Diagnostic Pathology

REVIEW

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An update on applications of digital pathology: primary diagnosis; *telepathology*, education and research

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Abstract

Digital Pathology or whole slide imaging (WSI) is a diagnostic evaluation technique that produces digital images of high quality from tissue fragments. These images are formed on glass slides and evaluated by pathologist with the aid of microscope. As the concept of digital pathology is introduced, these high quality images are digitized and produced on-screen whole slide images in the form of digital files. This has paved the way for pathologists to collaborate with other pathology professionals in case of any additional recommendations and also provides remote working opportunities. The application of digital pathology in clinical practice is glazed with several advantages and adopted by pathologists and researchers for clinical, educational and research purposes. Moreover, digital pathology system integration requires an intensive effort from multiple stakeholders. All pathology departments have different needs, case usage, and blueprints, even though the framework elements and variables for effective clinical integration can be applied to any institution aiming for digital transformation. This article reviews the background and developmental phases of digital pathology and its application in clinical services, educational and research activities.

Keywords Digital pathology, Whole Slide Imaging, Primary diagnosis, *Telepathology*, Education, Research

Background

"Digital Pathology" is the means to produce digital images of high resolution from sections of the tissues on the glass slides that are historically observed by means of an optical microscope. The digital pictures are saved on safe servers that can be accessed by the pathologists on the monitors of computers; this has several advantages in clinical practice including working and collaborating remotely in case of need of second opinions [1, 2], enhanced efficiency and cost savings especially with easy access to previous biopsies, preparation for tumor boards, and elimination of physical transfer of slides to other sites [3–5]. Yet, "digital pathology" is not adopted extensively [6] and its implementation as a primary diagnostic tool is low [7]. It is necessary to scale up the implementation of "digital pathology" so as to cope up with various relevant challenges [8] and to mitigate the decreasing workforce in pathology services [9]; the maximum benefits can be achieved through deployment of "digital pathology" as it is important to deliver equitable healthcare facilities to all patients. Pathology is associated with various other areas of healthcare and can lead to advances in digital health e.g. as telehealth, telemedicine, eHealth, mHealth, etc.

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[10]. This broader panorama needs consideration as histopathology appears to improve and expand its own diagnostic facilities. This was emphasized recently in Eric Topol's report of the influence of technology in the broader healthcare perspective [11] which highlighted new care models for better diagnoses and management incorporating Artificial Intelligence (AI) [12, 13]. On an international level, the World Health Organization (WHO) recognizes digital health technologies as tools of empowering healthcare system and improving patients' lives [14, 15] with rising AI role as a diagnostic tool in pathology [13, 16]. Other, regulatory bodies, such as the Clinical Laboratory Improvement Amendments (CLIA), the College of American Pathologists (CAP), and the U.S. Food and Drug Administration (FDA), also provide considerable insight into guiding principles and manufacturers still struggle in the provision of clinical laboratory instruments [17]. Application of digital health tools have various challenges e.g. profile of digital health programs is weak, and a substantial know-how has not been achieved in the field of e-Health [18, 19]. It is quite evident that efficient application involves interests about diversified problems that are different from the technology of concern i.e. the interaction of technology with patrons; environment and policy makers display a combination of challenges that require attention to warrant implementation and viability of a technology service in healthcare settings [20]. Therefore, widespread, effective and sustained digitalization of pathology services in clinical practice is necessary to realize AI capability (Fig. 1) [10, 21].

Method

The electronic literature search was done on PubMed. MeSH keywords were applied: Digital pathology, telepathology and whole-slide imaging. The available full-text review articles in English language with updated generalized overview of the technology were thoroughly reviewed. All references were downloaded to EndNote X8, removing the duplicates. By the electronic literature search on PubMed, 125 articles were explored and 97 are incorporated in this review article. The steps to the method are given in detail in Fig. 2.

Historical overview of development

In the beginning, only screenshots of histological images captured through a microscope's optics were digitized for detailed evaluation in research settings for documentation and teaching. The term *telepathology* was introduced in the 1980s, and referred to as a remotely operated, motorized microscope and a live view of the microscopic slides. This setup was used in frozen section evaluation, consultation practice, and special applications such as transplant pathology. The earliest digital microscope system's cost was approximately $300,000 for its establishment and it required more than 24 h for a single slide scanning. Development of slide scanners and subsequent advances in their image resolution, capacities, speed and decreasing costs have paved the way for WSI to be the standard for future, large-scale, high-throughput digital pathology [22]; image management software advances and their integration into laboratory information systems (LISs) have been a boosting addition. The ability to speedily produce huge amounts of microscopic

Fig. 1 Digital transformation of the field of pathology in clinical practice

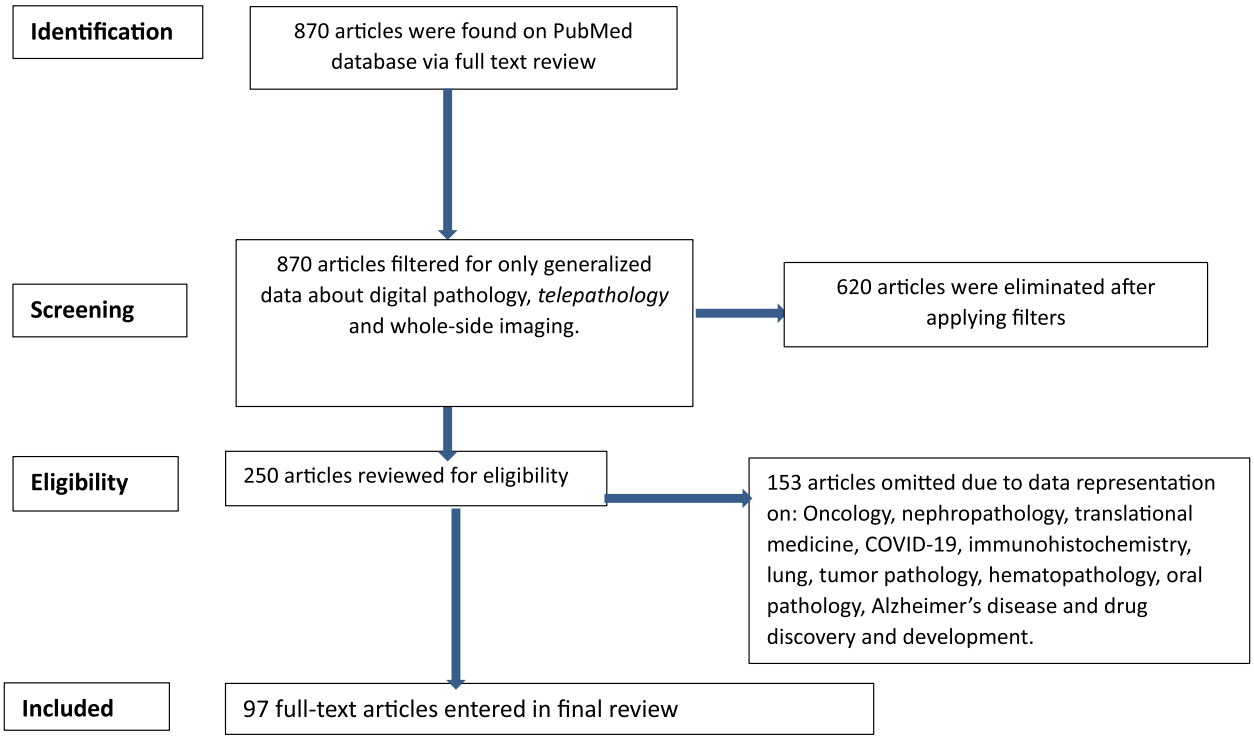

Fig. 2 Flow diagram for article selection

information has become possible due to the continuing technical developments in optical imaging innovations. Developments in storage and computational technology have made the management of big WSI datasets possible. Subsequently, slide scanners are now key tools that can uphold regular diagnostic services and pathologic scientific innovation and also have allowed for the expansion of automation tools like AI [23, 24].

Initiation of formal interaction between the Food and Drug Administration (FDA) and WSI stakeholders dates back to 2009 when an informational panel was held. Subsequently, in 2011 the FDA announced that WSI systems are considered as class III devices and thus vendors needed to follow a premarket approval (PMA) process. The Digital Pathology Association (DPA) got into a dialogue with the FDA in 2014 regarding the regulatory process. Pivotal trial design was agreed upon in 2015 and the first WSI system for primary diagnosis in surgical pathology, (Phillips IntelliSite Pathology Solution), was approved by the US FDA in April 2017 [25]. De novo WSI based device, (Phillips IntelliSite Pathology Solution) has lined the pathway for further companies who require just 510(k) clearance for application in place of PMA [26]. Accordingly, Leica Aperio AT2 DX System received clearance in 2019 followed by the clearance of Hamamatsu NanoZoomer S360MD Slide scanner system in 2022.

Following the noteworthy approval by FDA in 2017, a paper from the College of American Pathologists (CAP) Digital Pathology Committee reviewed frequently asked questions in this area and responded, as per available information [27, 28]. The FDA proclamation applied to the Philips IntelliSite Pathology Solution, for the assessment and interpretation of digital anatomical pathology slides which were produced from formalin-fixed, paraffin-embedded tissue. The foremost was demonstration of WSI non-inferiority to glass slides with respect to the diagnostic concordance in the clinical trials [29]. As per the outcomes, the FDA was convinced that the risk- benefit ratio related to WSI use was akin to that of standard light microscopy. Next, this dealer's establishing technical accuracy investigation displayed WSI reproducibility upon repeated single glass slide scanning with the same scanner or by other identical scanners. It was declared further by the FDA that microscopes be kept with the pathologists in clinical situations as per their judgement where it would be beneficial to adjourn glass slide review. Way forwarding to 2024, the FDA announced its Final Rule on laboratory-developed tests (LDTs) in April. LDTs are now considered regulated medical devices and the FDA will phase out its LDT enforcement discretion policy over a four-year period. Effect of this rule for digital pathology and AI applications are yet to be seen. Again in 2024,

as an important step towards standardization in digital pathology, FDA cleared Sectra's digital pathology solution together with Leica Biosystems Aperio GT 450 DX for the use of DICOM images for pathology diagnostics. Today, medical imaging devices from various manufacturers can be integrated, thanks to DICOM, which is used globally to store, exchange, and transmit medical images. DICOM is a standardized format, employed for the exchange and storage of patient data and related images [30]. Figure 3 demonstrates the timeline for sequence of events for use of digital pathology, for primary diagnosis.

Digital pathology in clinical service

Implementing digital pathology for primary diagnosis

Previously, absence of FDA permission was often mentioned as a main obstacle for adopting WSI for clinical uses [31]; however, even after the FDA approval, there has been initial reluctance among pathologists to adopt a digital solution as their main diagnostic tool instead of the traditional optical microscope. Nevertheless, the utility of WSIs in routine laboratory workflow and higher quality of patient care have been demonstrated with barcoding and tracking solutions, image management software, workload balancing, and rapid sharing of WSIs.

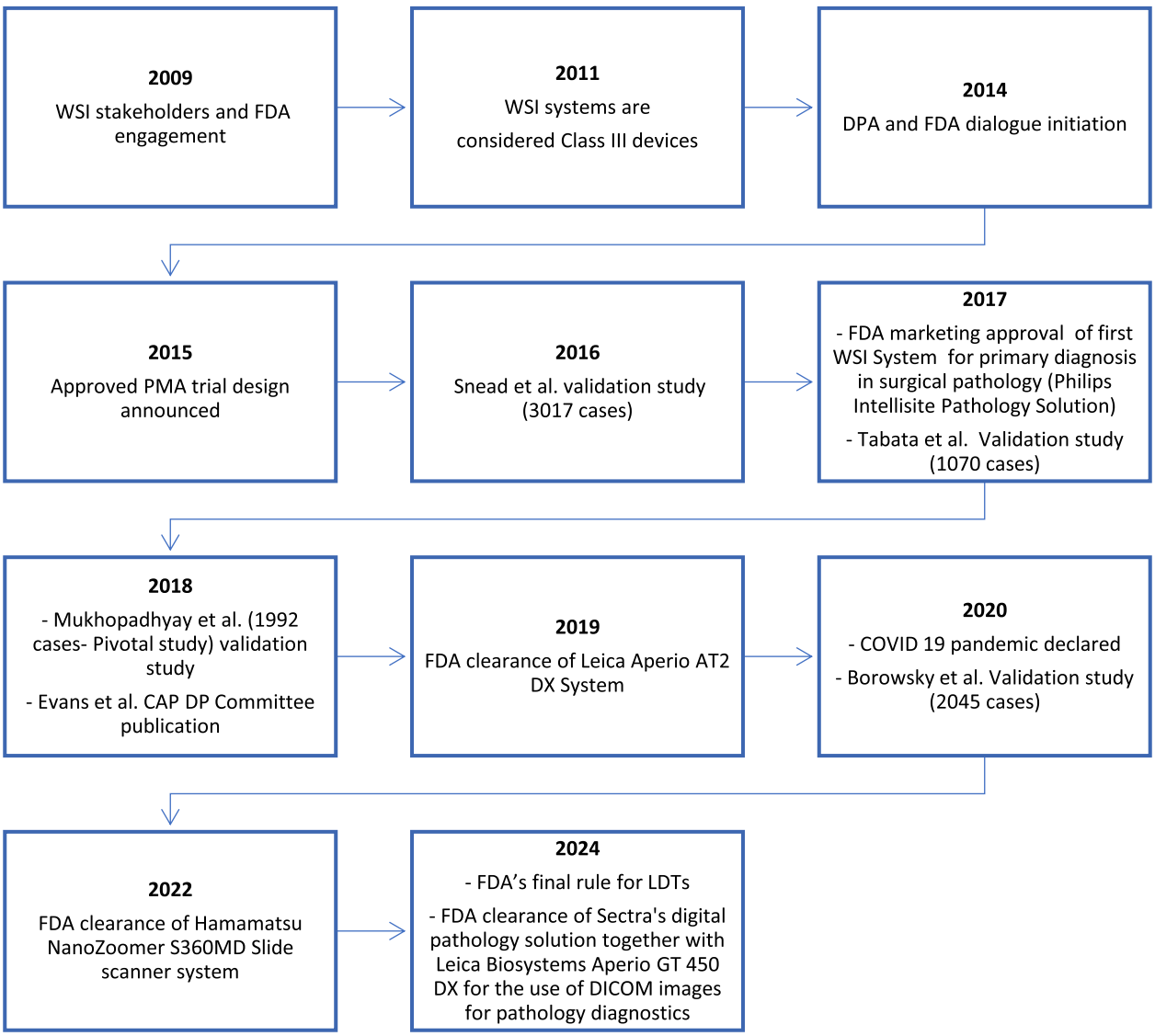

Fig. 3 The roadmap to use of digital pathology in primary diagnosis and beyond summarized as a timeline. *WSI: Whole slide imaging, FDA: Food and Drug Administration, DPA: Digital Pathology Association, PMA: Premarket approval, CAP: College of American Pathologists, LDT: Laboratory developed test, DICOM: Digital Imaging and Communications in Medicine*

Easier access to expert and/or subspecialty pathologists for consultation decreases interpretive errors in challenging cases across multiple sites in large health networks [32]. Eventually, the pathologists have come to appreciate the further benefits of digital reporting including but not limited to: elimination of lost slides or delays due to physical transfer, convenient access to previous biopsies for comparison purposes, opportunity to demonstrate and promote pathology in diverse spectrum of multidisciplinary meetings, and ergonomic benefits [33] (Fig. 4).

Process

A digital image is denoted by a 2-dimensional (2D) arrangement of numbers in a computer, every part of which signifies a pixel (image component). A digital picture constituted of pixels signifies an analogue picture with conversion to numerical type, with binary application (ones and zeros) so that it may be saved and utilized in a computer. The digital imaging process involves 4 main stages:

(1) Capture (picture acquisition).
(2) Saving (storing and managing).
(3) Editing (manipulation and annotation).
(4) Sharing (seeing, displaying, or transmitting images).

Microscopic digital pictures can be stationary with still images, seen live with real-time automated microscope, or observed subsequent to scanning of the glass slides with WSI [34] (Fig. 4). Attempts are being made to regulate the methods of acquisition, storage, and display of digital pictures in pathology, comparable to radiology [35, 36]. Commercial WSI scanners are being produced by many companies, and such systems obtain WSIs either through tile-based or line-based scanning, as proprietary systems. The OpenSlide library (vendor neutral C library) has the capacity to provide data transformation between some of these formats [37]. A range of dynamically supported open-source WSI systems is currently available, apart from the proprietary whole-slide software systems, supported by dealers e.g. caMicroscope, the Sedeen viewer, the Digital Slide Archive, and QuPath [38–41]. Some standards are required along with the validation of whole imaging process prior to wider implementation of digital images for regular clinical work [4]. The models for tiled pyramid-based data storage and reference frame were defined by a standard whole-slide format, established by a working group called Digital Imaging and Communications in Medicine (DICOM) standards committee [30]. Figures 5 and 6 summarize the process of whole slide imaging.

Validation

The non-inferiority of WSI for primary histological diagnosis, compared to light microscopy with glass slides, has now already been established with numerous large and small validation studies. This is valid across

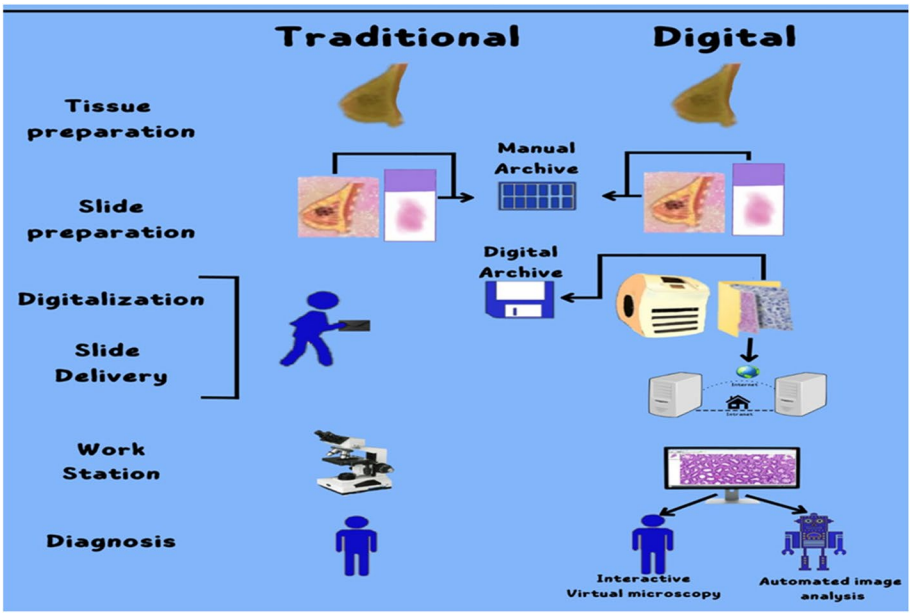

Fig. 4 Comparison of traditional and digital pathology. *In the traditional workflow the glass slides are studied under a light microscope to generate reports. Shifting the existing plan to a totally digital one would necessitate glass slide scans before transferring them to pathologists

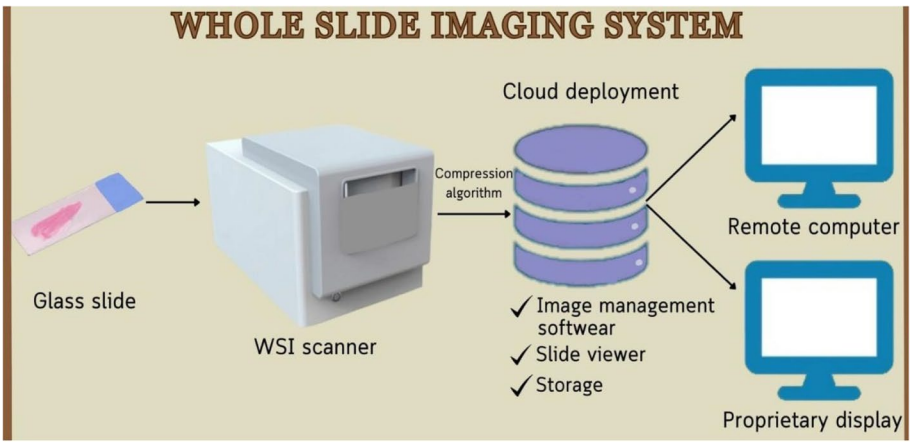

Fig. 5 Process of whole-side imaging

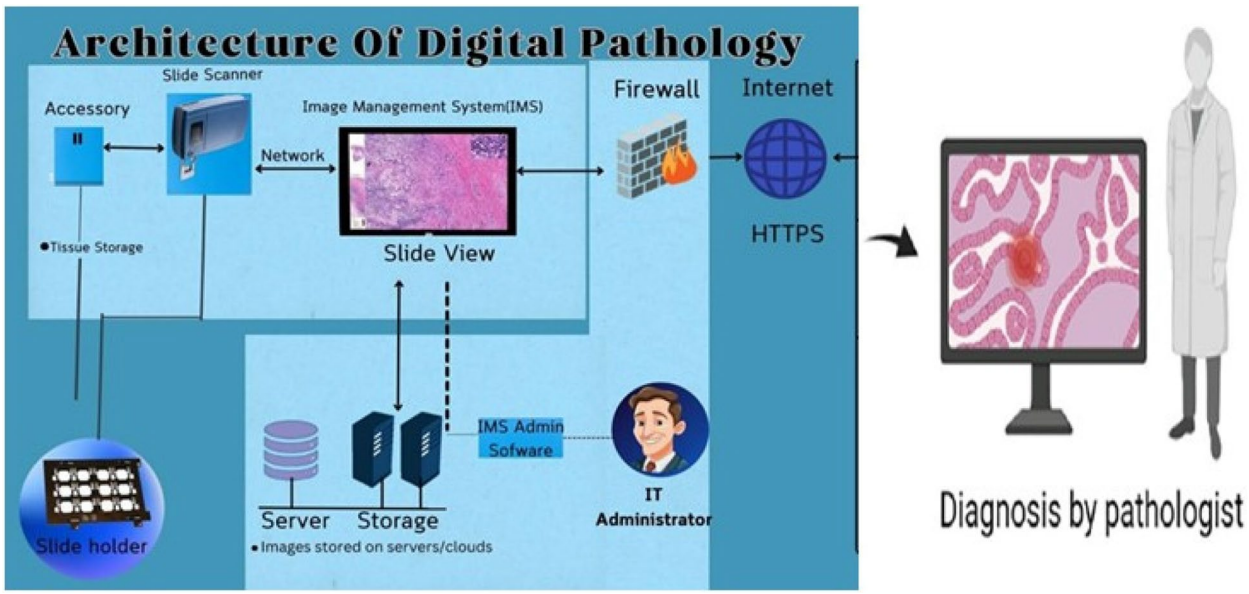

Fig. 6 Workflow of digital pathology

a wide variety of organ systems, collection methods, digitized optical magnification, and specimen types [29, 42]. Largest four validation studies are: a study by Snead et al. with 3017 cases and 10,138 scanned slides [43], a multicenter study by Tabata et al. with 900 cases and 1070 scanned slides [42], a multicenter blinded randomized pivotal study by Mukhopadhyay et al. with 1992 cases and 15,925 reads [44], and another multicenter double-blinded randomized study by Borowsky et al. with 2045 cases and 15,031 reads [45] (as listed in Fig. 2). When planning studies in the future to assess intraobserver equivalency, it may be useful to consider additional parameters in addition to diagnosis including margin status, lymphovascular invasion, perineural invasion, pathologic stage, and the need to order recuts, immunohistochemistry/special stains, as those would give a better reflection of daily routine practice in a pathology lab [46]. The validation of the digital microscopy workflow is critical in ensuring high diagnostic performance, therefore, the CAP issued an initial and an updated guideline, in addition to the technical performance assessment guidelines from FDA, with requirements to validate WSI systems in human pathology for diagnostic purposes. The recommendations are listed in Table 1.

Table 1 Recommendations for validating WSI systems [25, 47]

Recommendation for validating WSI systems (PMID:2,363,490, https://www.fda.gov/media/90791/download.93	Training in WSI should be offered to participants In a 2022 study by Rizzo et al., in which 45 validation articles were reviewed for diagnostic issues 9% of the articles reported issues with misinterpretation of diagnosis and 6% of the articles reported issues with lack of confidence emphasizing the importance of training [46]. Also, a 2024 study by Koefoed-Nielsen et al., on implementation of digital pathology at two departments stressed the need for more system specific training before implementation [25]
	A sample set of atleast 60 routine cases for one application and another 20 cases for each additional application should be used
	A washout period of atleast 2 weeks between viewing the slide sets in each condition should be present
	The performance of WSI review is considered non-inferior to light microscopy if the upper bound of the two sided 95% confidence interval of the difference between the overall major discrepancy rates of WSI review and light microscopy slides review diagnosis is 4% or less and if the upper bound of the two-sided 95% confidence interval of the overall major discrepancy rate of the WSI review diagnosis (relative to the reference diagnosis) is 7% or less for the same observer. If concordance is less than 95%, laboratories should investigate and take corrective action towards the cause

Technical and diagnostic issues

New issues to be cognizant and be cautious of and taken into consideration, when selecting an appropriate digital pathology system, have risen with the wider spread of digital pathology implementation in diverse pathology laboratory settings:

Turnaround time (TAT)

Digital workflow necessitates glass slides to be scanned before transferring them to pathologists, and this adds to the total diagnostic time cumulatively [23, 24]. In 2008, Velez et al. compared two whole slide image viewers to glass slides and found that examination of glass slides was the fastest [48]. A decade later, Hanna et al. reported an overall 19% decrease in efficiency per case with digital reporting with no significant difference by pathologist, subspecialty, or specimen type [46]; a recent study by Koefoed-Nielsen et al. showed that an increase in TAT is still a challenge in digital pathology [47]. In addition to experience and training, scanning time, image quality, LIS integration, WSI management, and case distribution also influence TAT [49]. Velez et al. emphasized this issue, stating that one viewer was faster than the other, pointing to the importance of user-friendly software and design [48]. Efficiency needs to improve for digital pathology to receive continuing support from the pathologist community [46]. It may be contemplated by utilizing rapid scanners and incorporating the scanning with cover slipping and the staining procedure [23, 24].

Pathologist friendly workflow booster features

Lee et al. listed some features such as automated tissue orientation, the ability to go from one level of tissue to other level on the same slide with one click, the ability to layer slides from one block on top of another, in order to be able to identify a region of interest at high magnification on the H&E and on corresponding special or immunohistochemical stains, eliminating the need to close and open multiple slides [49]. Another feature that is brought to attention by Fraggetta et al. is the availability of a macro image of a slide, which is the lowest resolution thumbnail that shows the label and all pieces of tissue on the slide to pathologists. Fraggetta et al. reported that displaying the macro image with the WSIs is critical as a quality control measure in digital pathology practice because it can help detect image-related problems and avoid misdiagnosis [50].

Technical features

Scanning time, rate of successful scans, average storage space, and overall image quality and digital artifact rate are technical features to consider; in a study by Rizzo et al. in which 45 validation articles were reviewed, 42% of the articles reported issues with scanning and viewing time, 20% mentioned scanning failure, 15% reported issues with storage. The need for higher magnification, lack of multiple focus planes, color inaccuracy and need for polarization have also been reported as technical issues in the literature [25]. In another study, scan failure was reported to be as low as 1.19% in a facility with experienced scanning staff and optimal slide preparations. In this same study, scanning of archival versus new slides did not show an impact on scan failure rates; also, TAT was not found to be impacted at that rate of scan failure [51]. Common image quality errors arising during the scanning process due to digitization of glass slides have been listed as Venetian blinds' artifacts from contaminated objective lens, bubbling from coverslip errors on frothy mounting media, insufficient slide cleaning prior to scanning (slides with dirt, dust, mounting media, and

markings), clipping from scanners, presence of tissue beyond the coverslip, and image stitching errors [51, 52].

Diagnostic factors

Grading dysplasia, counting mitoses, identifying the area of tumor invasion, identifying a specific cell, extracellular material, nuclear and cytoplasmic detail, and microorganisms are the diagnostic factors to consider. In the Rizzo et al. study, which examined 45 validation articles, 18% of the articles mentioned difficulties grading dysplasia, 13% reported mitotic count issues, and 6% mentioned microorganism identification problems [25, 53]. It was observed that the appearance of mucin, eosinophils, and melanin granules varied depending on the modality. It has also been reported that a 40×scan by digital pathology is unable to identify gram-positive cocci [49]. A 2024 study by Haghighi et al. found digital immunohistochemistry to generally surpass histochemical stains for microorganism detection. Digital interpretation of Ziehl–Neelsen and mucicarmine stains was recommended not be substituted for conventional review of glass slides [54]. Another study by Chen et al. (2024) came to the same conclusion that digital WSIs are not yet able to completely replace glass slide review for identification of H. pylori and recommended reviewing glass slides and/or performing ancillary stains, particularly when there is a discrepancy between histo-morphologic features and the presence of microorganisms on digital images [55]; Chen et al. did not report differences between practice settings and experience. In a meta-analysis about WSI comparison with light microscopy, 4% of discordant instances were discovered in 8069 cases, of which 32% were associated with diagnosis or dysplasia grading and 10% were recognized as the inability to discover a tiny object [56].

Telepathology

American Telemedicine Association defines *telepathology* as the kind of interaction between health professionals which involves the transmitting pathology pictures and related clinical information for different clinical purposes i.e. primary diagnoses, instant cytology explanation, intraoperative and second opinion consultations, etc. [56]. It is the diagnosis of surgical pathology cases by means of real-time video imaging or saved pictures at a distance. *Telepathology* can be categorized as static telepathology, WSI, dynamic non-robotic telemicroscopy and robust robotic telemicroscopy [57, 58]. Static images involve the assessment of still digital pictures or snapshots that are pre-captured and can be transferred by means of e-mail or saved on a joint server. It is a simple technology that is cost effective and requires minimal maintenance; the images are tiny and can be stored and managed with ease. There can be certain disadvantages like sampling error, restricted fields for observation, deficiency of remote controls, and requirement of trained personnel for selecting proper diagnostic fields; it can be laborious as well to acquire the images [59–61]. With WSI, there is digitization or scanning of glass slides for producing high-resolution digital slides which permits pathologists to view the whole sample at different magnification ranges. WSI is highly appropriate for *telepathology* as the digital slides have high resolution with user control of observation and magnifications. The disadvantages include greater cost of acquisition and maintenance, the longer time for slide scanning, necessity for internet with large bandwidth and storage problems due to the huge sizes of images generated [62]. In non-robotic telemicroscopy, there is real-time conduction of live images to the pathologists by means of video calling i.e. employing Zoom®, Facetime®, etc., with no command over the images, whereas robotic telemicroscopy allows pathologist's control over the live display. Approach to the full slide, user command over microscope and picture for the fields and magnifications, quality images with prompt driving speed are the benefits of robotic *telepathology* while greater costs of the technology, acquisition and maintenance along with high bandwidth needs are the drawbacks [5]. Through such platforms, *telepathology* options are also available in sub-Saharan African countries [63, 64].

Consultation pathology is often considered as the perfect digital pathology application. However, H&E (Hematoxylin and Eosin) staining slides together with Formalin-Fixed Paraffin-Embedded tissue blocks are frequently referred to for second opinion as cases require rework for further immunohistochemical stains or molecular evaluation. Also, consultants might desire to have the slides stained in their laboratories as established and uniform work-up can be of value in complicated cases. Further concerns include quality of the images, accurate calibration of digital slides and technical interoperability between digital pathology systems. The digital consultation pathology technically requires a vendor-independent board to review slides of different backgrounds. A Dutch setting with a platform for exchanging WSI for teleconsultation, and virtual expert panels has been reported [65].

Digital pathology in education

Medical education widely uses digital pathology, and its employment is quite simple. The specific digital microscopes used for presentation can facilitate the slide reviewing activity by live video streaming for giving perception about the histopathological assessment approach for trainings. Digital images can be annotated and accessible for self-and remote-study; incorporated

in presentations & used for examination [66]. Therefore, via medical teaching, the pathologists come to first contact with digital pathology [67]. There is evidence showing that the medical students favor the WSI system-based education over the light microscope and slide-based mode [68]. The WSI approach is more interactive, user friendly, and helps collaborating faculty and students [69, 70]; hence, virtual microscopy is being employed effectively in various varsities globally. Furthermore, disassembling light microscopy labs is in vogue, as demonstrated by the pathology teaching model at the University of Arizona [71]. In teaching, digital pathology is free from medico-legal requirements.

Digital pathology in research

Digital pathology is creating substantial revolutions in oncology, displaying accuracy particularly for malignancies of breast, lung, skin, and lymphomas [72]. Moreover, the phenotypic information in histopathology pictures can be employed for the monitoring of underlying mechanisms leading to disease progression and patient survival outcomes. As a vital addition to machine learning, digital learning has become a leading approach to analyze and interpret histology images [73–77]. The period of computer science spatial dataset exploration in 1990s gave rise to the modern software systems and systems for WSI data management, query, and observation procedures. The first Virtual Microscope software employed the Active Data Repository (ADR) system that was developed by the Saltz group for spatially retrieved data and producing output data at variable magnification extents [33]. This prototype approach was then advanced to uphold data caching, prefetching, assistance for instantaneous queries from several clients, and precomputed picture pyramids [78, 79]. A follow-on system utilized a distinctive backend design known as DataCutter. Both the DataCutter and ADR system were also tailored for supporting picturing as well as analyses and vision of three-dimensional (3D) pictures acquired from sequential segments [80, 81]. High profile and flexible software e.g. the ADR system, DataCutter [82], Hadoop geographic information system (GIS), [83] and SPARK GIS [84] were often used for applications like interpreting 3D pathology microanatomic objects but in subsequent years, various software have been established for supporting multiresolution 2D dataset traversal. It was found in several cases that support was needed to pan and zoom multi-resolution 2D datasets signified by picture pyramids. Keyhole EarthViewer (obtained by Google and incorporated into Google Earth), Zoomify, Lizardtech (also called Extensis), GeoExpress, and Microsoft's Seadragon technology are pioneer instances of such kinds of systems that are persistently evolving [26]. The US has been very active in digital pathology research, with the top most 10 publishing organizations. Active research topics related to digital pathology focus molecular, immunological, pharmaceutical, biological, psychological, histopathological, surgical pathology, education, and deep learning areas. The digital pathology-associated studies can be split into two main areas, globally: [1] WSI's verification and optimization and [2] AI's application and development in digital pathology. Established on the developments of computer technology and machine learning model, recently, the investigation outcomes for deep neural network technologies as per these two categories have been more focused. Deep neural networks perform robustly in quality extraction and image analysis, providing latest research map to improve digital pathology-assisted diagnosis; here the research hotspots exist as per recent reports [71]. Moreover, computational pathology (CPATH) uses a wide range of computational techniques such as machine learning (ML) and deep learning (DL) to examine patient specimens in order to investigate disease. Both ML and DL are examples of AI [85]. An AI-aided digital image analysis platform (Pathronus) was explored by Bencze et al. and the accuracy of the techniques was evaluated on subsequent tissue sections via comparison of statistical significance between groups to quantitative fluorescent IHC reference data. It was observed that AI-aided software can detect notable cells, differentiate organelles, nuclear counterstaining and protein-specific chromogenic labeling, thereby providing a practical and precise option instead of using the semi-quantitative scoring system [86]. For the automated detection of cancer in prostate biopsies, FDA recently approved the first AI-based prostate cancer detection software named Paige Prostate in 2019. This AI tool can assist in standardizing the Gleason score for prostatic cancers and other tumor scoring criteria [87].

For colorectal malignancy, microsatellite instability (MSI) is a helpful biomarker when immune-therapeutics are used [88]. A confrontational network-based, multiple-bias-rejecting deep learning approach to predict MSI from tissue microarray was reported by Bustos et al. in colorectal malignancy. The procedure was succeeded and validated on 1788 cases from EPICOLON and HGUA. It was claimed to be the first for incorporating multi-bias ablation procedures in the deep learning design of "digital pathology" and the foremost to utilize tissue microarray to predict MSI. The investigators noted that the procedure united a tissue-type classifier component for selecting required regions and a confrontational training-based multiple-bias rejection procedure. The attributes realized from the bias ablation method were largely discriminatory for the MSI prediction assignment with minimum statistical mean reliance on bias [89].

Ki67 is a biomarker with prognostic and predictive value in breast carcinoma [90]. In a study by Boyaci et al., 4 algorithms were built independently by use of the open-source digital image analysis platform (QuPath) in accordance with the Ki67 guideline of the International Ki67, in Breast Cancer Working Group (IKWG). The researchers studied reproducibility among pathologists and assessed the prognostic capability of the platform. This study was declared as the first individual validation of the IKWG guideline with numerous observers. It was exhibited that efficient reproducibility can be attained among pathology experts using IKWG automated Ki67 scoring guideline, getting intraclass correlation coefficient values identical to the ones in the IKWG research [91].

Currently used techniques for histological computation are operator and organ specific. Courtoy et al. developed a less operator-dependent, and tissue-transposable digital procedure for fibrosis analysis. This procedure includes a novel algorithm for more precise and sensitive finding of picrosirius red-stained collagen fibers, a computer-assisted division of histological arrangements, and an innovative, automatic morphological sorting of fibers on their compactness. This algorithm was shown to be more precise than conventional filtering, applying the elementary color components (red–green–blue) for picrosirius red detection [92].

A multicenter study with 156 cases having chronic liver disease was reported by Marti-Aguado et al. [86]. The link between digital pathology assessment and related pathologists' grading scores to evaluate hepatic necroinflammatory action was studied. Digital WSI analysis was performed based on IHC color (CD45+) and morphological characteristics to determine staining intensity areas (I-score) and clusters of staining intensities (C-score). Both I-score and C-score raised with inflammation grade and fibrosis stage, displaying a good correspondence with scoring via pathology experts. These scores worked better than other digital pathology algorithms, revealing the significance of morphometric estimation [93, 94]. It was established for hepatic necroinflammatory action that digital pathology grants an automated, quantitative, and morphometric estimation; it may potentially be helpful to pathology experts assessing chronic liver disease biopsies [95].

The clinical, histopathological, and genomic data are being integrated increasingly by use of AI and machine learning tools [96]. Big data was obtained from 1990 to 2020 by Moran-Sanchez et al. from the Clarivate Analytics Web of Science database. 525 documents were evaluated by document kind, study field, source title, institution, and state. To conduct scientific mapping investigation, SciMAT and VOSviewer software packages were used, and the United States and China were noted as the most productive countries. This investigation focuses on the incorporation of digital picture analysis and genomic sequencing in non-Hodgkin's lymphoma, chemotherapy response prediction, and the validation of novel prognostic models. It was further reported that these results not only plot future clinical and research paths for the pathology area, but also encourage collaborations and boost funding shares for public organizations [97]. One of the main obstacles to the use of AI in clinical practice is the fear of the workflow change. The somewhat ambiguous issue of AI algorithm performance thresholds is partially liable for this, as is the lack of explicability. Although there is evidence of reduced error rates and enhanced performance when DL-based model predictions are combined with pathologist diagnoses, there is significant skepticism about completely replacing human evaluation with machine assessment. Whether there is a real reduction in the overall turnaround time is another crucial question that must be answered. Moreover, diminished capacity to directly manage diagnostic workflow and the ambiguity around the degree of accountability given to pathologists, when reporting utilizing AI, must also be addressed [87].

Conclusion

Grander use of digital pathology is expected in the next 2 decades, thus increasing the pathologists' capabilities for patient care. The deployment of rational paths for validation, classifying, and exploring pathology imaging biomarkers incorporated in clinical decision-making method will be a significant pathology informatics input to precision medicine. It is very important to understand the relationship between morphology and molecular mechanisms for successful research aiming practically all major diseases. Digital pathology can enable many of such research. Many investigators have built and displayed a rich set of approaches like deep learning to carry out quantitative microscopy analyses. To manage this vision practically, for clinical work and research, it is vital to create and adopt setup for scanning, cataloguing, and storing enormous collections of WSI. Though the model of virtual microscope is very old, the implementation of "digital pathology" informatics devices in clinical practice is an obvious work under development and advancement.

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Authors' contributions
Shamail Zia (SZ) wrote the manuscript. Isil Z. Yildiz-Aktas (IA) created the tables and added references. Fazail Zia (FZ) worked on the illustrations and references. Dr. Anil V. Parwani (AP) reviewed the entire manuscript, decided on the title, assisted in refining the content, created illustrations, and wrote the introduction.

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