Review Article:

Artificial Intelligence in Pathology: Bridging the Gap Between Technology and Diagnostics

Sneha Chavarkar

Assistant Professor, Department of Pathology, D Y Patil, School of Medicine, Nerul.

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Corresponding author:
Sneha Chavarkar, Assistant Professor, Department of Pathology, D Y Patil, School of Medicine, Nerul, email: drsnehachavarkar@gmail.com

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Abstract:

In recent years, there has been a considerable increase in the development and application of Artificial Intelligence (AI) tools in pathology. In the current era of precision medicine, computational pathology (CPATH) and AI tools will drastically transform pathology services. Despite tremendous success in the development of AI tools, there exists a wide gap between the research and its clinical application in pathology. This article explores how Artificial Intelligence (AI) revolutionizes pathology by bridging the gap between traditional diagnostic methods and advanced technological innovations. It seeks to highlight the potential of AI to enhance diagnostic accuracy, efficiency, and precision while addressing the challenges and opportunities for integrating AI into modern pathology practices. The author conducted a PubMed search for articles published between January 1990 and August 2024. Terms like "AI artificial intelligence," "deep learning," and "machine learning" were searched using MeSH (Medical Subject Headings). Currently, AI plays a supportive role in pathology. It can also help to prognosticate malignancies. Supportive data indicates that with the aid of AI, pathologists can reach diagnosis swiftly and with more accuracy. We concluded that by bridging the gap between traditional diagnostic practices and cutting-edge technology, AI will help pathologists contribute more efficiently to precision medicine. While challenges like data quality, regulatory compliance, and ethical concerns remain, the future of pathology depends on seamless collaboration between AI tools and human expertise.

Keywords:

artificial intelligence, deep learning, machine learning, neural networks computer, algorithm

Introduction:

In standard diagnostic practice, pathologists analyse microscopic slides stained with haematoxylin and eosin (H&E), after which they often order additional tests like special stains if the case needs them. Even for a seasoned pathologist, intra- and interobserver variation is inevitable as the diagnosis is often dependent on subjective interpretation.[1] Also in daily reporting, they handle large amounts of data from numerous sources like clinical and radiological findings, histological and immunohistochemical findings, and molecular pathological information from sequence analyses.[2]

Digital pathology (DP) involves the technologies designed for converting pathology slides into digital formats, along with managing their associated metadata, storage, assessment, analysis, and the needed infrastructure for the same.[3]

Whole-slide imaging (WSI) is a more advanced technique in pathology, offering a significant improvement over traditional digital imaging technologies that capture fixed images with cameras.[4] Based on multiple studies, it has been established that there is a good concordance between the diagnosis done using traditional light microscopy and WSI.[3]

Digital pathology (DP) enables remote diagnostic reporting with adaptable work schedules, prevents disruption of services during difficult circumstances like the COVID-19 pandemic, and makes expert opinion consultations possible. AI-based algorithms can be integrated into daily practice as well.[5,6]

Some major milestones in DP are mentioned below

1956: John McCarthy introduced the term "artificial intelligence" (AI).

1959: The term machine learning (ML) was invented by Arthur Samuel.

1986: Rina Dechter introduced the term deep learning (DL).

1988: Yann LeCun invented a Convolutional neural network (CNN).

1990: Whole slide scanners introduced.

1998: In a landmark move, Tripath becomes the first company to get FDA approval for an automated PAP smear screening product.[7]

2003: For their ThinPrep Imaging System, Cytyc received FDA approval.[8]

2014: Generative adversarial network was developed by Ian Goodfellow.[9]

2017: FDA has authorized Philips' IntelliSite Pathology Solution, a digital pathology whole-slide imaging system.[10]

2021: Paige prostate was approved by the FDA to diagnose cancer of the prostate.[11]

Materials and methods: PubMed search was conducted by the author for articles published between January 1990 and

August 2024. Terms like "ai artificial intelligence", "deep learning" and "machine learning" were searched using MeSH (Medical Subject Headings). A total of 60 articles were identified out of which 47 were included in the review while the others were excluded because of duplication, being more than 10 years old and other similar reasons.

Current Application of AI in Pathology:

Deep learning is a subset of machine learning (ML) that employs artificial neural networks to replicate a logical framework similar to human thinking.[12]

It has enabled computers to independently identify key patterns in pathology images and create the most effective algorithms on their own., without requiring manual intervention.[13,14]

AI is especially useful in oncopathology, transforming how cancer is diagnosed and classified.[15]

Significant progress has been achieved in integrating AI tools into the diagnostic workflows. AI methods have been utilized for various tasks, such as identifying, detecting, and segmenting objects. WSI in conjunction with computer algorithms and several other AI tools has made possible the seemingly impossible task of retrieving information and aiding in diagnostics. A few of the examples are precise objective assessment of immunohistochemistry biomarkers like Ki-67, and PDL-1, cell quantification, and recognition of pattern.

AI can be used to screen lymph nodes for isolated tumour cells especially when there is a suspicion of metastatic deposits. This not only makes the testing more sensitive but also saves time.[7]

Lee et al introduced co-occurring gland angularity for prostate cancer using ML algorithms that rely on the inherent domain knowledge of pathologists and oncologists. This method calculates the entropy of gland orientations within localized areas of tissue samples. In high-risk prostate cancer, glands tend to be more disorganized compared to those in low or intermediate-risk cases. As a result, the entropy linked with these "gland angularity features" (GAF) is greater in aggressive forms of the disease and lower in more indolent cases.[16] AI tools also assist in standardizing the scoring criteria for various tumours, including the Gleason score in prostate cancer and breast cancer grading.[7]

By utilizing AI tools, Khurd et al applied texture characterization and classification techniques to determine the Gleason grade of prostate specimen images. They employed filtering and clustering methods to analyse texture patterns, which produced distinctive signatures for each tumour grade, enabling efficient differentiation

between Gleason grades 3 and 4.[17]

Molecular testing for breast cancer is expensive and not easily accessible. Deep learning (DL) leverages H&E-stained histopathology images to determine which patients may benefit from such testing. An image-based classifier can assess tumour grade, ER status, PAM50 intrinsic subtype, histologic subtype, and predict the risk of recurrence.[18]

An important application of AI-powered search tools is content-based image retrieval (CBIR), which enables pathologists to locate visually similar images from extensive histopathology databases. This is particularly useful in aiding the diagnosis of rare and complex cases that pathologists may encounter in clinical practice. The retrieved images highlight similarities in relevant histopathological features, not just visual resemblance, helping to provide an accurate diagnosis quickly, especially for challenging cases.[19,20]

AI can be integrated into the pathology workflow during the pre-analytical phase to prioritize cases and identify issues like suboptimal tissue sections or contamination. Additionally, AI helps determine the order of case reporting, ensuring critical cases such as malignancies are addressed first. While reports are generated, AI operates in the background, performing quality control checks and assisting with clinic-pathological and surgico-pathological correlations.[12] AI can play an important role in ensuring Quality control of histopathology slides. WSI can detect errors including staining quality, tissue representation, processing mistakes, the quality of external and internal controls, and even tissue fixation.[21]

Independent reporting algorithms can reach a diagnosis without a pathologist's aid. Examples are screening algorithms that can recognise normal tissue (i.e. colonic, gastric biopsies, breast biopsies etc) to formulate reports. Algorithm developers must account for the broad range of normal tissue variations during development to prevent overlooking rare microlesions or focal lesions that might be missed during screening but hold important clinical relevance. Many pathology samples deemed "normal" fall within a spectrum of morphology that shows no major pathological abnormalities, with their appearance often influenced by factors like age, location, and biopsy techniques.

Diagnosis-aided tools utilize algorithms to evaluate various features on pathology slides, such as the grade of the tumour, its histologic type, and extent. [21]

Precise pathological diagnoses rely on experienced pathologists who assess and integrate multiple findings. The performance of AI algorithms is determined by how well

they integrate into the diagnostic process and enhance pathologists' evaluations. Key factors for evaluation include the attributes analyzed, speed of result delivery, and overall accuracy. For instance, breast cancer grading algorithms offer the benefit of objectivity, consistency among different readers, and clearer prognostic insights, unlike the variability seen among human observers. Therefore, in this scenario, the main advantage of the AI algorithm is improved reproducibility rather than increased efficiency.[18,22]

To evaluate quantitative biomarkers, many Digital Image analysis platforms are utilized.[23]

ImageJ was created in 1997 by the National Institutes of Health (NIH) in Bethesda, Maryland, USA which is one of the first open-source tools for image analysis. In 2006, CellProfiler software was developed for image-based diagnosis using supervised machine learning-based classification. QuPath software utilizes machine learning without supervision to spot the cells, can classify whole slide images with supervision, diagnose tumors, and assess biomarkers quantitatively.

The Ventana Companion Algorithm image analysis software has been approved by CE and US IVD for use with Roche IHC assays in breast cancer. This allows for the assessment of important breast cancer biomarkers, including ER, PR, HER2, Ki67, and p53.

In the year 2014, AstraZeneca created Tissue Phenomics software, which has been integrated into immune-oncology clinical programs to identify biomarkers.

HALO, created by Indica Laboratories, offers modules for quantitative immunofluorescence analysis, mainly for research use.

The Cognition Master Professional Suite, developed by VMscope, enables the quantitative assessment of Ki67, ER, PR, CD3/4/8/15/20, and TILs. Moreover, the QuantCenter, a 3DHISTECH image analysis framework, offers tools for tissue classification, IHC quantification, and molecular pathology.[24,25,26]

Another significant achievement in DP/AI was the PANDA challenge, the largest histopathology contest to date. Around 1,290 developers collaborated, utilizing 10,616 digital prostate biopsy samples to create AI algorithms for Gleason grading. In external validation sets from the United States and Europe, the algorithms showed concordance of 0.862 (quadratically weighted **κ**, with a 95% confidence interval (CI) of 0.840–0.884) and 0.868 (95% CI, 0.835–0.900) when compared to expert uropathologists. Prospective clinical trials are needed to use this algorithm in different patient populations and laboratories. [27]

Taking inspiration from Computer Engineering, CPATH challenges were held as an opportunity for rookies to showcase their talent. CAMELYON16 was the first-ever grand challenge held for developing DL algorithms to detect breast cancer metastases in H & E-stained slides of sentinel lymph nodes.[28]

Prognostic and Predictive uses of AI in pathology:

One of the potential applications is its ability to forecast patient outcomes and treatment responses by analyzing morphological features.[29,30]

Correlating the varied features of tumour morphology like histological pattern, tumour microenvironment, and genetic profiles with survival outcome though very important, can be challenging for humans.[21, 31]

The clinical outcome can be foreseen by evaluating architectural organization and spatial configuration of different tissue types using AI tools. [15]

Wang et al. utilized an ML model to speculate recurrence in early-stage non-small cell lung cancer (NSCLC) based on HE-stained slides, analyzing features like orientation of nuclei, their shape, texture, and arrangement of tumor cells.[32]

At present, convolutional neural networks (CNNs) are the most widely used DL algorithms in pathology. A CNN is composed of multiple sequential layers (convolutional filters) that process an input, like an image, by progressively breaking it down into low-level features. Thus, it creates a higher-level representation by integrating seemingly low-key features like edges, curves, and shapes to identify the key characteristics of the image.[7]

Araujo et al. used CNN for subgrouping photomicrographs 'of breast biopsy specimens into 4 classes –normal tissue, benign lesion, in situ carcinoma and invasive carcinoma. Also, broad division into carcinoma vs non carcinoma was done.[33]

In 2018, Saltz et al. used CNN to assist pathologists by automatically detecting the pattern of arrangement of tumor-infiltrating lymphocytes (TILs) in images from The Cancer Genome Atlas (TCGA). Using CNN they could predict outcomes across 13 cancer subtypes.[34]

Yuan et al conducted a study on a cohort of 181 triple-negative breast cancer (TNBC) patients to statistically determine the spatial distribution of tumour infiltrating lymphocytes (TIL) on WSI. They created a quantitative metric for determining the ratio of lymphocytes within the tumor, which was strongly linked to disease-specific survival. They also found a correlation between the heterogenous immune infiltration at the morphological

level with CTLA4 expression, target of ipilimumab.[35]

In another study conducted on 160 p16+ oropharyngeal tumors, a spatially aware cell cluster graph (SpACCl) was used to show that stromal nuclear architecture plays a role in predicting disease aggressiveness and superior prognostic accuracy can be achieved by combining nuclear architecture from stromal and epithelial regions.[36]

Efficacy of AI in training and education:

AI tools can play a significant role in the training programs of young pathologists' by creating a healthy teaching environment through helpful annotations and other interactive functions. Teaching by WSI is already followed in various academic conferences and tumour boards.[4, 21]

The Ohio State University Wexner Medical Centre uses a "digital cockpit" for fully digital sign-outs. Their residents avail the Philips integrated management system (IMS) for previewing digital slides. By using annotation tools they can view, pan, zoom the images, and mark the area of interest for a more interactive learning experience.[37,38]

Some AI tools like Visopharm can accurately identify isolated tumour cell metastases in lymph nodes. Integrating them into our daily workflow can enhance the diagnostic skills of trainees. AI tools can thus play a complementary role to traditional training and education provided by pathologists.

Equipped with these tools, second opinions and consults for difficult cases are just a click away.[21,37,38]

Limitations and challenges:

Ethical Challenges in AI Implementation:

A common issue faced while working with AI algorithms is the "Black box phenomenon". It indicates an inability to understand how the algorithm draws any specific conclusion.[39,40]

Despite their clear benefits in accuracy and efficiency, deep neural networks are heavily criticized for their lack of interpretability, which hinders their integration into clinical settings. To tackle this issue, many studies have used follow-up methods to thoroughly assess AI model outputs. However, such follow-up analyses seem redundant, as depending on additional models to explain how an AI model works is not optimal.

Before they can be integrated in clinical settings, these algorithms need to be meticulously validated. [7]

To date, no prospective randomized trial has been conducted on AI-based technologies.[41]

"Overfitting" is the term used when AI algorithms trained on a particular dataset struggle to perform well on other datasets.[42]

It is a very arduous task to find reference datasets of WSI of different types of cancers to be used for algorithm training. Still, numerous differences are found between the pre-and post-analytical factors, including slide preparation techniques, scanner models, and digitization techniques used by different centres. Hence it becomes imperative that rigorous quality assurance and standardization techniques need to be implemented from time to time. This necessitates the creation of extensive databases and collections of annotated whole slide images (WSIs) that are reviewed, adjusted, and regularly updated by a team of skilled pathologists. 31,43

The concept of 'good data management' remains largely undefined and is typically left to the discretion of the data owner. Therefore, it would be highly beneficial to provide clarity on the objectives and key aspects of good data management and establish straightforward guidelines for those who publish or preserve scholarly data.

In 2016, Wilkinson et al introduced the Fairbanks Data Principle, aimed at enhancing the infrastructure to facilitate the reusability of academic data. These principles are also complementary to the Joint Declaration of Data Citation Principles (JDDCP) which emphasize the importance of making primary scholarly data citable, discoverable, and accessible for reuse, to enable more rigorous academic research. The FAIR Principles also support the work of 'Data Seal of Approval' (DSA) whose focus is to make the data reusable for scholars other than the ones who produced them. The DSA focuses primarily on the duties and practices of data creators and repositories, while FAIR is mainly concerned with the data itself. [44]

Significant expenses will have to be incurred for procurement, implementation and operational applicability of AI which will not be feasible for many. The upfront expense of purchasing scanners, along with ongoing costs for training, technical support, data storage, and regulatory compliance, can pose a barrier to implementing AI in clinical practice.[45]

Conclusions and Future of AI:

Traditional pathology practice can be improved substantially by utilizing AI as it has tremendous potential to minimize errors, generate reproducible results and consultations by expert pathologists. However, the application of AI in daily practice will not be feasible unless it is affordable, practical, interoperable, explainable, generalizable, manageable, and reimbursable.[46]

A strong positive correlation is observed between the accuracy of AI algorithm and the amount of data used. It was observed

by Campanella et al. that the validation error decreased by a factor of 10 when 100 times more cases were analysed.[47]

Only a small proportion of histopathology slides are digitised and available for analysis. We should also note that availability of digital images is not enough. We need a detailed review and exact description of this data by expert pathologists. Hence it is of utmost importance that pathologists should be involved from the beginning.

Despite the growth in AI tool development, their adoption in clinical practice has been slower due to challenges involving interpretability, validation processes, regulatory hurdles, generalizability, and cost concerns.[7]

Currently, the main challenge in implementing AI-based methods is the significant absence of prospective, randomized, multicentre studies that assess the advantages for both pathologists and patients.[41]

If these issues are resolved, AI and digital pathology could revolutionize the field, enabling pathologists to perform their tasks more quickly and with improved precision.

Conflict of interest:

The author declares that there is no conflict of interest.

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