impact of Whole Slides Imaging goes far beyond convenience. Digitisation of histopathology opened the door to integrating computational techniques, notably machine learning algorithms and Artificial Intelligence, with histopathology.

This convergence of Artificial Intelligence and histopathology, enabled by WSI, has raised a controversial question – Will AI techniques replace the practice of histopathology in the future, making the role of a histopathologist redundant? To answer this, this essay will explore AI's current capabilities in histopathology, potential future roles, its limitations and barriers and finally the regulatory and ethical concerns stemming from the introduction of these technologies.

The Capabilities of AI

Histopathology, being a discipline grounded in visual interpretation, is naturally suited to the application of computer vision models. Thanks to WSI, vast archives of digitised images are now available to train deep-learning models. Once trained, these models can analyse new images on their own, highlight segments of the image of interest and even suggest potential diagnoses.

A 2019 study showed that deep-learning computer vision models could be trained using datasets where the only labels for images were reported diagnosis [2]. Remarkably, these models had impressive results with areas under the curve, a measure of AI model accuracy, of over 0.98 for all the cancer types it was trained to detect [2]. Additionally, the authors estimated that such models could reduce the number of slides histopathologists needed to review by up to 75% while retaining 100% sensitivity [2], a substantial reduction in workload while maintaining safety standards.

In fact, in 2021, the FDA in the US approved Paige Prostate, an AI-based diagnostic software for detecting prostate cancer, after clinical trials demonstrated that histopathologists who used the software to assist them had a 70% reduction in false negative diagnoses and a 24% reduction in false positive diagnoses regardless of their experience level [3]. Not only does technology like this streamline a histopathologist's workflow expediting turnaround times for interpretation of a patient's tissue sample, it also improves patient outcomes due to improved diagnostic accuracy.

AI-based algorithms are even able to go much further than simply diagnoses, they are able to predict genetic mutations & gene expression that are clinically relevant to the treatment of some cancers,

just from whole slide images alone. Models like HE2RNA [4] and SEQUIOA were able to accurately predict genes that were associated with key cancer processes like genes involved in the inflammatory response, cell cycles and metabolism [5] from just whole slide images of haematoxylin & eosin-stained slides across several different cancer types. One such use case demonstrated in the HE2RNA study was the detection of microsatellite instability, a predictive biomarker of response to immunotherapy and of a better prognosis compared to those with microsatellite stable tumours in colorectal cancer [4]. These advances suggest that AI could contribute significantly to the rising field of personalised medicine, especially in low-resource settings where genomic testing may not be readily available.

Against the backdrop of an overstretched National Health Service and other healthcare systems worldwide, the argument for Artificial Intelligence is compelling. With rising caseloads and understaffed departments, a situation that will only get worse with an aging population and sociopolitical turmoil, AI offers an opportunity to reduce workloads, enhance accuracy and provide critical information more rapidly. In that sense, it seems almost unethical to not be throwing our full support behind incorporating AI systems.

Other Future Roles of AI

Beyond diagnostic accuracy, AI also has the potential to contribute to histopathology in other ways.

Triage and prioritisation

AI systems can be used to triage slides, flagging those of most concern and deprioritising unequivocally benign cases. This will help to ensure timely diagnoses for the most concerning cases which would improve patient outcomes.

Assistive grading and quantification

Tasks such as tumour grading or biomarker quantification are notoriously susceptible to inter-observer variability. Studies have shown that AI assistance can help reduce variability and improve

reproducibility in these scenarios, especially in grading systems, for example the Gleason score for prostate cancer [6].

Quality Assurance

AI tools can be used to monitor for artifacts, changes in staining or inaccuracies in labelling to serve as an automatic quality analysis and audit system to ensure good standards are upheld. It can also serve as a safety net to reduce reporting error by flagging up reported morphological findings that are inconsistent with any molecular tests, immunohistochemistry or the AI's own findings prompting a repeat review to reduce reporting errors.

Education and Training

By highlighting diagnostically relevant regions on tissue slides, AI has great potential as an educational tool, accelerating learning and providing valuable feedback for early-career trainee histopathologists.

The Limitations of Artificial Intelligence & Causes

Despite the considerable promise of artificial intelligence in histopathology, there are several key limitations to be considered that constrain widespread clinical use, challenging the prospect of complete replacement of human histopathologists with AI algorithms. These limitations span a number of domains – technical, human interpretability, automation bias as well as regulatory and ethical.

Generalisation & Domain Shift

In Machine Learning, there exists a well-known issue called "Domain Shift", where if the training data pool is too different from the data that the model is actually used on, it can negatively impact its performance and its ability to be used in data from different places (e.g. different centres). One study demonstrated that Artificial Intelligence models trained on H&E Whole Slide Images are highly sensitive to domain shift factors such as variations in slide preparation, staining or scanner

characteristics [7]. Strategies such as stain normalisation do exist to mitigate this, models are still vulnerable to domain shift and are not fully reliable [7].

Opacity of Deep-Learning Models and Human Interpretability

Another major limitation with deep-learning artificial intelligence models is that of opacity. This is known as the "Black Box Problem". Deep-learning algorithms offer little transparency at to how and why they have arrived at their predictions. This lack of interpretability is a significant challenge for clinical adoption of Artificial Intelligence Models as histopathologists and regulatory bodies require clear justifications of any diagnostic outputs. While techniques to increase interpretability, such as saliency maps, which are visual representations that highlight the most important regions or features in an image that a machine learning model uses to make a prediction, do exist, their reliability remains a point of contention. A study by Arun *et al.* in 2020, assessed eight different saliency map generation techniques, it was found that none of them consistently passed key tests of reliability set by the authors, such as repeatability, reproducibility and accurate localisation of relevant features in medical images [8]. As such, while techniques like saliency maps could offers some level of interpretive value, their limitations caution against complete reliance on Artificial Intelligence.

Automation Bias

Automation Bias refers to the tendency for individuals to over-rely on an automated system, favouring the output of the system even when the data suggests otherwise. Evidence from literature consistently demonstrates that clinicians are prone to over-reliance on automated decision-support systems, often at the expense of their own judgement. A review by Parasuraman & Manzey in 2010 revealed that both novices and experts were susceptible to automation bias and complacency (a lack of appropriate vigilance) [9]. In a clinical context, a study on e-prescribing found that prescribers sometimes switched from an originally correct prescription to an incorrect one, based solely on misleading suggestions by the clinical decision support system [10]. More recently, a 2024 study by Rosbach *et al.*, demonstrated a 7% automation bias where pathologists overturned their initially

correct evaluations in favour of the AI's incorrect advice [11]. These findings highlight that limitations with Artificial Intelligence are not solely technical, it is also behavioural on the part of humans interacting with the AI systems.

Regulatory, Ethical and Infrastructural Barriers

Regulatory and ethical consideration pose significant obstacles to the widespread adoption of Artificial Intelligence models and replacement of histopathologists. For one, there is the legal question of liability. If an independently operating AI system makes a critical diagnostic error that leads to adverse outcomes for the patient affected, who is liable? The software developers who trained it, the businesses that marketed it or the healthcare institution that bought and implemented it?

Beyond regulatory concerns, infrastructural constraints present further hurdles. Many histopathology departments are not fully digitised, limiting the feasibility of widespread AI deployment in the immediate future. In the long term, integrating AI systems into healthcare requires substantial investments in equipment like WSI platforms, data storage and processing infrastructure and workforce training [12]. Considering the chronic underfunding of most healthcare systems around the world, it is simply beyond their capacity and even if it could be done, it raises questions of whether that's the most beneficial way to spend such a substantial monetary investment.

Finally, from an ethical standpoint, Artificial Intelligence models are only as unbiased as the datasets that they are trained upon. Training data often reflect structural inequities of healthcare systems and these biases can be perpetuated or even amplified by the AI systems. Underrepresentation of rare diseases or samples from specific systemically & historically underrepresented demographic groups can result in lower performance of AI modes for those populations [13] resulting in these patients receiving delayed, inadequate or incorrect treatment. This contravenes fundamental principles of equity and justice in healthcare. If AI in histopathology is to be viable, there would have to be strict

protocols when training them, ensuring diverse datasets are used and the models are continuously monitored in practice to ensure no biases are present.

To replace or not to replace

So, will AI techniques replace the practice of histopathology in the future? Will it make the role of a histopathologist redundant? Probably not. While Artificial Intelligence does have much to offer in histopathology the idea of it fully replacing histopathologists remains implausible, at least in the near future. As a discipline, histopathology encompasses more than just image recognition and AI will struggle with some of these other tasks.

The regulatory landscape also points towards a move towards Artificial Intelligence as a tool for augmentation instead of replacement. Both the Philips IntelliSite Pathology Solution and Paige Prostate were approved for use by histopathologists as an assistive tool, not as independent decision makers [1,3].

Historically, parallels in radiology also illustrate this. Predictions that AI detection software would replace radiologists have not materialised. Instead, radiologists continue to thrive, supported by assistive AI tools that enhance productivity, with the human still remaining the expert decision maker. Rising diagnostic volumes in healthcare systems around the world make AI a valuable tool, but the expertise of the pathologist remains irreplaceable.

The most realistic and perhaps the most socially desirable is one of collaboration, with AI serving as a supportive tool rather than a substitute for histopathologists. By combining computational precision with human expertise, the field of histopathology can achieve the best of both worlds – delivering faster, more accurate and more equitable care for all patients.

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