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The advent of digital pathology: A depth review

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Abstract
Digital pathology is an image based information environment which is enabled by computer technology that allows for the management of information generated from a digital slide. Digital pathology is enabled in part by virtual microscopy, which is the practice of converting glass slides into digital slides that can be viewed, managed, shared and analyzed on a computer monitor. Growing demand for accurate and reliable diagnosis along with issues of patient safety is pushing traditional diagnosis towards an update. Over the last two-three decades the field of optics has made great advancements in the form of ever-improving optics and digital cameras. Persistent gains in computer processing power, data transfer speeds, advances in software and cloud storage solutions have enabled the use of digital images for a wide variety of purposes in pathology. High-resolution images are generated from whole glass slides which can be analyzed and managed using software. Digital Pathology has become a useful and valuable tool in clinical and research pathology. A fully digital workflow would mean that image analysis could be performed on any pathology image without the need for specific image preparation. Image analysis software is already widely available, and has FDA regulatory approval. The digital decade will likely redefine how pathology is practiced and the role of the pathologist.

Keywords: Whole slide image, scanner, Z- stacking, virtual microscopy, image analysis

1. Introduction

Pathology, as with most medical specialties, is currently facing a growing demand to improve quality, patient safety and diagnostic accuracy because there is an increased emphasis on sub-specialization. The ever advancing practice of histology and cytology is demanding the wide use of human perceptual and cognitive processes. The changing diagnostic scenario coupled with factor like economic pressure to consolidate and centralize diagnostic services is driving the development of systems that can optimize access to expert opinion and highly specialized pathology services [1].

The field of optics has made great advancements over the last two-three decades in the form of advance optics and digital cameras. Since the 1990s, persistent gains in computer processing power, data transfer speeds, advances in software and cloud storage solutions have enabled the use of digital images for a wide variety of purposes in pathology [2].

High-resolution images are generated from whole glass slides which can be analyzed and managed using software [3]. Hence, these digitized slides or virtual slides can significantly optimize the workflow of the pathologist [4]. The still or dynamic images captured with microscope mounted cameras are transferred by the means of network connections to remote sites to be assessed by another pathologist, commonly called telepathology as second opinion and frozen section consultations.

Digital pathology has the potential to transform the practice of diagnostic pathology. However the way radiology has been revolutionized by the introduction of digital imaging over the past 30 years, despite the promise of digital pathology to offer similar benefits, its uptake for diagnostic pathology has been slow [5]. The present review attempts to analyze the present scenario, scope and limitations of Digital Pathology.

2. The Digital Pathology workflow

Standard Digital Pathology workflow begins with the procedure performed on the patient, most commonly a biopsy or a resection. The material is then sent to a pathology division associated by an order (ideally in a digital way), along with appropriate clinical information.

Once received, samples are registered in the local laboratory information system on or before undergoing the necessary procedure in order to be managed to glass slides. Then, the glass slides are observed under a light microscope in order to create report.

Switching the current workflow to a fully digital one would require scanning of glass slides prior to sending them to pathologists, which can add cumulatively to the overall diagnosis time. This can be concentrated by using speed scanners and integrating the scanning with the cover slipping and the staining method (Fig 01). Thus, digital pathology workflow is incorporated into the institution's overall operational environment [6].

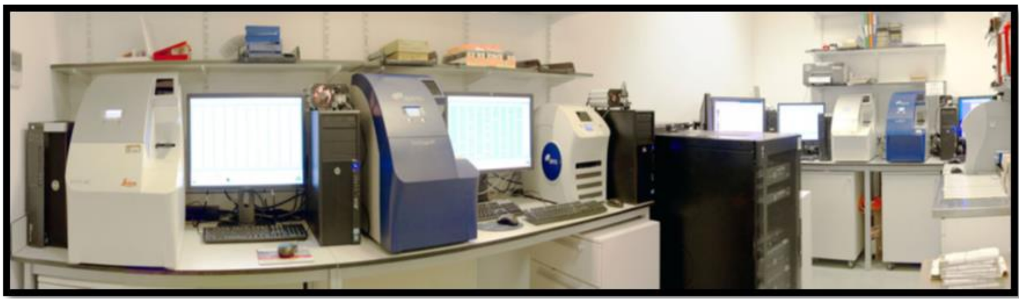

Fig 1: A typical arrangement of slide scanners and servers required for full digitization of a laboratory workflow

2.1 Digital Imaging Process

A digital image is represented in a computer by a two-dimensional array of numbers, each element of which represents a pixel (picture element). A digital image composed of pixels represents an analog image converted to numerical form using ones and zeros (binary) so that it can be stored and used in a computer. The digital imaging process includes four key steps: (1) image acquisition (capture), (2) storage and management (saving), (3) manipulation and annotation (editing), and (4) viewing, display or transmission (sharing) of images. Before digital images become widely used for routine clinical work, standards are needed and the entire imaging process needs to be validated [4].

Multiple types of devices are used to acquire digital images (Fig. 02). Microscopic digital images can be static (still images), viewed live (real-time robotic microscopy), or viewed after scanning of the glass slides (whole slide digital imaging (WSI) or virtual microscopy [3]. Efforts are underway to standardize the process of acquiring, storing, and displaying digital images in pathology similar to radiology [7].

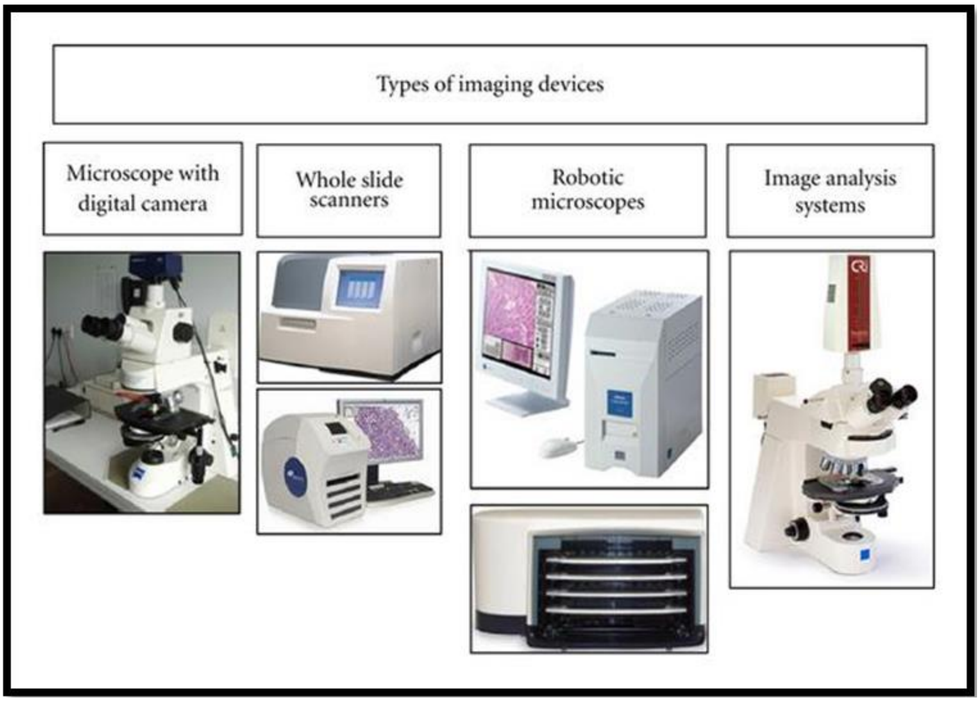

Fig 2: Types of imaging devices

Whole Slide Digital Imaging

In the last decade, digital imaging in pathology has been significantly impacted by the development and application of whole slide imaging (WSI) technology [8]. The automated WSI scanner (Fig. 03) is a robotic microscope capable of digitizing an entire glass slide, using software to merge or stitch individually captured images into a composite digital image. The critical components of an automated WSI device (system) include the hardware (scanner composed of an optical microscope and digital camera connected to a computer), software (responsible for image creation and management, viewing of images, and image analysis where applicable), and network connectivity.

All the functions are regulated by software which include control of illumination, focusing of slide, change of objective, continuous movement of stage in X and Y axis, photography of each field under the objective and production of composite whole slide image [9].

The scanner takes pictures of every field of the slide on the moving stage. Thus every part of the slide is photographed and thousands of pictures are taken. Then these pictures are stitched and blended together by the software there by producing a composite image alternatively referred as whole slide image. This image can be viewed on computer screen, laptops and android mobile phones just as a glass slide is seen under the microscope. The viewer can see the image in different magnifications and all areas of the slide can be viewed [9].

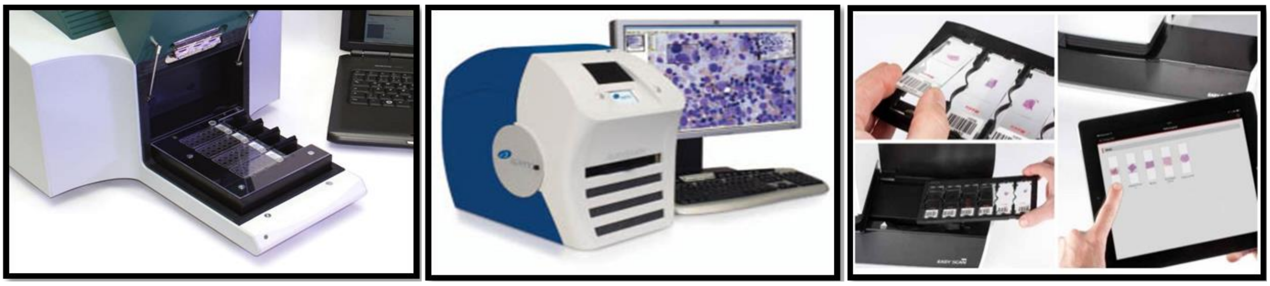

Fig 3: Digital Slide Scanner

Whole slide imaging technology has evolved to the point where digital slide scanners are currently capable of automatically producing high-resolution digital images within a relatively short time. The virtual image may represent an entire glass slide or a user-selected area of the glass slide, and is often referred to as a whole slide image or digitized slide. Upon retrieval of the digital file, the captured image of the slide can be viewed on a computer monitor without the use of an actual microscope. The software interface used to view digital slides simulates the operation of light microscopy. Several types of WSI scanners have been developed by vendors, all capable of producing automated, high-speed, high-resolution whole slide digital images [10].

Some workers [11] in their study compared whether images captured with optical microscopes and scanners provided better image quality in terms of contrast, color, and stains. They digitized biopsies (breast, prostate) and cytology (effusion) slides prepared with different stains using a robotic microscope and a whole slide scanner. Images were acquired at 40X magnification in bright field without compression. Quantitative evaluations employed several perceptual features such as color decomposition, intensity adaptation (dependent on luminance), and contrast, among others. Subjective (perception) testing involved six expert observers who scored microscopy and scanned images. These investigators only evaluated a limited number of images (image fields) for their study when one considers that a digitized slide is made up of more than 1,000 images. Nevertheless, the results from this study indicate a slight preference for the WSI scanner over the microscope in terms of better image quality. The main cause for subjective discrepancies between the microscope and scanner was related to focusing, with color distortions indicated to be a secondary problem.

2.3 Image analysis

Image analysis has long been promised as a way to remove the subjectivity and variability in pathology diagnosis. A number of image analysis tasks in DP involve some sort of quantification (e.g., cell or mitosis counting) or tissue grading (classification). These tasks invariably require identification of histologic primitives (e.g., nuclei, mitosis, tubules, epithelium, etc.) [12].

A fully digital workflow would mean that image analysis could be performed on any pathology image without the need for specific image preparation. Image analysis software is already widely available, and has FDA regulatory approval in the USA, for the quantification of nuclear markers such as oestrogen receptor or cell membrane markers such as human epidermal growth factor receptor HER2/neu. An increasing number of laboratories are incorporating such software into their workflow [13]. An analysis of one such system demonstrated that semi-automated HER2 quantification could reduce inter-observer variability but raised concerns over the false positive rate and the potential for over-treatment [14]. In this setting an image analysis may be best placed in helping resolve equivocal HER2 measurement or in prompting pathologists to submit these specimens for a second opinion or in-situ hybridization [14].

Automated image analysis has often been targeted at tasks associated with high inter and intra observer variability. Workers [12] also showed that the estimation of tumour cell percentage in lung cancer was subject to marked inter-observer variability. Recent advances in targeted therapies for lung cancer requires accurate measurement of epidermal growth factor receptor EGFR and Anaplastic lymphoma kinase (ALK) mutations in tumour tissue, and the interpretations of these tests can be altered by the estimated tumour cell percentage on a glass slide [14]. An image analysis system that is capable of automatically measuring tumour area and calculating percentage of tumour cells and tumour nuclei was designed and validated by [15]. This system exhibited better concordance than estimation by eye when compared with manually counted tumor cells. Accurate DNA extraction based on this method can enhance molecular testing by reducing false negative rates and therefore give patients access to molecular therapies that may have otherwise been denied. In the study hand counting of tumor cells took an estimated 100 hours per slide compared to 3 minutes using automated image analysis [15]. The study clearly demonstrates the efficiencies that targeted image analysis techniques can bring to clinical practice. With more molecular therapies becoming available across multiple classes of cancer, accurate analysis of tumour mutation content is essential to ensure patients are correctly stratified to receive these treatments [16].

Simpler diagnostic tasks such as quantifying fat in the liver, which is prone to significant subjectivity, can easily be performed reliably and accurately by image analysis tools, and it has been asserted that the time for manual evaluation of hepatic steatosis has passed [17].

However, the widespread adoption of image analysis in diagnostic pathology faces significant barriers including the need for more robust standards for validation of image analysis, and the development of systems that facilitate pathologist workflow when incorporating image analysis into a clinical case.

While there have been a number of papers in the area of computational image analysis of DP images for the purposes of object detection and quantification in the last few years, there appear to be two main drawbacks to existing approaches [16]. First, the development of task specific approaches tends to require long research and development cycles. For example, to develop a nuclei segmentation algorithm, one must first understand all of the possible variances in morphology, texture and color appearances. Subsequently, an algorithmic scheme needs to be developed which can account for as many of these variances as possible while not being too general as to result in false positive results or too narrow as to result in false negative errors. This process can become quite cumbersome as it is often infeasible to develop an algorithm by deductive reasoning and thus an extensive repetitious trial and error approach needs to be undertaken [18].

3. Validation studies

Validation, in the context of new technology or instrumentation, refers to a process that aims to demonstrate that the new method performs as expected for its intended use and environment prior to its application for patient care. The last decade has seen an abundance of validation studies in digital pathology mostly examining concordance between a diagnosis made on glass and digital images. The College of American Pathologists (CAP) [8] and the Digital Pathology Association (DPA) [19] has published guidelines detailing the design and execution of validation studies. Both guidelines agree that studies should evaluate the entire WSI system in the intended practice setting and specify proper training and record keeping of the process.

One of the largest validation studies to date involved the glass and digital slide review of over 3000 cases [20]. The study was adequately powered and followed the DPA and CAP guidelines on study design. Complete concordance between glass and digital slide diagnosis was seen in 97.7% of cases with less than 1% of non-concordance being clinically significant. Many validation studies comment on the limitations of digital pathology including difficulties viewing small objects, lack of three dimensional (“z stack”) information, and possible image quality issues in some clinical areas. Validation is recommended to determine that a pathologist can use a WSI system to provide an accurate diagnosis with the same or better level of ease as with a traditional microscope and without interfering artifacts or technological risks to patient safety.

3.1 Applicability & Acceptance of Digital Pathology

Digital pathology is currently being used for a wide spectrum of clinical applications including diagnosis of frozen sections, primary histopathological diagnosis, second opinion diagnosis, subspecialty pathology diagnosis, education, competency assessment and research [21].

Virtual microscope systems are widely used and are trusted to provide high quality solutions for tele-consultation, education, quality control, archiving, veterinary medicine, research and other fields [22].

Digital slides offer several advantages over glass slide review in terms of fidelity of the diagnostic material, portability, ease of sharing and retrieval of archival images, and ability to make use of computer-aided diagnostic tools (e.g. image algorithms). Image analysis tools can automate or quantify with greater consistency and accuracy than light microscopy [23].

3.1.1 Reduced Patient identification errors

Patient identification errors occur in up to five percent of all cases processed in the pathology laboratory [24]. Many of these errors occur at accession or during copying of patient details between request forms, cassettes and slides. A laboratory system employing end to end digital identification (for example with barcodes or radio frequency identification tags) would remove these manual steps to a single identification, ideally at specimen retrieval (i.e. at the time of biopsy or surgery).

3.1.2 Saves on time

In a totally digital pathology department the journey of a glass slide would finish in the laboratory after scanning. Digital slides are then available to view at any workstation. This saves time spent by pathologists organizing, searching for and moving slides, processes that place demands on a pathologist’s time and attention [25]. One time and motion study of a digital workflow claimed opportunities to improve pathologist workflow releasing up to 13% of every pathologist’s time [26].

Anyone who uses a microscope potentially benefits from digitized pathology images. Until the advent of this technology, histological slides and photographs the primary ways images seen under a microscope lens could be shared with others.

3.1.3 Efficient Management & Sharing

A digital workflow also creates opportunities for better management of a pathologist’s workload. Digital dashboards can provide information such as the number of cases to be reported, the progress of immunohistochemistry and special stains, and the assignment of specific cases to trainees. In addition the pathologist could assign cases to work lists such as teaching sets or multi disciplinary team meetings. These are areas where efficiency improvements are cited in digital radiology [27] but similar improvements have not yet been quantified in pathology. One published example of a digital pathology dashboard was in a haemato pathology setting [5].

The digital pathology workstation offers benefits in quality and efficiency. Digital slides can easily be annotated and regions of interest identified and linked to the written report. The report itself can be constructed using voice recognition software, a technology that has improved both turnaround time and report accuracy in radiology [27].

Digital Pathology eliminates some of the issues associated with sharing slides such as the degradation of samples and inability to share samples of live cells. In addition to preserving quality, specimen images can be transferred to colleagues in a timely fashion [5].

3.1.4 Increased Accuracy

Nowadays most of the slide viewing software are allowing calibrated measurement of various important features such as distance to a surgical margin and tumour dimensions. In one comparison of digital versus glass slide review of prostate cancer core biopsies, a greater inter-observer agreement in length of affected core was found when pathologists used digital measurement [5].

In addition, utilizing digital images for teaching and consultation can be more effective for storage purposes and have easier accessibility as compared to traditional print photographs and slides [28].

4. Use in Telepathology

Telepathology is a term coined in the 1980s to describe remote pathology diagnosis using digital image transmission, after the first clinical uses of telepathology in the late 1960s [29]. Such telepathology systems are confined to live transmission of a digital image of part of a pathology slide, and only a small proportion of overall laboratory workload is examined digitally with these systems, usually where remote diagnosis is essential (such as intra operative frozen sections or second opinion practice). Components of a telepathology system include a digital imaging workstation to acquire images, telecommunications network to transmit images, and monitor or screen to remotely view digital images.

Telediagnosis is the most prominent application as it offers the advantage of exchanging histologic and cytologic images for diagnosis and consultation, especially at remote institutions where pathologists are not always able to be on-site and in cases in which a second opinion by an expert is required [30].

Currently, when a difficult case is encountered during daily practice, this is carried out by sending the consultant the glass slides or paraffin blocks by courier or ordinary mail, but consultation often takes too long. Telepathology has been considered, in many veterinary and human cases, an alternative approach.

5. Barriers for Worldwide Adoption

The implementation of digital pathology is not without challenges. None of the four steps required for the process of digital imaging have been standardized which is needed for routine clinical work [31].

While the potential benefits can be significant, there are questions and concerns about the technology that pose barriers to the adoption of whole slide imaging (WSI). Technical concerns pertaining to digital slide scanning technology, e.g., the ability to scan slides at high magnification and multiple focal planes (the z-axis), image quality, image access speeds and computer hardware limitations for processing and storing extremely large image files are realized [32].

Of greater concern are the regulatory issues. How will regulation be applied to care models in which components of WSI are purchased and operated by different entities (e.g., image capture in one facility, image hosting and manipulation in a second and interpretation in a third facility).

Standardization is needed for pre imaging steps (eg, consistent staining, optimal slide preparation without artifacts), image acquisition (eg, optimal resolution, number of z-stacks, and interval space), post imaging processes (eg, color calibration), and sharing/transmission of digital images (eg, interoperable file formats, vendor agnostic viewers). Albeit slow, efforts with Digital Imaging and Communications in Medicine (DICOM) are underway to help standardize the use of WSI in pathology [33].

Additionally, the whole pathology laboratory system must communicate effectively with other hospital systems such as electronic specimen labeling and the electronic patient record.

6. Acceptance by pathologists

A pathologist viewing digital slides may defer to a glass slide for a number of reasons including unfamiliarity with the viewing software, network latency, a perceived inefficiency of digital diagnosis and a higher level of confidence with light microscope (LM) diagnosis [34]. Deferral has been identified as a significant issue in some studies and many pathologists feel that digital slides are too slow for routine diagnostic work. The design of a digital workstation is therefore of paramount importance in matching or surpassing the efficiency of LM diagnosis.

Workers [5] concluded that most of the observed inefficiency using this system amongst pathologists was due to a combination of several factors including: (i) the smaller field of view afforded by the digital slide system (ii) issues with the design of the software used for viewing the slides, and (iii) a lack of experience and training using digital slides with the participants. Workers [35] from central India conducted an interesting survey to give a better overall picture of the attitude of pathologists and pathology residents in India toward the spectrum of digital pathology (DP) applications and examine the perceived future direction of this technology. Maximum of 48% pathologist agreed to its use for academic purposes whereas only 24% utilized it for consultation point of view. When asked about whether DP or TP is helpful to take an expert opinion, 82% pathologists agreed over the view. About 74% of individuals in the survey agreed about the advantage of digital microscopic images in pathology. It may also identify opportunities for further education, research and software development in this field.

7. Indian Scenario

However, in India, the exact usage and applications of the technology are not very well known. There is very little data assessing the utilization of microscopic digital images in India [35].

Therefore, standardized applications of these methods are not identified or are thought to be under utilized in pathology laboratories across the country.

For digital pathology to be integrated into a clinical setting, rapid and stable scanning must be achieved. An international standard for digital archiving is also required. This includes re-working laboratory protocols and developing new scanning rules to attempt standardization of digital imaging procedures. A standardized method of obtaining, storing and sharing digital images is needed and can lead to better diagnostic techniques and consultation methods for pathology diagnosis, however, these procedures have yet to materialize.

The difficulties of implementing digital pathology technologies are greater in low-resource countries[36]. In remote areas where there is a lack of trained pathologists, real-time digital pathology and telepathology can massively increase the efficiency of image analysis in these locations, but the requirement for a high bandwidth constrains the use of this technology in low-resource countries. Where only dial-up connections are available, frequent timeouts and low quality images mean that the use of digital slides are impossible on large networks - the use of digital slides within local networks has been found to be more promising. Moreover, there are barriers in the form of high equipment cost and the limited student access to laboratory workstations for educational applications. Whilst there are clear advantages to implementing digital pathology technologies, both in high and low resource countries, many challenges still need to be overcome; the growing market for digital pathology does indicate that a universal implementation may be achieved in the future.

In spite of recent Government initiatives to improve the telecommunication facilities, and the necessity that is obviously there, digital and telepathology is yet to permeate into everyday activities for pathologists in India. The reasons for this are manifold. The lack of agreement on a preferred technology and the lack of uniform standards acceptable to the pathology community have been the major factors responsible for the underdevelopment of telepathology all over the world [37] (Baruah, 2005). One major drawback in rural India is the sub-optimal preparation of slides. Images for remote diagnosis, after all, can only be as good as the original slides. A relative reason for the failure of telepathology consultation and the inability of experts to come to a conclusive diagnosis, apart from sub-optimal images, is the absence of a rapport between the sending pathologist and the consultant pathologist.

8. DP in Veterinary Science

Several Veterinary colleges worldwide have integrated virtual microscopy in their curriculum, and some diagnostic histopathology labs are switching to virtual microscopy as their main tool for the assessment of histologic specimens. Current digital pathology technologies have their potential in all fields of veterinary pathology (ie, research, diagnostic service, and education). A future integration of digital pathology in the veterinary pathologist's workflow seems to be inevitable, and therefore it is proposed that trainees should be taught in digital pathology to keep up with the unavoidable digitization of the profession [16].

9. Conclusion

Pathology is the motor that drives healthcare to understand diseases. While it does the job via the same methods that it has been using for the last 150 years, it’s time to change. Digital technologies could push the field into becoming more efficient and more scalable. They could transform the job of pathologists into a more creative and data-driven profession while allowing patients to receive diagnoses faster and more accurately.

Digital pathology is a disruptive technology as it changes the core of processes in pathology. It will enable better primary diagnostic, help pathologists easily access digital images from different sites, and create a platform for better multidisciplinary teams. Also, this technology has a huge potential for educating new generations of pathologists. But of course, there are challenges too. Standardization and regulation of digital pathology isn’t at the point where it should be, and pathologists still have certain problems with adopting this new technology. And we can’t ignore the fact that these digital pathology systems are still very expensive. But as market grows, these systems will be much more affordable for medical institutions around the world. It seems that adoption of digital pathology systems is an imminent process.

The goal of pathology digitalization isn’t to replace pathologists with computers, but to use computers for menial and time-consuming tasks. This way, pathologists will have more time to spend on making better diagnosis, and for a lab this means more time for improving planning and sample tracking.

Current progress concerning these and other issues, along with improving technology, will no doubt pave the way for increased adoption over the next decade, allowing the pathology community as a whole to harness the true potential of WSI for patient care. The digital decade will likely redefine how pathology is practiced and the role of the pathologist.

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