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Emerging Perspectives of Artificial Intelligence in Diagnostic Pathology

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Abstract

IDigital pathology (DP) increasingly entering routine clinical pathology diagnostics, which provides easier, more accurate, and faster results. In light of advances in digitizing routine caseloads, using digital image analysis (DIA) algorithms and artificial intelligence (AI) tools becomes not only feasible, but desirable. Advances in precision medicine are being made in cancer as a result of this. In addition to providing diagnostic quality, high-resolution images of entire glass slides, automated whole slide imaging scanners (WSI Scanners) have become available, and when combined with advanced DP tools, images can now be integrated into all aspects of pathology reporting, including anatomical, clinical, and molecular pathology. It has been approved by the US Food and Drug Administration for use in primary surgical pathology diagnosis, opening the door to wider application of this technology in routine surgical pathology, the prostate AI algorithm, which will pave the way for the use of this exciting technology in primary diagnosis. Anatomical and clinical pathology workflows can benefit from AI tools. Our review describes landmark trials and milestones in using AI in clinical pathology and discusses the direction it is going in the future.

Keywords: Artificial intelligence, Machine Learning, Algorithms, Diagnostics

Introduction

AI is a broad term that encompasses a wide range of AI approaches, including machine learning (ML). In DL networks, the input layer is layered with hidden layers, while the output layer is layered with the output layer. This mimics human neural architecture [1]. It is possible to create newer visualizations of the image using hidden layers and with the appropriate number of repetitions, the representations can be identified and the differentiation between the interesting features can be possible [2, 3]. There has been an increase in the use of AI in pathology practice for a wide variety of image analysis and segmentation tasks. The tasks include simple ones, such as recognizing cells, and more complex ones, such as using image pattern recognition to predict disease diagnosis, prognosis, and treatment. This AI approach is based on extracting image patches for training algorithms by using them as inputs. The use of AI has enabled the development of morphometric analysis approaches that facilitate quantitative histomorphometry analysis approaches for interrogating the entire tumor histologic landscape on a standard hematoxylin and eosin slide for detailed spatial interrogation (e.g., nuclear orientation, texture, shape, and architecture). By automating time-consuming tasks for pathologists, these AI applications will aid in fast and accurate diagnosis by saving time on high-level decision-making [4]. In this way, it is possible to support the overall reporting process, speed up the reporting process, and measure morpho-biological features objectively using AI technology. As pathologists face increasing workload demands, AI-aided reporting of certain features and lesions will also enable them to focus on challenging cases. The implementation of technology in pathology services does not replace human resources, such as pathologists and laboratory technicians, but rather supports them, assists them, and enhances diagnostic and performance efficiency by better allocating resources, increasing cost-effectiveness of the service, and providing more consistent pathology reviews [2, 5].

Oncologists and pathologists can develop domain-inspired features in their algorithms or domain-agnostic features without this inherent domain knowledge. Feature engineering is the process of developing features. The co-occurring gland angularity feature (GAF) presented by Lee et al. computed the entropy of gland directions within local neighborhoods on tissue sections is an example of a domain-inspired feature [6]. In prostate cancers with an aggressive risk, glands were arranged more chaotically compared to those with a low or intermediate risk. In fact, the GAF associated with aggressive diseases have a higher entropy than indolent diseases [7].

Features that are domain-agnostic can improve the characterization of images across several diseases and tissue types. The shape, size, and texture of cells and glands are examples. A series of wavelet and tissue texture features have been used to automate the grading of prostate pathology images for low and high Gleason grades [8]. In order to diagnose, prognosis, grade, and predict response to therapy for breast cancers, prostate cancers, and brain tumors, hand-crafted feature-based approaches have been used both domain-agnostic and domain-specific.

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There are several advantages and limitations to handcrafted and unsupervised features [9]. The pathologist or oncologist will find handcrafted features more intuitive and transparent. Domain-inspired features require an in-depth understanding of the pathology and how it manifests in the tissue, making them more challenging to develop [10]. Deep learning strategies based on unsupervised feature generation lack interpretability despite the fact that they can be applied quickly and seamlessly to any domain or problem.

Technical requirements

The WSI process consists of four sequential steps: image acquisition, image storage, image processing, and image visualization [11]. An image acquisition device contains two hardware components: an image capture system and an image display system. The images are captured by a trinocular microscope equipped with a high-resolution camera and robotic illumination intensity control. Different from still microscopic images, WSI scanners capture sequential images in a line scanning or tile scanning manner, which are then stitched together to create VSs, exact replicas of the glass slides [12]. It is important to minimize the artifacts of microtomy or mounting in surgical pathology, such as section thickness, position of section on slide, and avoidance of coverslip edges. Since most scanners accept only one slide-thick stack, thick slides or broken slides may not be automatically scanned. Due to the standardized preparation and staining process, liquid-based cytology (LBC) smears or cell blocks offer an advantage in this regard [13].

To provide an image similar to what we see directly through the microscope, digital scanners must use the z-axis in addition to the x and y-axis. There is a difference in the method of z-focusing between the commercially available scanners. Some focus on selected tiles or focus points and others focus on every tile [2, 14]. Focusing on each tile during image acquisition is the most efficient way to achieve the highest quality results in WSI; however, this is a time-consuming process that compromises the scanner's throughput [15].

Magnification is a factor that determines the resolution of VS during scanning. For routine surgical pathology and immunohistochemistry slides, scanning at 20 magnification is considered suitable. Cytology slides, however, may not follow the same rule [16]. The results of a study evaluating WSI in cervico-vaginal cytology showed higher diagnostic accuracy with ×40 or ×40 z-stack scanning. Based on the cell distribution on the smear, advanced cell layer topographical analysis can be used to select cytological samples for scanning. This helps speed up the workflow and provide feedback to the laboratory regarding how certain samples should be collected. Through continuous technological advancements, high-throughput scanners (with capacities of 400 slides) have become available, scanning times have been reduced (30 s to several min), and software has developed to digitize whole tissue mounts, glass slides of larger sizes, fluorescent-labeled sections, and smears [2].

By using the WSI system, the intended use dictates how VS should be viewed and managed. Many vendors offer image viewing software that can be installed locally or as a part of a software package that is installed on a network server. Images can be annotated and exported to other formats using these image viewers [17]. Onscreen virtual keyboards are available in a few advanced image viewers, such as surface slide, Aperio ImageScope, and PathXL. VS images can be discussed interactively in large meetings using mobile devices, XDesks, or Microsoft surfaces.

The use of AI in diagnostics

The development of AI has recently opened up new horizons for the diagnosis and classification of cancer. In pathology practice, AI tools have been incorporated into the diagnostic workflow in several ways [18]. The use of AI approaches has been seen in the recognition, detection, and segmentation of a wide variety of objects. By combining WSIs with computer vision algorithms, several features can be extracted, enabling diagnostic predictions to be made. Pathologists increasingly rely on AI tools to provide information they can't identify themselves. There are various immunohistochemical biomarkers that can be measured objectively, including Ki67, PD-L1, cell quantification, and the spatial arrangement of cells, their expression and density [19]. Furthermore, AI can be used to detect metastatic carcinoma cells in lymph nodes, improving sensitivity of detection. As an additional benefit, AI tools can facilitate standardizing scoring criteria in several cancers, such as Gleason scores for prostatic cancers or breast cancer grading, in which morphological characteristics are presented as continuous biological processes. Using AI search tools, pathologists can find similar images from a collection of large histopathology databases, using the technique of content-based image retrieval (CBIR). In their clinical practice, pathologists occasionally come across rare and complex cases, which are especially important for guiding them in diagnosing the cases. Rather than simply comparing images, the images retrieved from the database reflect similarity in associated histopathological features. For seemingly challenging cases, CBIR facilitates a timely diagnosis while providing the correct diagnosis [20].

Diagnose-aided tools, independent reporting algorithms, and automated quantifiers are all possibilities for incorporating diagnostic algorithms into DP workflows. Reports can be generated automatically without the input of pathologists using independent reporting algorithms. In biopsies, there is a possibility of identifying normal tissue such as colonic, gastric, breast, etc. While algorithm development is important, it is essential to consider the wide variety of normal tissues, in order to avoid missing rare microlesions (such as benign mimickers of cancer) or focal lesions that are rare variants of cancer. Algorithms are used to determine the histological features of tumors, such as their grade, type, and extent [2, 21]. The trained eye is required to assess and combine multiple features in order to make an accurate pathological diagnosis. Whether AI algorithms are useful depends on how easily they can be integrated into diagnostic workflows and how much value they can add to a pathologist's diagnosis. An assessment of this can be made based on the features assessed and the time required to provide results. For instance, grading algorithms for breast cancer may be more objective, inter-reader reliable, and provide better prognostic information than clinical observations. This AI algorithm would therefore be more useful in this case for its reproducibility than its efficiency. To maximize AI's effectiveness, we must use it intelligently rather than simply using algorithms. When used as a pathologist assistance tool, AI can be more effective in detecting lymph node metastases, underscoring the relevance of the clinical context. Increasing efforts have been made to provide an objective estimation of immunohistochemical markers, as well as to estimate their prognostic and predictive values through automated quantification. It might only take a pathologist a few minutes to manually estimate breast cancer receptors, but an automated method would be more efficient and reproducible [22].

Pathologists are increasingly using DIA platforms to aid their assessments, especially when evaluating biomarkers quantitatively. In 1997, the National Institutes of Health (Bethesda, Maryland, USA) developed ImageJ, one of the first open-source tools for image analysis. With CellProfiler software published in 2006, imaging-based diagnoses can be performed using supervised ML. Since its debut in 2017, QuPath has become increasingly popular for image analysis. With the help of the software, whole slide images can be detected and classified automatically using unsupervised ML, tumors can be identified, and biomarkers can be quantified [23]. Roche IHC assays for ER, PR, HER2, Ki67, and p53 breast biomarkers have been approved by CE and US IVD for an image analysis software called Ventana Companion Algorithm. In 2014, AstraZenecain created the Tissue Phenomics software for identifying biomarkers in immunooncology clinical programs. Research applications are the main focus of the modules developed by HALO (Indica laboratories). With the help of VMscope's Cognition Master Professional Suite platform, it is now possible to score Ki67, ER, PR, CD3/4/8/15/20, and tumor-infiltrating lymphocytes (TILs). For tissue classification, IHC quantification, and molecular pathology, QuantCenter provides modules for 3DHISTECH image analysis applications. Prior to their use in diagnostic settings, DIA tools must be validated and standardized due to the rapid emergence of DIA solutions and integrated platforms [24].

As of today, convolutional neural networks (CNNs) are the most widely used DL algorithms in pathology. A CNN is a deep, feedforward network composed of several sequential layers (convolutional sheets), which can deconstruct an image into low-level cues in order to calculate an output from an input [25]. A high-order structure identifies features of interest by aggregating low-level cues, such as edges, curves, and shapes. CNN was used for the classification of WSI into benign, malignant, in-situ and invasive breast cancers. As well as distinguishing benign lesions from malignant lesions, CNN also performed equally well compared to dermatopathologists in identifying seborrheic keratosis and benign nevi from malignant melanomas [26]. In a study of digital dermatoscopic images of pigmented skin lesions, Tschandl et al. showed that CNN had similar diagnostic accuracy as humans. In diagnostic practice, AI based methods have been found to be useful in several ways (Figure 1).

Applications of AI in prediction and prognosis

Using histological features as a predictive factor, AI can predict prognosis and therapeutic response. Imaging features of tumors, surrounding microenvironment, and genetic profiles could be directly linked to survival results and treatment response in adjuvant and neoadjuvant chemotherapy. For humans, it can be difficult to integrate various morphological features, such as tumor microenvironment patterns and tumor histological patterns, into a single prognostic index. Through the correlating of important histological features like tumor morphology, stromal architecture, nuclear texture, lymph vascular invasion, etc., image-based AI tools can provide a novel classification system that depicts clinical outcome, probability of recurrence or metastasis, and therapeutic response [27]. There has been considerable interest in predicting clinical outcomes using graphical approaches to evaluate architecture and spatial configuration of tissues. In an analysis of HE stained TMA slides, Wang et al. developed a ML model that uses nuclear shape, texture, and tumor architecture to predict recurrence in early-stage non-small cell lung cancer (NSCLC). The model's predictive accuracy for predicting recurrence in two validation cohorts was 82% and 75%, respectively.

Additionally, there are studies which highlighted the prognostic implications of AI based tools. For the detection of TILs in images from The Cancer Genome Atlas, a CNN was used to augment pathologist feedback [28]. Among 13 cancer subtypes, this feature was found to be prognostic of outcome. On triple-negative breast cancer WSIs, Yuan et al. used a similar model to analyze lymphocyte spatial distributions with respect to tumor cells. In addition to identifying three types of lymphocytes, they also found a direct correlation between late recurrence and immune cell distribution in ER-positive breast cancers. TMAs from breast cancer have also been analyzed histologically and molecularly by CNN. Oncotype DX-defined risks of disease recurrence vary significantly based on the presence or absence of mitotic figures in breast cancer WSIs detected by CNN. Similar prognostication study in colorectal cancer was studied. An independent prognostic factor for disease-free survival was established using CNN's quantification of 'tumor-to-stroma' using pathologist-defined 'stromal hotspots' [2].

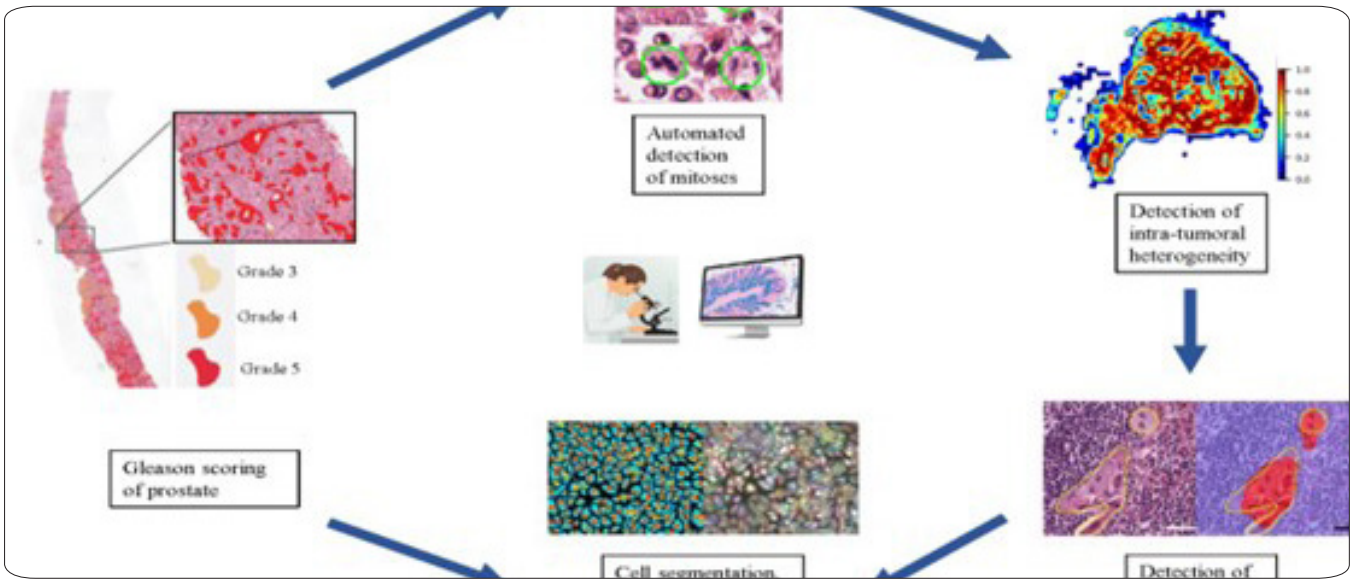

Figure 1: AI and ML approaches currently used by pathologists to analyze tumor images.

Research applications of AI (Drug discovery and development)

Pathologists' training is enhanced with AI tools, which can provide helpful annotations and other interactive functions to create a dynamic teaching environment. This can enable the practice of high-quality personalized and precision medicine by integrating morphology with novel approaches and advanced technologies. Presenters and tumor boards have already been using whole-slide imaging for teaching at conferences, virtual workshops, and presentations. A "digital cockpit" has been developed by the Wexner Medical Center at Ohio State University for fully digital sign-outs. Philips' integrated management system is used regularly by residents to preview digital slides. Enhanced digital slides can be viewed, panned, and zoomed, encircling regions of interest, including a single questionable cell. There are many bioinformatics driven tools that are used in the daily practice of pathology, including the clinical and research registries, organ-based databases, laboratory information systems (LIS, colloquially known as "beaker"), and synoptic reporting templates. WSI is also integrated into the LIS using several university add-on components [29]. Clinical workflows are incorporating DP tools at the forefront of the field. Through the use of Visopharm AI tools, lymph node metastases can be detected rapidly in difficult cases. Such AI tools can be integrated into the daily sign-out workflow to supplement key information for trainees, enabling them to come up with a differential diagnosis and potential auxiliary tests for ordering, thereby honing their diagnostic skills. Resident training can also be improved by accessing relevant educational resources. Educating in this manner can complement the conventional educational processes provided by pathologists, and other institutions can adopt them. Not only has it improved in-house training and inter-subspecialty consultations, but also collaboration with other institutions and providing efficient consultations and second opinions have been greatly improved [1].

A paradigm shift has occurred in cancer treatment over the past few years as a result of immune checkpoint inhibitors (ICIs). Due to the fact that many patients receiving ICIs fail to respond to this therapy, it may be necessary to combine AI with DP to stratify patients according to their likelihood of benefiting from the treatment. In the study, Wang et al. [28] assessed the potential role of nuclear and perinuclear features in stratifying recurrence risk of early-stage non-small cell lung cancers (NSCLCs). Adjuvant chemotherapy was recommended for high-risk patients [3, 14]. It is possible to predict therapeutic responses to targeted agents, ICIs, and chemotherapy drugs using AI tools, such as hand-crafted machine-learning approaches. A study by Wang et al. [28] described how spatial orientation of nuclei and TILs could predict response to anti-PD-1 antibody nivolumab in late-stage NSCLC.

Challenges for application of AI

The validation of algorithms and the overfitting of models

Before AI algorithms can be implemented clinically, they must undergo rigorous multi-institutional validation. The algorithmic approach/model is usually applied to a training/learning discovery set, followed by a validation set for confirmation. Currently, AI algorithms are predominantly based on small-scale data and images from a single center, augmented with random rotations and flips, color jittering, and Gaussian blurs. It is important that all categories of interest are represented equally in the training set. On the validation dataset, further optimization is performed after the algorithm has been trained after several iterations in the discovery dataset. Obtaining pertinent datasets and cohorts can be a challenge, and this process can be quite laborious and challenging [30].

Quality of data

It is imperative that input data be of the highest quality and quantity in order for AI based approaches to perform at their optimal level. A training set with a high signal-to-noise ratio, and that is well curated, comprehensive, and well measured, will achieve the highest predictive accuracy. AI tool is used to detect prostate cancer automatically in WSIs, highlighting the importance of high-quality data. Because of loss of granularity at increased resolution, magnification led to a decrease in overall performance. The majority of existing slide scanners can scan slides at a maximum of ×40. While higher resolution images (> ×20) can be scaled down to be used by an algorithm trained at a resolution of ×20, considerable loss of data fidelity can occur with the use of an AI approach developed at ×40 when the maximum scanning resolution available is ×20. As a result, it is essential to ensure data fidelity as a means of standardizing the evaluation of AI algorithms' performance [3].

Challenges associated with technology

For small biopsy specimens, the scanning time varies from 1 to 5 min, for surgical specimens from 5 to 20 min, and for liquid cytology smears between 3 and 5 min. Furthermore, most current scanners require enormous amounts of storage capacity. For example, a 1 mm^2 image at 40 magnification requires 48 megabytes of space! This problem is overcome by using image compression algorithms (JPEG, JPEG 2000, and LZW) in WSI platforms. In this compression technique, image artefacts are introduced which can compromise pixel quality [6].

Ethical principles

FAIR is a guiding principle for scientific data management and stewardship developed by Wilkinson and his coauthors during 2016. A stringent data management process requires easy access, operator independence, and reusability of data. In addition to fostering knowledge discovery and innovation, it ensures reusability of data after publication by the broader community.

The 'black box' problem

The 'black box' problem is the inability of deep learning algorithms to demonstrate how they arrive at their conclusions. Despite obvious advantages of accuracy and efficiency, deep neural networks face sharp criticism due to lack of interpretability, which forms a huge roadblock in clinical adoption. Several studies aimed to overcome this skepticism used post hoc methods to comprehensively analyze the outputs of AI algorithms. However, post hoc analyses of deep learning methods seem superfluous as additional models should not be required to explain how an AI model works [2].

To use or not to use

An apprehension about the change in workflow is one of the key roadblocks to integrating AI into clinical practice. AI algorithms' performance thresholds are somewhat unclear partly due to the lack of interpretability and partly due to their lack of interpretability. DL-based model predictions combined with pathologist diagnoses have shown to reduce error rates and improve performance, but replacing human evaluation entirely by machine assessment is met with considerable cynicism. For breast cancer metastases in sentinel nodes, Wang et al. [28] study showed a combined approach can reduce human error by 85%. It is also important to address whether the overall turnaround time has decreased [5]. It is important to resolve some practical issues before a meaningful human-machine collaboration can occur in the clinical setting, including a lack of clarity on the degree of responsibility assigned to pathologists when reporting with AI.

Opportunities and Directions for Future

The development of AI tools for detecting cancer has increased over the past few years with companies like Visiopharm, Halo, Proscia, DeepLens, Inspirata, and PAIGE.AI. The two major companies involved in DL-algorithm training are PAIGE.AI and Inspirata. As the path towards digitizing clinical workflows began to take shape in 2017, Philips' whole-slide scanner was approved by the FDA. We at The Ohio State University Wexner Medical Center were forced to adopt digital workflow in daily clinical practice by the COVID-19 pandemic. While DP has faced numerous challenges and obstacles in adopting AI-enhanced workflows, a paradigm shift has occurred [31]. Using open-top light sheet microscopy, which generates three-dimensional (3D) images of tissues without any destruction of the tissue, might provide a substantial improvement in spatial and architectural information needed for the application of AI. MUSE microscopy, which uses ultraviolet rays to generate high-resolution images of tissues, may be a viable alternative to tissue staining and processing. In the future, most AI applications will likely remain narrow, focusing only on a single task, even though current applications can recognize tumor scores and grades.

Conclusion

AI approaches to pathology have grown rapidly in recent years. With these tools, diagnostic workflows can be improved, human errors can be eliminated, interobserver reproducibility can be increased, and prognostic predictions can be made. Although AI tools have been developed at an increasing rate, their implementation in clinical practice has been somewhat slow, largely due to issues related to interpretation, validation, regulation, generalizability, and cost. After standardizing usage recommendations and harmonizing with current information systems, AI applications may be implemented and used appropriately in conjunction with human pathologists in order to provide personalized cancer care. In order to provide comprehensive patient-specific tumor precision therapy, a multimodal approach incorporating proteomics, genomics, and AI based multiplexed biomarker quantifications may be necessary.

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Conflict of Interest

None.

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