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PERSPECTIVE ARTICLE

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How to use AI in pathology

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Abstract

AI plays an important role in pathology, both in clinical practice supporting pathologists in their daily work, and in research discovering novel biomarkers for improved patient care. Still, AI is in its starting phase, and many pathology labs still need to transition to a digital workflow to be able to enjoy the benefits of AI. In this perspective, we explain the major benefits of AI in pathology, highlight key requirements that need to be met and example how to use it in a typical workflow.

KEYWORDS
computational pathology, digital pathology, pathology AI

1 | FROM PATHOLOGY TO AI

Artificial intelligence (AI) in the medical domain has significantly advanced personalized medicine.[1,2] It has commonly been used in the medical domain for advanced analysis of complex, high-dimensional data to identify meaningful patterns even in small subgroups of patients. Pathology provides such high-dimensional data: images of tissue specimens at sub-cellular resolution. In pathology, tissue samples such as biopsies or resections are processed to be dehydrated, formalin-fixed, paraffin-embedded and cut into 2–5 µm thin slices. The transparent tissue slices are then put on glass slides and stained with different staining protocols.[3]

The most common staining protocol is the unspecific and non-expensive hematoxylin and eosin (HE) staining, visualizing morphological and cellular structures of the tissue. Healthy tissues have characteristic cell shapes and tissue morphologies, such that trained experts can identify diseased patterns and lesions in those images.

Other protocols for special stains, as e.g. *van Gieson*, *Giemsa* and *PAS*, aim to illustrate different tissue characteristics such as glycogen-rich areas or different cell types for various applications.

Finally, immunohistochemical (IHC) staining protocols[4] utilize specific antibodies that may or may not bind in the tissue depending on whether the corresponding antigen is present or not. Antibody binding is visualized by an enzymatic reaction in the tissue. IHC staining protocols tell pathologists information about the presence, spatial distribution and even quantity of a particular protein or antigen in the tissue. This can be important to further subtype the disease or indicate further tests or targeted therapies (e.g., treatments for *Her2*-low vs. *Her2*-high breast cancers[5]).

There are many more processing protocols and tests for tissue examinations, including molecular pathology and genetic sequencing especially in patients with cancer. All tests increase the information complexity of the case and enable pathologists to make an accurate and personalized diagnosis and help oncologists to provide an optimally targeted therapy for the individual patient.

As pathology data get more complex, the discovery of meaningful patterns and relevant biomarkers for specific disease subtypes becomes more and more challenging. Artificial intelligence can help to analyze the data with a comprehensive and ever growing toolbox of machine learning models that efficiently learn relevant patterns automatically.[6,7]

2 | THE TWO DOMAINS OF AI IN PATHOLOGY

The application of AI in pathology has multiple use cases that we divide into clinically applied AI and more explorative research AI.

In the *clinically applied* domain, methods of artificial intelligence support pathologists at repetitive, subjective, or quantitative routine tasks. For example, estimating the relative amount of proliferating cancer cells in IHC stained tissue samples can be automated with AI[8] thus eliminating the subjective and error-prone aspect of pathology to count dozens of hundreds of small cells. This process called *staining estimation* in IHC images can be extended to various other specific stains. Another example is the automatic detection and quantification of mitotic figures,[9–11] a process that is time consuming and cumbersome if done manually. AI can measure these metrics reproducibly in seconds, and provides a tool for pathologists to save up to a third of their time for this task.[12] Further, large AI models, trained on thousands of cases, can detect and grade complete morphologic patterns of prostate cancer[13,14] or breast cancer,[15,16] highlighting relevant cancer regions in digital pathology slides. This leads to significant time savings for pathologists in these tasks,[17] and thus will be an important tool in the future especially with respect to the increasing workload of pathologists.[18] As a second opinion, AI provides a quality control for diagnostic reports. Human's second opinions are a powerful tool for pathologists, but also an expensive resource due to a general global shortage of pathologists.[19–21] AI has the potential to improve pathologists' confidence in their diagnoses by a systematic backup or indication of potentially missed regions.

In the *research domain*, AI helps to identify novel patterns in complex medical data sets that can be relevant for individual treatments, prognoses, or outcomes of diseases. The research for such patterns is complex and requires large, relevant data sets, but can lead to a deeper understanding of diseases and cancer and to new actionable biomarkers. For example, AI can help to predict prognosis of patients with renal cancer with an accuracy of over 80%, outperforming other clinical parameters in this difficult task.[22] The same group has developed AI that is capable to predict prognosis and therapy response for patients with colorectal cancer.[23] AI further showed strong potential to predict microsatellite instability[24] and individual mutations and biomarkers in digital whole slide images without the need for DNA sequencing.[25,26] All these research studies show that AI will continue to play an important role for the analysis of medical image data in pathology and for the development of new therapeutic targets.

3 | DIGITAL PATHOLOGY AS A REQUIREMENT FOR AI

In order to use AI in pathology effectively, tissue slides have to be available in a digital format. Therefore, a digital transition in pathology is necessary, including barcoding and scanning of pathology slides as well as structured reports.[27] Many pathology labs report successful digital transition of their workflows,[28] enabling digital pathology,[29] remote sign-out,[30] facilitating sharing of slides and consulting of second opinions, and accelerating retrieval of prior cases.[31] However, digital transition is an institutional effort[28] that interferes with the core of a pathology lab and the way how pathologists sign-out cases, and therefore requires major investment in time and money to be implemented. Still, the benefits of digital pathology are significant and widely reported,[32–34] even without using AI, mostly driven by a reduced turnaround time or cases and improved efficiency in the workflow.

4 | HOW TO USE AI IN PATHOLOGY

Once digital pathology has been established in a laboratory, AI can be used immediately. Figure 1 shows the workflow of integrated AI in a lab. After digitizing, images are automatically registered in an image management system (IMS), usually bundled with the scanner's software. AI runs on the digital images and on cases as well. This can be triggered by the IMS or autonomously by the AI itself. To apply the correct AI on a slide, slide meta data such as staining type, fixation type, procedure type is needed. This meta data can usually be found in the LIS which is why a communication between LIS and AI is desirable. The digital slides are also registered in the laboratory information system (LIS). At the time of opening a case from the LIS, the pathologist sees the digital slides and also the AI results. For this, the AI vendors either offer an own viewer, or the AI is integrated into existing systems.

If a lab aims to use AI for research purposes only, it is free to use any commercial or open-source tool available. These AI tools are usually not well integrated into the lab's IMS and LIS and require manual access to digital slides. Many software programs exist, and two examples are QuPath,[35] a free viewer and AI tool for digital pathology slides, and TMARKER,[8] a free viewer and AI tool for automated staining estimation.

However, if the lab aims to use AI in a clinical setting and more routinely, several major factors must be considered. First, the software has to be integrable into the pathologist's workflow, that is, it must be compatible with the scanner system and the laboratory information system. The amount of manual interaction with additional programs required by the AI has to be minimal (ideally zero). Second, regulatory questions if digital pathology and AI can be used in a clinical setting must be clarified. This includes a validation of the digital workflow, and of the AI. The College of American Pathologists (CAP)[36] and the Royal College of Pathologists[37] both offer guidelines for the validation of a digital pathology workflow. Methods of AI should be validated in adequate studies, and regulatory bodies such as the FDA can clear commercial AI in pathology[38] as well. Finally, the lab should set guidelines on how to report AI results in the pathology reports.

In the recent years, several companies emerged in the field of pathology AI that not only address the aforementioned points, but also help pathology labs to successfully transition to a digital and AI-supported workflow. Similar as scanner vendors or laboratory equipment vendors offer consulting service for an efficient lab workflow during a procurement process, pathology AI vendors offer their expertise from pathologists and laboratory-IT experts and their experience from different lab environments to help in the

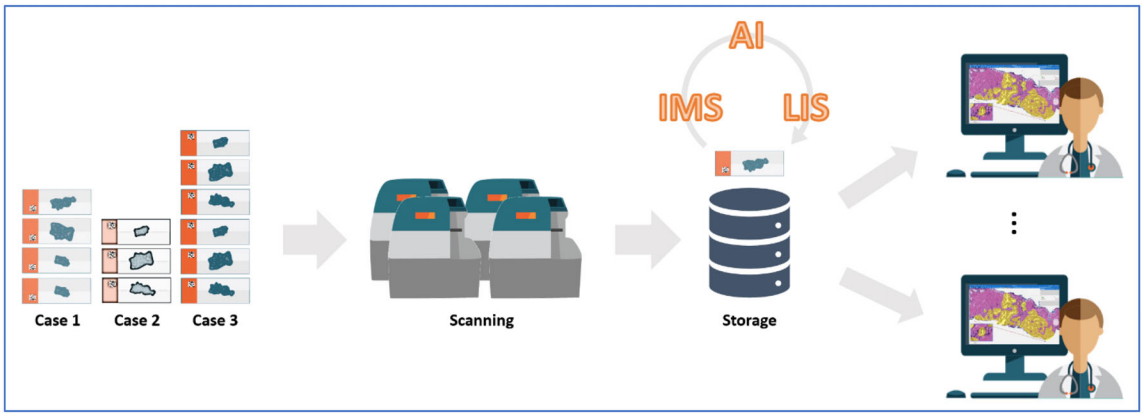

FIGURE 1 Workflow of AI supported pathology. Digital slides and cases are registered in the image management system (IMS). AI runs after scanning on slides and cases. Cases and slides are registered in the LIS. The AI results are available to pathologists as soon as they open the case from the LIS. Note that storage and AI can both be hosted in the lab or in the cloud.

transition phase. Further, most of the vendors also offer trial licenses to test their models and software on proprietary data, as well as trainings for their proprietary systems. In return, these systems are very well integrated in the lab's environment. A list of the top 10 AI companies in digital pathology can be found here.*,†

5 | CONCLUSION

AI has arrived in pathology in the past decade, and first commercial platforms are already available that integrate well into laboratory workflows. With these platforms, AI can be used effectively in clinical routine. Still, pathology AI for clinical routine is a niche, and only few labs use it nowadays. A possible reason for this is a significant investment required for the digital transformation due to scanner hardware needs and additional personnel needs. Further, pathologists might still be hesitant to adoption digital sign-out processes due to unfamiliar image review on a computer screen. Finally, trust in the AI itself has surely to be built. Although many studies exist that support the positive effects of AI on diagnostic accuracy and efficiency, AI needs to be experienced by pathologists individually like a new tool, and be tried and tested to learn about its pros and cons. As this process continues over time, AI will be more present and more integrated in future pathology systems, and likewise will pathologists use it and its new possibilities to help themselves where needed.

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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ENDNOTES

* https://lumeadigital.com/top-10-ai-companies-for-digital-pathology/.

† https://www.ventureradar.com/keyword/Pathology%20Slide%20AI%20Analysis.

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