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Artificial Intelligence and Computational Pathology: A comprehensive review of advancements and applications

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ABSTRACT

Conventional pathology is essential for disease diagnosis, but challenges like inter-observer variability can impact treatment decisions. Immunohistochemistry assays improve patient identification, but advanced quantitative tools are needed for accurate marker quantification and spatial analysis. AI enhances accuracy in pathology by contextualizing spatial data and revolutionizing medicine through advanced data processing and machine learning. Clinical informatics and AI integration advance patient care and open new horizons in pathology. Artificial intelligence (AI) is crucial in pathology, leveraging deep learning techniques to integrate pathological images with radiological, clinical, and genomic data. These pattern recognition methods enhance disease diagnosis and prognosis assessment. This review article provides an overview of AI in pathology, recent advancements, and future prospects. It emphasizes digital pathology, image acquisition, data preprocessing, and feature extraction for AI-driven pathology analysis. A comprehensive analysis of the key findings and outcomes from recent studies incorporating AI in pathology is done. A focus on various applications, including but not limited to cancer diagnosis, grading, and prognosis, as well as the identification of specific tissue patterns and rare diseases. The impact of AI on workflow optimization, quality assurance, and predictive analytics in pathology is also discussed. This section explores the implications and challenges of AI adoption in pathology. We discuss benefits like enhanced accuracy and resource allocation but also cover limitations such as dataset requirements, ethics, interpretability, and regulations. Ongoing research and collaborations aim to address these concerns and ensure responsible AI implementation in pathology.

KEYWORDS: Artificial intelligence, Computation pathology, Global service model, Image analysis, Machine learning, Spatial contextualization

INTRODUCTION

Conventional pathology provides diagnosis and evaluation of protein expression, but inter-observer variability poses challenges in immune cell staining interpretation. [1, 2] This can produce inconsistency in diagnoses, which may impact treatment decisions. [3–7] Immunohistochemistry assays improve patient identification for immuno-oncology therapy, but accurately quantifying complex immune markers in a spatial context requires advanced quantitative tools. AI in pathology enhances quantitative accuracy and enables spatial data contextualization. [8–12]

Artificial intelligence (AI) simulates human thinking and actions, offering promising solutions for pathologic diagnosis, classification, and prognostication. Conventional pathology requires extensive reading time and is subjective, while AI can reduce pathologists' workload and eliminate subjectivity. The Camelyon Grand Challenge 2016 demonstrated AI's potential, achieving a 92.4% sensitivity in tumor detection, surpassing human pathologists' 73.2% sensitivity. Computational pathology revolutionizes digital pathology, molecular pathology, and pathology informatics, improving diagnostic accuracy, patient care, and cost efficiency. It fosters global collaboration and plays a pivotal role in achieving individualized precision medicine. [13–16]

Pathology has been slower in adopting AI compared to radiology and other clinical branches due to factors like scarcity of expertise, inadequate training, substantial investments, fragmented ventures, lack of guidelines, and inertia. However, AI can effectively address all aspects of pathology, from diagnosis to research and exploration. Machines can learn and improve performance through accumulated experience, although they lack genuine thought. Classification is the cornerstone of machine learning, enabling predictions and inference.

METHODS

Digital pathology, machine learning and computational pathology

Advancements in brightfield and fluorescent slide scanners have revolutionized pathology by enabling the virtualization and digitization of entire glass slides. [17] This transformation into digital pathology involves converting histopathology, immunohistochemistry, or cytology slides into a digital format using whole-slide scanners. The resulting digitized whole-slide images can be securely stored in a centralized cloud-based space, facilitating remote access and flexibility in examination and analysis.

The availability of digitized pathology data has paved the way for the application of artificial intelligence (AI) techniques in pathology. AI algorithms can analyze these digitized slides, offering opportunities for automated analysis, pattern recognition, and decision support [18] AI in pathology can enhance diagnostic accuracy, aid in prognostic assessment, and optimize patient care.

AI can be broadly categorized into weak AI (artificial narrow intelligence or ANI) and strong AI (artificial general intelligence or AGI). Weak AI involves the use of pre-trained statistical models for specific tasks, such as classification based on available data. [19] Strong AI aims to develop systems capable of independent and intelligent functioning, utilizing machine learning techniques on diverse and normalized datasets.

The combination of digital pathology and AI holds great potential for improving pathology practice, driving advancements in diagnostic capabilities, workflow efficiency, and ultimately, patient outcomes.

Machine learning is a core aspect of AI that enables computer systems to autonomously learn and improve their performance without explicit programming. It utilizes training data to construct algorithms that can interpret and make informed decisions on new data . [20] In pathology, machine learning approaches leverage morphological patterns to support diagnosis, automating tasks like identification, segmentation, and classification. By utilizing machine learning algorithms, these methods enhance the accuracy and efficiency of pathology diagnosis by analyzing key features such as cancer cells, cell nuclei, and blood vessels. This integration of machine learning in pathology holds promise for more precise and effective diagnostic processes. [21]

Deep learning, a subfield of machine learning, utilizes artificial neural networks (ANNs) to establish statistical models based on training data. [22] ANNs consist of interconnected artificial neurons organized into input, hidden, and output layers. [23] The connections between neurons are evaluated using statistical methods such as clustering algorithms, support vector machines, and logistic regressions. [24]

Deep learning models, such as convolutional neural networks (CNNs), utilize learnable filters called convolutional kernels to process and classify visual images. By reducing image dimensions and preserving essential characteristics, CNNs enable computer vision models to analyze and categorize images. With advancements in slide scanning technology, an increasing volume of whole-slide imaging (WSI) data is available for training CNN models. Combining WSI data with clinical information and biomarkers, computational pathology can enhance pathology workflows, provide comprehensive insights into disease progression, and improve patient care. [25] By leveraging advanced computational techniques, computational pathology enables pathologists to analyze large datasets and make informed decisions, leading to personalized treatment outcomes. [26]

Algorithm training process

An algorithm is a defined computational technique that solves a problem by accepting input and producing the required output. In computational pathology, algorithms are used to process multiple sources of data, extract relevant information, and generate diagnostic inferences and predictions. This clinically actionable knowledge is presented through integrated reports and interfaces, empowering healthcare stakeholders to make informed medical decisions based on the best available information. [27]

Case selection

Patient selection plays a vital role in training computational pathology algorithms. The training and validation sets should encompass diverse sample types and variants associated with the diseases of interest, including different stages, grades, classifications, and complications. Collaborating with experienced pathologists helps establish criteria for sample selection and inclusion in the learning set, minimizing false negatives and positives. Confounding variables, such as co-existing medical conditions, are carefully considered and eliminated. Ensuring high-quality slides and addressing technical issues is crucial for accurate results. Comprehensive clinical information and relevant laboratory results are incorporated to enhance algorithm accuracy and reliability. Thorough data collection during initial and follow-up stages ensures robust algorithms. By considering a wide range of factors, these algorithms provide better insights and decision-making. Meticulous data collection throughout the patient journey is vital for developing computational pathology algorithms that improve patient care and outcomes.

Whole slide imaging (WSI)

Whole slide scanners rapidly capture separate images of each field of view on a slide, which are then stitched together to create a single, high-resolution digital image. Typical digitization resolutions range from 0.25 to 5 microns per pixel (corresponding to 100X to 2X of conventional microscopy). Pathologists cannot view the entire slide at high resolution due to the large amount of information. Instead, they pan through the slide at lower resolutions (typically 2X or 4X) and zoom in for detailed examination of specific regions. Pathologists focus while panning and zooming to ensure accurate analysis of regions of diagnostic interest. This process allows pathologists to efficiently navigate and analyze digital slides, improving diagnostic accuracy and workflow.

Pathology images can have file sizes ranging from 1 to 3 GB per image, requiring powerful computers to handle them efficiently. The number of slides needed for algorithm development varies based on tissue type and diagnosis.

Campanella et al. found that a minimum of 10,000 slides is required for effective algorithm training. [28] Image attributes like brightness, contrast, and sharpness are crucial for accurate algorithm predictions.

Standardization and Normalization

Standardization and normalization play crucial roles in advancing computational pathology. Standardization ensures harmonized data acquisition and analysis, promoting integrity and comparability. Normalization reduces biases and confounding factors, enhancing the accuracy and reliability of computational models. High-quality slide preparation steps, such as embedding, cutting, staining, and scanning, are vital for successful adaptation of whole-slide images. [17] Variations like folded tissue, staining inconsistencies, and scanning settings can lead to unreliable data and inaccurate results. Standardized protocols and quality controls are needed to minimize errors and ensure reliable predictions. Accumulating a large and diverse data set is crucial for accurate algorithms, especially for rare diseases and specific populations.

RESULTS

Image analysis and automation struggle to differentiate objects efficiently, unlike humans who require minimal examples. Bridging this gap unlocks automation's potential.

Senaras et al. [29] introduced DeepFocus, a deep-learning framework that analyzes digital slides to identify and address blurriness. By improving image quality through automated re-scanning, DeepFocus enhances digital slide analysis for pathologists and computational pathology algorithms.

Janowczyk et al. [30] introduced HistoQC, an open-source tool for assessing color histograms, brightness, and contrast in digital pathology slides. HistoQC identifies outliers in staining characteristics, ensuring consistency and reliability in analyses while aiding in slide improvement for better quality and accuracy.

Deep neural networks have revolutionized computational pathology by enabling AI-powered image analysis. This automation boosts efficiency, quality, and reliability, benefiting patient care. Pathologists can now prioritize critical tasks, unburdened by manual slide annotation.

Patch-based whole-slide images, ranging from 224x224 to 256x256 pixels, are widely used for training classifiers in computational pathology, with proven effectiveness.

Campanella et al. [31] used multiple instance learning (MIL) with CNNs and RNNs to classify prostate cancer images, yielding promising outcomes.

Kapil et al. [31] used deep semi-supervised architectures and AC-GANs to automatically analyze PD-L1 expression in non-small cell lung cancer biopsies, enabling automated assessment of this crucial cancer immunotherapy biomarker.

Barker et al. [32] achieved 93.1% accuracy in differentiating glioblastoma multiforme from lower-grade glioma using elastic net linear regression and a weighted voting system.

These studies showcase the effectiveness of machine learning techniques, including MIL, deep semi-supervised architectures, AC-GANs, and elastic net linear regression models, in computational pathology. By utilizing patch-based whole-slide images and advanced neural network models, these approaches facilitate accurate and efficient pathology analysis and decision-making.

Global pathology service model

A central cloud-based AI lab and data bank enable a global network of computational pathology, converting histology slides to digital images and numerical data. [33] These are transferred to the central lab with EHR and multi-omics data for analysis. [34] Patients worldwide benefit from improved diagnosis and treatment, while pathologists access information for patient care and collaboration. Deep-learning platforms aid complex connections and clinical decisions. Challenges include the availability of experienced clinicians, hardware limitations, data validation, and ethical concerns.

AI applications in pathology sub specialties

AI detection expands across subspecialties, achieving precise classification on an unprecedented scale, and fostering widespread computational pathology. [35–37]

Lymph node metastases

Campanella et al. validated a deep neural network algorithm for image analysis of 44,732 whole-slide images in three cancer types. $\times 5$ magnification showed higher accuracy. They trained a statistic model with a MIL-based tile classifier, achieving AUC above 0.98 for all cancers. Implementation would enable pathologists to exclude 65–75% of slides while maintaining 100% sensitivity. [28]

Colorectal polyps

Korbar et al. developed accurate deep-learning algorithms to classify colorectal polyps, achieving 93% overall accuracy across hyperplastic, sessile serrated, traditional serrated, tubular, and tubulovillous/villous polyp types. [38].

Breast cancer

Wang et al. trained classification models using breast sentinel lymph node patches, achieving high accuracy and significant improvement in pathologist diagnoses. [39]

Cervical cytology

Martin et al. used convolutional neural networks to classify cervical cytology images, achieving varying accuracies for different diagnostic categories . [40]

DISCUSSION

AI researches in computational pathology focuses on tumor detection and grading, but it has broader transformative potential in the medical system.

Computational pathology, through spatial contextualization, can play a significant role in the complex process of analysis and judgment by integrating various data sources, including demographic information, digital pathology data, -omics data (such as genomics, proteomics, and transcriptomics), and laboratory results. [41] By combining these diverse data sets and applying advanced AI algorithms, computational pathology can provide valuable insights and support for pathologists in their diagnostic and prognostic tasks.

Clinical data is used in mathematical models to generate diagnostic predictions, aiding medical decisions. [42]Deep neural networks assess breast tumor bio markers such as HER2, ER, and Ki67. [43]Novel convolutional neural networks connect mammographic abnormalities to histopathological features (Hamidinekoo et al. [44]). Genomic survival models integrate histology images and genomic data to predict patient outcomes accurately (Mobadersany et al. [45]).

Electronic health record (EHR) systems enable comprehensive data collection, including demographics and medical history, for disease-specific algorithms. Pathologists can gain insights and adapt treatment algorithms based on patient status and disease stage. [46, 47]

Health apps and personal trackers provide real-time health data (e.g., temperature, heart rate, glucose levels) that can be integrated into EHR and LIS [48], creating a digitalized and comprehensive patient profile beyond human capability. [49]

Pathology plays a vital role in integrating data, algorithms, and analytics to enable data-driven care. Computational pathology and big data mining can revolutionize evidence-based, personalized medicine. [50]

CONCLUSION

This comprehensive review explores the application of artificial intelligence (AI) in pathology, highlighting its potential to revolutionize disease diagnosis and treatment. By leveraging machine learning algorithms, AI systems analyze pathological images with remarkable accuracy, aiding pathologists in making precise diagnoses. The review emphasizes the benefits of AI, such as speed, objectivity, and standardized diagnosis, while acknowledging the ongoing development and integration of AI into pathology practice.

The article also discusses AI's potential in disease prediction, precision medicine, clinical decision support, and workflow optimization. It explores how AI can address the shortage of pathologists in underserved areas through remote diagnosis and consultation. AI-based tools enable large-scale data analysis and the development of personalized treatment strategies. The integration of AI in pathology has the potential to improve patient outcomes and enhance healthcare delivery globally.

However, challenges like data privacy, algorithm standardization, interpretability, and regulatory frameworks must be addressed to ensure responsible and ethical AI deployment in clinical settings. Continued research and collaboration are crucial to unlock the full potential of AI in pathology and determine its definitive role in various aspects of disease management.

In conclusion, while AI in pathology is still evolving, it holds great promise for disease diagnosis, personalized medicine, and optimizing healthcare workflows. Through responsible implementation and ongoing exploration, AI can revolutionize pathology practice and improve patient care worldwide.

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Abbreviations used in this article -

AI - Artificial Intelligence

WSI - Whole Slide Imaging

H&E - Hematoxylin & Eosin

ANI - Artificial Narrow Intelligence

AGI - Artificial General Intelligence

ANN - Artificial Neural Network

CNN - Convolutional Neural Network

RNN - Recurrent Neural Network

SVM - Support Vector Machines

DICOM - Digital Imaging and Communications in Medicine

MIL - Multiple Instance Learning

AC-GAN - Auxiliary Classifier Generative Adversarial Networks

LIS - Laboratory Information System

EHR - Electronic Health Record

AUC - Area Under receiver operating Curve

mpp - micron per pixel

GB - Giga byte

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