Implementation of Whole Slide Imaging for Clinical Purposes

Issues to Consider From the Perspective of Early Adopters

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● **Context.**—There is growing interest in the use of digital pathology, especially whole slide imaging, for diagnostic purposes. Many issues need to be considered when incorporating this technology into a clinical laboratory. The College of American Pathologists (CAP) established a Digital Pathology Committee to support the development of CAP programs related to digital pathology. One of its many initiatives was a panel discussion entitled "*Implementing Whole-Slide Imaging for Clinical Use: What to Do and What to Avoid,*" given for 3 years at the CAP annual meetings starting in 2014.

Objectives.—To review major issues to consider when implementing whole slide imaging for clinical purposes as covered during the panel discussion.

Design.—The views expressed and recommendations given are based primarily on the personal experience of the authors as early adopters of this technology. It is not intended to be an exhaustive review of digital pathology.

Results.—Implementation is best approached in phases. Early efforts are directed toward identifying initial clinical applications and assembling an implementation team. Scanner selection should be based on intended use and budget. Recognizing pathologist concerns over the use of digital pathology for diagnostic purposes, ensuring adequate training, and performing appropriate validation studies will enhance adoption. Once implemented, the transition period from glass slide to image-based diagnostics will be associated with challenges, especially those related to a hybrid glass slide–digital slide workflow.

Conclusions.—With appropriate preparation, planning, and stepwise implementation, whole slide imaging can be used safely and reliably for frozen sections, consultation, quality assurance, and primary diagnosis.

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Interest in the use of digital pathology in clinical practice continues to grow. Digital pathology is being used for clinical work such as telepathology, education, and research.[1] Telepathology is defined as the transmission of pathology images and patient information for a variety of clinical applications including frozen sections, consultation, quality assurance, and primary diagnosis.[2] These activities can be performed by a number of modalities such as sending of static images by email, real-time video microscopy, static-dynamic robotic microscopy, whole slide imaging (WSI), and hybrid devices with robotic microscopy and WSI capabilities. Whole slide imaging is based on the creation of high-resolution digitized replicas of glass slides, using a slide scanner.[3] The resulting images, or virtual slides, are manipulated by software that simulates the experience of a light microscope and allows viewing of digital slides over a broad range of magnifications. Depending on the clinical application, there may be advantages or disadvantages associated with WSI as compared to other digital pathology modalities.[3,4]

There is a growing emphasis and public expectation on improving quality in pathology. In part, this can be achieved by establishing health care networks within which challenging cases can be readily shared between pathologists. Telepathology based on WSI has an undeniable value proposition in this regard, enabling enhanced access to subspecialty expertise without the need to physically transport glass slides. This can reduce long-term costs, avoid the risk of losing or breaking valuable patient slides during transport, eliminate superfluous paperwork, improve turnaround times (TATs), and effectively distribute workload across a group of pathologists who may work in different locations. Digital sharing of cases can also provide

Table 1.   Commonly Cited Barriers to the Adoption of Whole Slide Imaging for Clinical Use
Cost: hardware, software, information technology support/infrastructure and maintenance
Pathologist perception of inferior performance compared to light microscopy
Lack of standards and/or best practice guidelines
Regulatory issues: lack of US Food and Drug Administration approval in the United States
Medicolegal liability, licensure, and credentialing issues
Absence of defined professional billing codes or business models

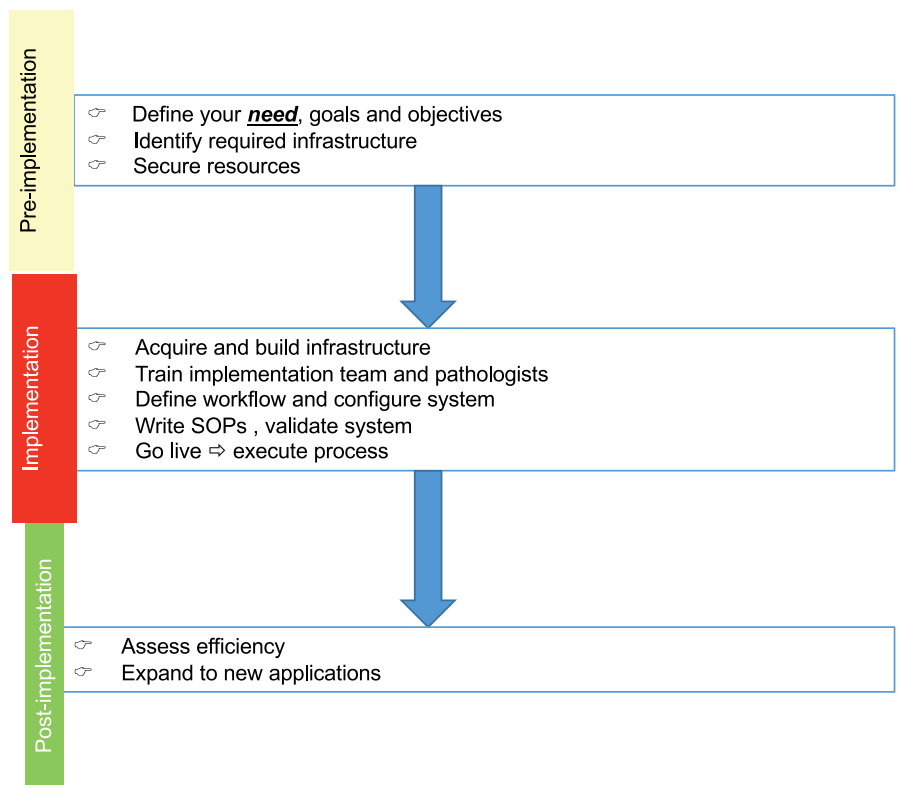| Table 2.   Issues to Consider When Implementing Whole Slide Imaging (WSI) for Clinical Purposes |
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| Applications of WSI in patient care: where to start and how to assemble an implementation team |
| Strategy for selecting a WSI scanner |
| Resources required to operate and maintain a clinical digital pathology program |
| Validation of the system to be used |
| Strategies to encourage adoption of WSI by pathologists |
| What to expect after going live, based on the experience of early adopters |

support to solo or small-group pathology practices in remote locations, as well as facilitate the development of personal health information portals allowing patients to access their complete medical record, including their pathology slides.

Telepathology has had its share of barriers to adoption. Table 1 lists some of the most commonly cited barriers associated with WSI in particular. However, it is important to note that many of these barriers have been or are being addressed in the form of guidelines and peer-reviewed literature. In recent years, several important guideline documents on the validation and implementation of WSI systems for diagnostic use have been developed by professional bodies such as the College of American Pathologists (CAP), the Canadian Association of Pathologists, the Royal College of Pathologists in the United Kingdom, the Royal College of Pathologists of Australasia, and the American Telemedicine Association.[5] These documents, while not standards of care, provide an important resource for new adopters of this technology. It is anticipated in the near future that these guidelines will be revised on a regular basis to account for advances in technology, changing regulations, and emerging literature describing the experiences with WSI (good and bad) in diverse practice settings. This body of information will contribute to the safe evolution of this technology as it applies to clinical use. Regulatory approval is required by WSI vendors in order to market these systems for clinical use, most notably primary diagnosis whereby a first diagnosis intended to guide patient care is established solely by review of digital images. Whole slide imaging systems have already received approval for use as a diagnostic tool for all purposes, including primary diagnosis, in Canada and Europe.[6] However, such approval is still pending in the United States.[7] As of the time of writing, the US Food and Drug Administration (FDA) designated WSI systems as Class III medical devices with respect to primary diagnosis, placing WSI in the highest risk category for patients. Although the Class III designation may be changed, it is based on the premise that insufficient information exists in terms of general controls to establish safety and effectiveness. This requires vendors to complete statistically rigorous premarket approval clinical trials. The FDA began official dialogue with vendors and stakeholders on the regulatory pathway for WSI in 2009. Following a period of relative silence for 5 years, the FDA released a list of nonbinding draft recommendations to assist vendors in the technical performance assessment of WSI devices in 2014.[8] In 2015, the FDA released details on an acceptable premarket approval study design into the public domain,[9] the details

of which are summarized here. The study design requires 4 separate reading sites with 1 WSI scanner and 4 reading pathologists per site. Approximately 2000 cases are to be retrospectively reviewed as both digital and glass slides by pathologists who represent the intended use population. Study sponsors are encouraged to include rare or unusual diagnostic entities in the study set. Study diagnoses by light microscopy and WSI are to be compared to each other and to "truth" diagnoses given either at the time the cases were originally reported or as determined by an expert panel. The primary end-point of the study is the demonstration of noninferiority in diagnostic error rates for WSI relative to light microscopy. Assuming the completion of the clinical trials and data analysis by both vendors and the FDA could take some time, the earliest FDA approval for WSI to be marketed for primary diagnostic use will likely appear in late 2017.

In 2012, CAP established a Digital Pathology Working Group (now a committee) chaired by Eric F. Glassy, MD. The Digital Pathology Committee (DPC) comprises pathologists who have practical experience in digital pathology and are recognized thought leaders in the application of this technology for a variety of purposes. Many of the pathologists on the DPC helped developed CAP guidelines released in 2013 for validating WSI for clinical purposes. The mission of the DPC is to support the development of products and requirements that contain digital pathology applications, and to serve as a resource for the CAP public position on digital pathology applications and practice tools. With the increasing deployment of WSI technology in many pathology practices in the United States, there was a demand to educate pathologists about how best to safely and effectively implement this technology in their laboratories. One of the many initiatives developed by the DPC in response to this demand was a course entitled "*Implementing Whole-Slide Imaging (WSI) for Clinical Use: What to Do and What to Avoid.*" This course was given for 3 years at the annual CAP meetings starting in 2014. The objective of the course was to review major issues to consider when implementing WSI for clinical purposes (Table 2). The issues covered in the course are summarized herein. While most are relevant to all institutions considering the use of WSI for patient care, there are certain issues that will be unique to particular practice situations. The views expressed and recommendations given are based primarily on the personal experience of the authors as early adopters of this technology. It is not our intent to provide an exhaustive review of digital pathology. The authors acknowledge that the entire field of digital pathology, including WSI, is rapidly evolving. As such, the information given below concerning regulatory issues, vendors, workflow, and instrumentation may change within the next 1 to 2 years.

Figure 1. *Whole slide imaging implementation phases. The three phases of preimplementation, implementation, and postimplementation are listed on the left, with the major components of the implementation listed across the figure. Abbreviation: SOPs, standard operating procedures.*

Pre-implementation
- ☞ Define your ***need***, goals and objectives
- ☞ Identify required infrastructure
- ☞ Secure resources

Implementation
- ☞ Acquire and build infrastructure
- ☞ Train implementation team and pathologists
- ☞ Define workflow and configure system
- ☞ Write SOPs , validate system
- ☞ Go live ⇨ execute process

Post-implementation
- ☞ Assess efficiency
- ☞ Expand to new applications

APPLICATIONS OF WSI IN PATIENT CARE: WHERE TO START AND HOW TO ASSEMBLE AN IMPLEMENTATION TEAM

Starting the Process for WSI Implementation

The process for implementing WSI into routine practice involves more than just deploying hardware or development of an information technology (IT) infrastructure to support digital pathology. In particular, there are workflow and change management issues that need to be addressed. The importance of managerial and organizational skills when implementing digital pathology is underscored in a recent review by Meyer and Paré,[10] particularly where larger telepathology networks are being considered. A number of possible telepathology network structures exist and each one may have differing requirements in this regard.[10]

The fundamental question most pathologists or laboratory directors will face when planning the implementation of a WSI system is "where do I start?" Although there are likely many successful approaches to this question, we will focus on our approach based on our experience as early adopters. This approach incorporates several elements including various implementation phases, system components, assembling an implementation team, and developing a suitable workflow for the intended WSI application. It is our opinion that the most important first steps associated with successful implementation are the identification of 1 or more clinical needs for WSI, establishing achievable goals and objectives, and identifying a team of people who will make it happen. This should be done before a digital pathology system is purchased. It is not uncommon to find expensive WSI systems that are underused or completely unused in pathology departments. The most frequently encountered reason for this wasteful scenario is the lack of a well-developed plan to use the equipment.

Whole Slide Imaging System Implementation Phases

Whole slide imaging implementation is a dynamic process that moves through 3 phases. Figure 1 outlines these phases, which include preimplementation, implementation, and postimplementation stages. It is critical to emphasize that this process is dynamic and very much application dependent. In other words, this process will likely need to be repeated for each particular clinical use. Once WSI has been implemented for its first application, many of the processes and lessons learned will be useful for subsequent applications as they are introduced.

Preimplementation Phase

During the preimplementation phase, the need for WSI is defined and realistic goals and objectives should be set. If several needs are identified, we strongly recommend starting with the simplest use case and one that ideally will have the highest impact on your operation. There must be a critical assessment of what may or may not work in your practice setting. Consultation with colleagues who are early adopters as well as reviewing publications such as the *CAP Digital Pathology Resource Guide*[11] will be helpful for identifying required infrastructure components. These often include combinations of hardware (eg, scanners, viewing workstations, and storage servers), software, IT infrastructure (eg, networks), and implementation personnel. Before you initiate the implementation you need to secure these resources including appropriate budget and operational support.

Implementation Phase

The acquisition of a WSI system is a necessary initial step that will require vendor installation of both hardware and software. Early engagement of IT resources from your institution is recommended and is often essential during
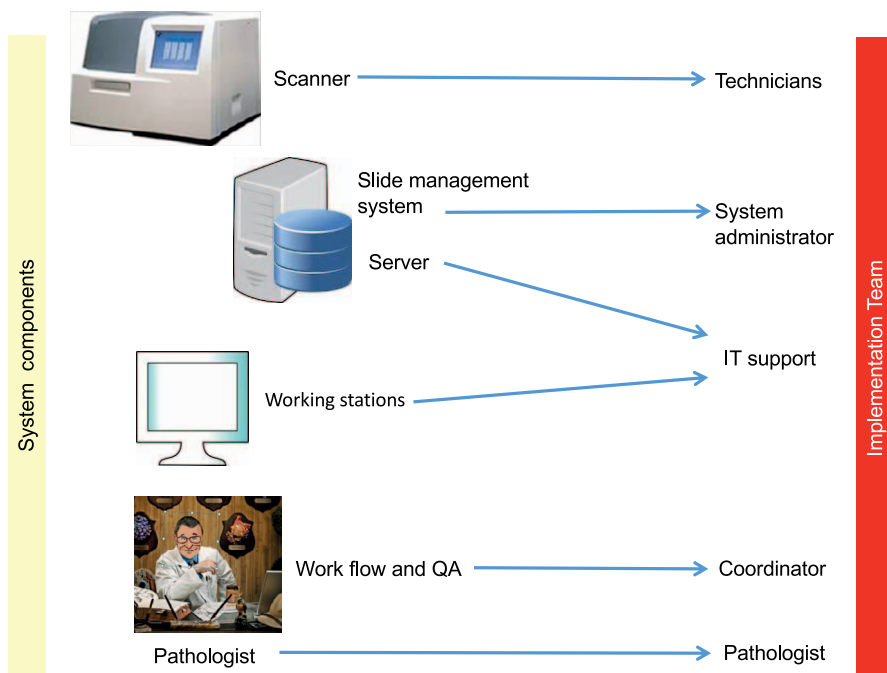
Figure 2. *System components are represented on the left side and are paired with the appropriate implementation team member on the right side of the figure. Major whole slide imaging system components include a slide scanner for image acquisition, digital slide management environment, server space, work stations, and a developed workflow. The implementation team should include technicians, system administrator, IT support, workflow coordinators, and pathologists. Abbreviations: IT, information technology; QA, quality assurance.*

setup of the system. It is recommended that a dependable maintenance contract be obtained for your WSI system. Assembly and training of scanner operators, slide management system administrators, and pathologists often occurs during this early stage or right after a WSI system is acquired. Team assembly is a major strategic undertaking that requires careful planning on the medical director's part. Training is often conducted by the vendor and it is important to document that training took place. When implementing WSI, it is critical to consider federal regulations (eg, medical licensure for out-of-state tele-pathology) and, if necessary, international law (eg, Safe Harbor Privacy Principles for global telepathology) as it relates to your intended use. In addition, you must be aware of CAP Laboratory Accreditation Program checklists for digital pathology if you are a CAP-accredited laboratory.

Once system acquisition, implementation team assembly, and training have been completed, the next step will be to define the new workflow and to write standard operating procedures for the initial WSI application(s).

Postimplementation Phase

In the postimplementation phase you will need to assess the efficiency of your system. For example, if the application is adopting WSI for tumor board use then you may need to assess efficiency on parameters such as clinical team satisfaction using surveys or impact of process modification on presentation time or preparation time.[12] Expanding to a new application requires assessment of infrastructure adequacy and often requires training of implementation personnel and defining new workflows. This process will likely be more efficient with each successive round of implementation for a new clinical activity.

System Components and Assembling an Implementation Team

Major WSI system components include the device for image acquisition (eg, the scanner), the digital slide management environment, server space, workstations, and

the workflow linking these elements together (Figure 2). The implementation team should include technicians (eg, histotechnologist), system administrator, IT support staff, workflow coordinators, and pathologists. The pathologist is the essential cornerstone for a successfully functioning WSI system. Several key elements must be kept in mind with respect to the implementation team's assignments. Having a super user is probably the most important task for a successful implementation. This role is fulfilled by a champion who could be a pathologist or medical laboratory professional who will be committed to taking full responsibility for the project. This role will require mastering a spectrum of skills that spans those of all implementation team members (Figure 3). The champion should be able to invest a significant amount of time learning the essentials of each component. A technologist may perform the slide
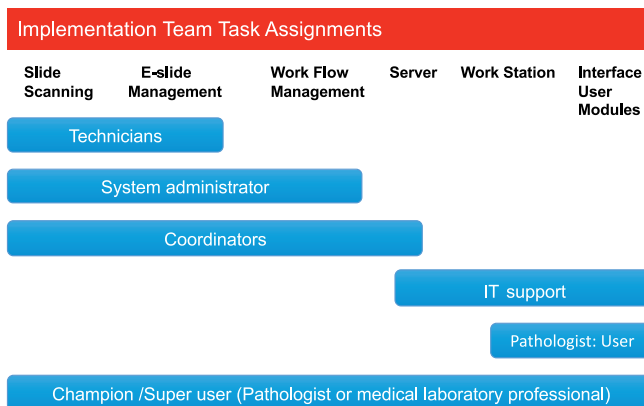

Figure 3. *This figure highlights the principal task assignments for each implementation team member where system components are represented in order across the top row. The corresponding implementation team member is assigned tasks indicated by the blue bars. Note the essential overlap in assignments between different team members, which enables continuity and efficiency in the implementation process. Abbreviation: IT, information technology.*

scanning, but should also be trained to handle other management functions of the system, including slide assignment to specific data groups and minor troubleshooting. The system administrator should act as a controller for managing data, along with appropriate privilege assignments to various users and maintaining their account access. The system administrator will often troubleshoot unexpected failures in the system and propose workflow solutions as needed. As such, this individual should have a solid working knowledge about each stage of the workflow. Maintenance of servers and workstations, as well as viewing software installation and updates, is tasked to IT personnel. Depending on the application, workflow coordinators (eg, a histology laboratory manager) may be needed. Whole slide imaging applications for consultation or tumor board conferences require a coordinator that is optimally an individual who has familiarity with the laboratory information system (LIS) and a good knowledge and understanding of the laboratory's workflow. Figure 3 highlights the essential overlap in task assignments between different team members, where a given task can be performed by several members. This will help with the continuity and efficiency of the process throughout different shifts or with unexpected employee absence. As the number of clinical applications for WSI increases, it is likely that more than 1 team member will be required for any given role.

SCANNER SELECTION STRATEGY AND REQUIRED RESOURCES

Scanning Devices

There are many WSI scanners available for pathology laboratories to choose from, all of which permit high-speed digitization of glass slides to produce high-resolution digital (virtual) slides. However, they vary with respect to the features and functionality they offer.[4] When selecting a scanner it is important to try to match the attributes of these devices with the intended use. Important questions to ask upfront include the following:

What is my intended use? Scanning slides for clinical (eg, telepathology for intraoperative consultations) or nonclinical (eg, education, research) reasons may differ. For most clinical work light microscopy may suffice, whereas for research fluorescent images may be needed.

What type of glass slides need to be scanned? Scanning wet slides (eg, during frozen section) or slides of unusual size (eg, whole mounts) may present challenges with certain scanners.

What volumes of slides need to be scanned? This requires balancing scanning speed and slide-scanning capacity. Ideally, laboratories would like to avoid overpaying for surplus capability (eg, paying for a scanner that holds 400 slides for a remote frozen section service that generates fewer than 10 slides per week; a scanner that holds up to 5 slides would be optimal for this purpose).

What type of material is being scanned? For cytology slides it may be desirable to scan with z-stacking. For scanning hematopathology slides (eg, blood or marrow smears) oil-scanning is a critical component.

What companion software do I need? A digital pathology solution may need specific software to manage clinical workflow, share cases, or perform image analysis.

Is integration with the LIS important? For diagnostic work WSI-LIS integration may be critical to support clinical workflow.

What is my budget? This is a key question for clients. Paying for WSI scanners and related direct as well as indirect costs may be a major barrier to adoption.

When evaluating the physical characteristics of a scanner, instrument size and slide handling are important. Whole slide imaging instruments vary in size (Figure 4, A through D), which is an important consideration for laboratories with space constraints, especially in a frozen section room where counter space may be limited. Desktop scanners with a compact footprint may be suitable for frozen section rooms, or for placement in areas of a hospital where on-site telecytology services are needed (Figure 4, A). However, smaller scanners can scan only 2 to 4 slides at a time (Figure 4, B), which may not be ideal for handling higher-volume intraoperative consultations. For high-throughput work there are high slide capacity scanners (eg, 120–400 slides). These devices have large racks, cartridges, or trays to load slides (Figure 4, C). How slides get loaded into these machines is also important. For wet slides such as frozen sections where the coverslip may move, it may be preferable to load slides on a horizontal tray as opposed to a vertical rack. Continuous autoloading is helpful if the operator needs to handle certain slides without interrupting the scanning of other slides. For users that want to scan whole mount slides, a specialized WSI scanner will be needed. These devices are available from several vendors, for example, the TissueScope scanner from Huron Digital Pathology (Waterloo, Ontario, Canada), which can scan slides up to 8″ × 6″ (Figure 4, D).

For digitization of slides it is important to consider the light source, scan time, scan failure rate, image resolution, and image quality.[13] Most scanners use bright-field microscopy, while some can scan slides for fluorescent work (eg, 3DHISTECH panoramic scanners [3DHistech Ltd, Budapest, Hungary], Aperio FL and Ariol scanners [Leica Biosystems, Vista, California], Leica SCN400 F scanner [Leica Biosystems], Zeiss Axio Scan.Z1 [Zeiss, Oberkochen, Germany], NanoZoomer scanners [Hamamatsu Photonics, Hamamatsu City, Shizuoka, Japan], and VECTRA from PerkinElmer [Perkin Elmer Inc, Waltham, Massachusetts]). It is important to note that the spectrum range available for fluorescent scanners may restrict fluorophore usage. Given that histology processing time may increase significantly over baseline with the presence of a WSI robot in the histology workflow,[14] scan times are an important consideration for high-volume work. Most current scanners offer high-speed scanning of glass slides (eg, around 1 minute). To compare different scanners it may be easier to evaluate their scan speed per square millimeter of tissue (eg, 15×15 mm^2). Scan time will increase with tissue size, tissue section density, scanning at high magnification, and with z-stacking. True throughput, or TAT, for scanning slides includes several steps, in addition to the scanning process itself. This includes slide preparation (eg, trimming overhanging labels), slide loading, and possibly manual quality control checks after scanning. In one study, the authors[15] reported that the time for them to prepare and scan a slide ranged from 5 to 15 minutes with an average of 10 minutes, not counting additional time for slide cleaning or field selection. Slides were scanned in batches of 80 to 120 and required 12 to 24 hours of scanning per batch. Their slide scanning failure rate was 13.1%, and 6.6% of slides required 2 or more scans. Scanners that include barcode readers can help expedite scanning if there are many slides.
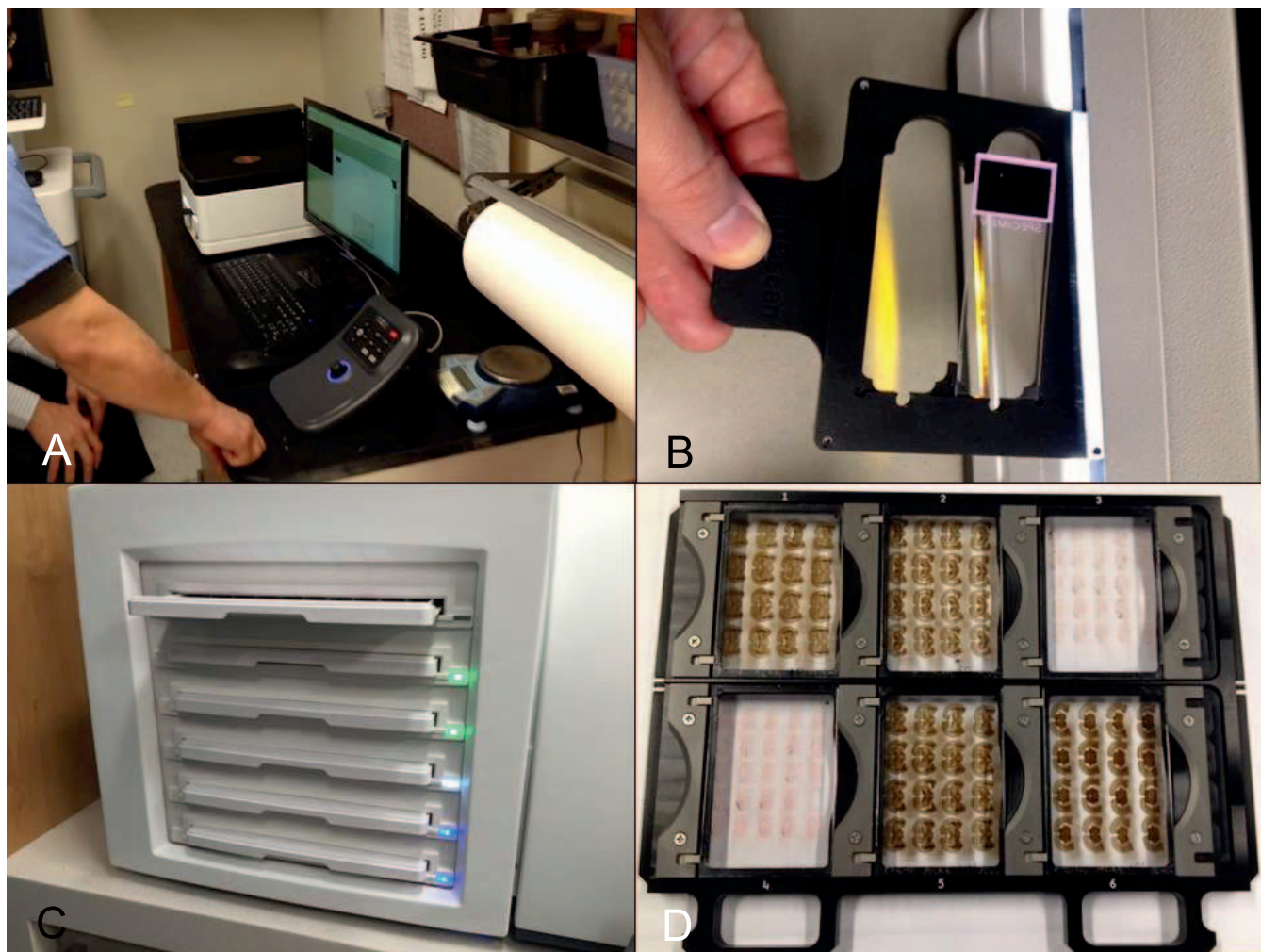
Figure 4. *A, Frozen section room is shown with a small desktop WSI scanner that does not occupy much counter space. B, A low-volume scanner is shown with a slide tray that holds only 2 glass slides. C, High-volume WSI scanner that allows multiple slides to be loaded by using slide trays. D, Huron WSI scanner tray (Huron Digital Pathology, Waterloo, Ontario, Canada) that can accommodate large glass slides from whole-mount sections. Abbreviation: WSI, whole slide imaging.*

Whole slide imaging devices may use line or tile-based scanning to digitize scans. Some devices use other techniques such as independent dual sensor scanning to enhance scan time while maintaining continuous accurate focus.[16] Tissue detection algorithms can also speed up scanning by helping to eliminate white background. Whole slide imaging scanners use microscopes with objective lenses and they have digital cameras within them. Both of these components impact image magnification and resolution. For routine surgical pathology, it is the authors' experience that scanning glass slides using a low-magnification objective (eg, ×20) appears to be sufficient.[17] Scanning at higher magnification (eg, ×40 or greater) generates images of greater resolution, which may be necessary for identifying small objects such as microorganisms,[18] although routine scanning at ×40 may be preferred by some pathologists. There are instruments that can perform oil-immersion scanning (eg, Aperio CS-O and VERSA scanners [Leica Biosystems]), which is very helpful when dealing with hematopathology smears.[12] While optical resolution depends on the objective lens and its numerical aperture, it is important to be aware that digital resolution also depends on the scanner's digital camera

sensor and the monitor where these images are displayed.[19] When comparing scanners with respect to image resolution, micrometer per pixel rather than scan magnification is the preferred vendor-neutral descriptor to use (eg, 0.5 μm/pixel versus ×20, or 0.25 μm/pixel versus ×40). Whole slide imaging scanners that offer lower micrometer-per-pixel values allow pathologists to get more information from the image. A detailed explanation of the difference between magnification on light microscopy, scan magnification, and image resolution is beyond the scope of this article. Interested readers are referred to the work of Sellaro et al.[19]

For certain glass slides (eg, cytology cases) it may be important to visualize material in both horizontal (x and y) and vertical (z) axes.[20,21] Indeed, scanning cytology slides can be problematic if they have thick smears or if specimens contain 3-dimensional cell groups. For WSI in such cases, focusing can be addressed by z-axis scanning (so-called z-stacking). This involves scanning the same glass slide at different focal planes along the z-axis and stacking the images on top of each other to produce a final composite (z-stack) multiplane image (Figure 5). Some WSI scanners that offer z-stacking capability include 3DHISTECH panoramic devices, Huron TissueScope scanners, Leica SCN400,

Figure 5. *Screenshot from a NanoZoomer scanner (Hamamatsu Photonics, Hamamatsu City, Shizuoka, Japan) showing how multiple z-stacks can be selected from the drop-down menu for z-stack scanning of a cytology slide (Papanicolaou stain, digital magnification ×40).*
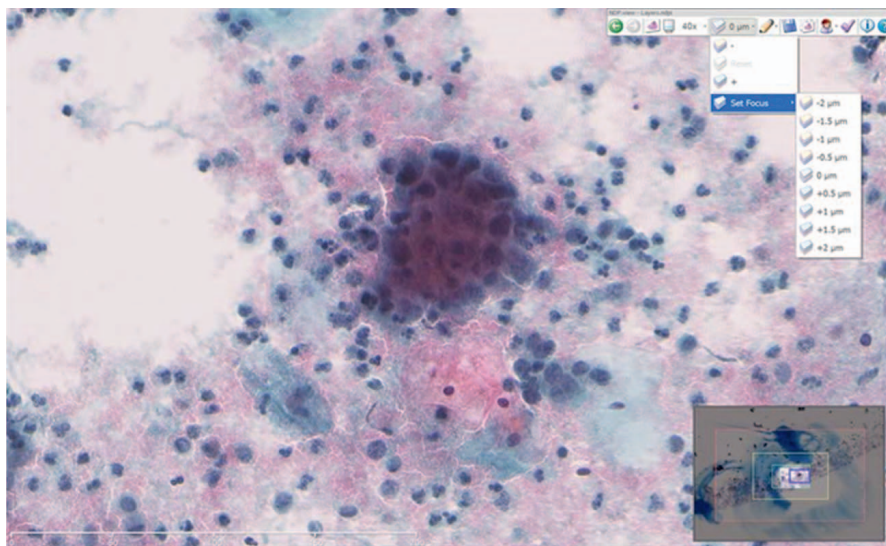
Ventana iScan Coreo (Ventana Medical Systems, Inc, Tucson, Arizona), and the Hamamatsu NanoZoomer. Of course, z-stack scanning takes longer to perform and produces substantially larger digital files. Pathologists using these larger digital files may experience slow loading, pixelation, and freezing of images if their computers and/ or network is suboptimal, which may result in observer frustration.[22]

More recently, some vendors have started manufacturing versatile hybrid scanners that offer both WSI scanning and live video robotic modes. Examples of such scanners are the VisionTek M6 from Sakura (Sakura Finetek, Leiden, the Netherlands), Aperio LV1 from Leica, and the Glissando scanner from Objective Imaging (Objective Imaging Ltd, Cambridge, United Kingdom) (Figure 6). Apart from producing static whole slide images, these instruments contain a motorized microscope that allows users to remotely move the stage for slide navigation and to switch between different lens objectives for magnification; they can also control focus. Such real-time robotic functionality is attractive for imaging frozen sections, which frequently have tissue folds. They have also become increasingly popular for on-site telecytology.[23] For such use cases these small, remotely controlled, low-volume scanners are becoming a

Figure 6. *Aperio LV1 whole slide imaging scanner (Leica Biosystems, Vista, California) with robotic control allows users to remotely access live slides. Users can remotely switch between 4 slides, move slides in x- and y-axes, change magnification (between ×2.5, ×10, ×20, and ×40 objectives), and adjust the fine focus (image courtesy of Leica Biosystems).*

cost-effective solution. Users should be aware that remote sharing of images with several of these instruments may rely on third-party applications (eg, TeamViewer [TeamViewer, Göppingen, Germany] desktop sharing software).

Companion Software

When selecting a WSI scanner it makes sense to also evaluate accompanying software and related services (eg, cloud hosting) provided by the vendor. This includes image viewers, image management software, and algorithms for assisting workflow and performing image analysis. Most scanners generate proprietary image file formats (eg, .SVS, .RTS, .NDP) that require specific viewing software to be viewed. While some files may be converted to open formats (eg, .JPEG 2000, .TIFF), proprietary digital files generated by one scanner may not be universally viewable with viewers from other vendors. Image viewer software can be installed locally on a client workstation or server. Not all vendors have Web-based viewers or viewers allowing slides to be reviewed on mobile devices such as tablets or smartphones. Moreover, some Web-based viewers may not offer the same functionality. All image viewers offer commonly used features including panning, zooming, adding annotations, performing measurements, taking snapshots, exporting images, and making image adjustments such as brightness, contrast, sharpening, or color intensity. Others may offer more unique tools such as autopanning, magnifier windows, the ability to rotate or overlay images, displaying multiple images (Figure 7) with coregistration, presenting a digital slide tray with thumbnails of all slides, jumping over white space between scanned tissue pieces, and tracker tools showing tissue that has been reviewed. A demonstration by the vendor will help determine whether their viewer's user interface is intuitive, easy to use, and well organized.

The need for software that facilitates image management and drives workflow will depend on the intended digital pathology use case (eg, diagnostic work, teleconsultation, education, and/or research). Examples of companion WSI management solutions are VENTANA Virtuoso (Ventana Medical Systems), Aperio eSlide Manager (Leica Biosystems), Omnyx's Integrated Digital Pathology (IDP) (Omnyx LLC, Pittsburgh, Pennsylvania) as part of their Precision Platform, and Optra IMAGEPath (Optra Systems Inc, Pune,
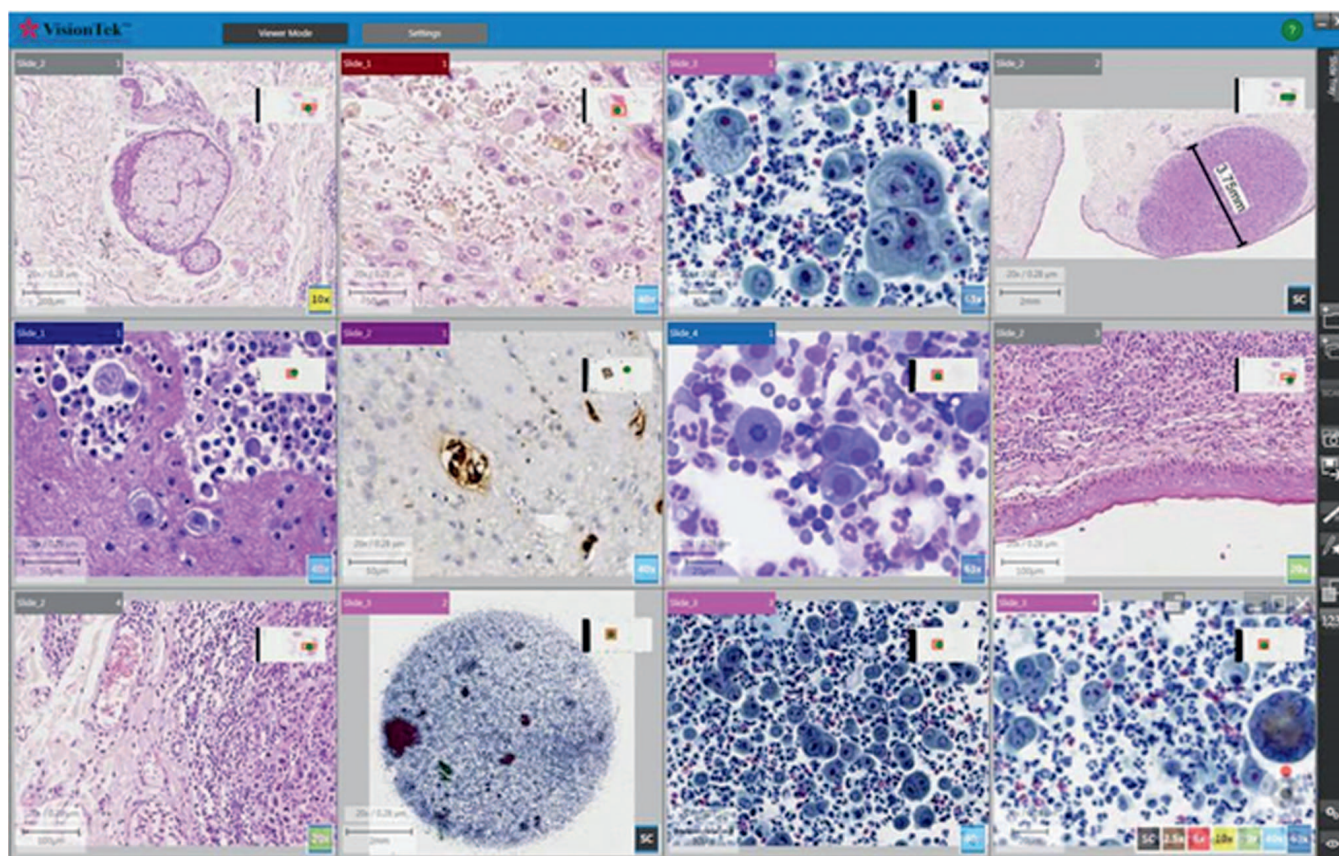
Figure 7. *The VisionTek M6 Digital Microscope (Sakura Finetek, Leiden, the Netherlands) allows multiple scanned slides to be viewed simultaneously at different magnifications and at different focal planes (image courtesy of Baggi Somasundaram, Sakura Finetek).*

India). Some WSI vendors may have partnered with others to provide such software functionality (eg, Philips [Philips Healthcare, Amsterdam, the Netherlands]) and Inspirata [Inspirata, Tampa, Florida]). To support workflow image management the software should provide standard functionality (eg, various user levels, case creation, case assignment). Some vendors may have added further functionality such as algorithms to prioritize cases, a mechanism for report generation, a process for tumor boards, and secure image sharing for telepathology. A number of vendors now offer image analysis algorithms (eg, for scoring estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2). Dedicated software (eg, Aperio's Digital SlideBox [Leica Biosystems]) may be available for educational needs (eg, creation of digital teaching slide sets, in-built heat mapping technology). Also, some may supply image hosting and cloud-based software as a service (SaaS) with a pay-per-use or subscription model.

Required Resources

When implementing a WSI system it is important to be aware of the resources required to deploy and sustain the system. From an IT perspective, there are technical elements and personnel to consider. Acquisition of IT equipment includes not only the WSI scanner(s), but also perhaps computers to operate the device. In addition, scanned images may need to be uploaded to a server. Digital slide file sizes are typically much larger than those of radiology images.[24] Hence, it is essential to have a robust, scalable

data storage and retrieval platform. Data storage plans should include backup and image retention and/or purging policies. Depending on the use case it may be necessary to establish a test and clinical production system. End users may need to have their monitors (ie, digital cockpit) upgraded. Finally, the network infrastructure should be gauged for bandwidth and security. Bandwidth may need to be increased for images to be uploaded from scanners to servers.

The other major resource required for implementing a successful digital pathology solution is people. The vendor may provide consultants to help with installation. However, local IT personnel are imperative for successful installation and will be required for ongoing maintenance and to resolve technical problems that may arise. Dedicated staff (eg, technologist) is necessary for scanning slides and to manage images. Laboratory staff will likely need to help with training, participate in validation, create documents (eg, standard operating procedures), and assist with quality assurance. Administrators may need to help with contracts and other business-related activities. As mentioned above, pathologists will also need to invest time and effort. In the beginning, there should be at least 1 pathologist whose dedicated efforts will be invaluable for convincing other pathologists to adopt the technology and to oversee its safe implementation into patient care.

Clearly, financial resources are essential. Both direct and indirect costs need to be taken into account. Direct costs include the hardware (eg, scanner, server, other computer equipment) to be purchased. Software may be an additional

Table 3. Factors Contributing to Pathologist Discomfort With Whole Slide Imaging (WSI) Systems

Lack of training or experience with the technology
Time required to review cases by WSI such that confident diagnoses are rendered
Fundamental mechanical and ergonomic differences between WSI and light microscopy
Concern that WSI will introduce unfamiliar digital artifacts over and above those generated by routine histologic processing
Lack of US Food and Drug Administration approval to use WSI for primary diagnosis in the United States

expense. Indirect costs include maintenance and possible licensing fees. The cost of using existing staff or hiring new personnel (eg, slide scanning technologist) may be considerable. Finally, if LIS integration is part of the picture this expense will need to be incurred by the client.

CREATING COMFORT WITH WSI: ADOPTION STRATEGIES FOR PATHOLOGY PRACTICES AND THE IMPORTANCE OF VALIDATION

Pathologist Concerns About Using WSI for Clinical Purposes

Addressing concerns of pathologists who must use the WSI system to make diagnoses is crucial to incorporating WSI into practice. For a number of reasons, however, pathologists may not be comfortable using WSI for clinical purposes. Such concerns may lead to resistance or avoidance of using the technology in practice. Resistance does not necessarily indicate "technophobia" and/or change aversion. It is important to engage pathologists early in the implementation process to overcome their resistance and eliminate barriers to adoption, both perceived and real.

Pathologists' discomfort with using WSI arises from several sources (Table 3), some of which have an emotional component to consider. Primary among these is *fear* of making a diagnostic error when using WSI instead of more familiar conventional microscopy. *Anger* may exist over being mandated by others (eg, hospital administration, clinicians, department chairs) into using WSI for certain applications, such as delivering digital consultations across a multisite health system. The fact that WSI cases may take more time per case to review than conventional glass slide–based cases can create *anxiety* as time pressures mount to complete one's assigned workload. Pathologists may have little or no training or experience in using WSI systems. Fundamental mechanical and ergonomic differences from conventional microscopy exist when using WSI for slide review. Examples include the need for an input device such as mouse or touch pad to navigate slides[25] and the fact that the field of vision on a computer screen may not correlate exactly with the field of vision on a microscope.[26] In addition, WSI may introduce unfamiliar "digital artifacts" to recognize in the digital representation of microscopic images, beyond more familiar routine histology artifacts.

Several facts underpin these concerns. However, measures can be taken to address them and improve pathologists' comfort with WSI. Pathologists are typically data oriented, and providing them with literature that shows good correlation between WSI and glass slide review may help alleviate concerns about making diagnostic errors. Performing an internal validation of any WSI system implemented for its intended uses is important not only to ensure that the system functions as expected in its clinical environment, but also to provide an additional measure of confidence for pathologists.[27] Pathologists can gain experience with WSI by using it for applications that are less stressful than diagnostic work. Examples include educational conferences, tumor boards, and research. When implementing WSI, as with any new system, adequate training is essential to improve user acceptance and proficiency. Finally, including in the workflow a mechanism for pathologists to defer their diagnosis to glass slide review for cases in which they are not comfortable making a diagnosis on WSI provides a "safety valve" that should further help address concerns.

Validation of WSI for Clinical Diagnosis in Surgical Pathology

Validation of a new system is the process of demonstrating that it reliably produces expected results or outcome in a given setting.[27] It also involves specifying the performance characteristics to be assessed and determining acceptable levels of performance for each characteristic. For example, when validating WSI for clinical purposes, performance characteristics include scanning accuracy, and an acceptable performance level is generally determined as the level (percentage) of concordance between diagnoses (or feature interpretation) rendered when examining a glass slide and the same case by WSI.[28] In recent years, published validation studies from a number of pathology groups have repeatedly demonstrated excellent concordance between WSI and glass slide diagnoses.[1,15,27,29–32] In particular, some validation studies of WSI for clinical use have focused on individual subspecialties and second-opinion consultation practices.[33–40]

The need to validate WSI for diagnostic purposes has been associated with some controversy. One argument states that diagnostic pathology is inherently interpretive and is more akin to medical practice than it is to performing a quantitative "test," leading to the question "how can such an interpretive or judgment-based process be validated with an analogous but more quantitative system?" The answer lies in the fact that technology (complex hardware and software components) is required to function correctly in order to serve appropriate digital images to pathologists for interpretation. Hence, use of such a system for clinical diagnostic interpretation merits performance verification of the technology being used. By such reasoning, consensus has emerged that laboratories or practices intending to use WSI for clinical purposes should perform their own internal validation studies before implementation.[27,31]

In 2013, the Laboratory Quality Center of the CAP published guidelines on validating WSI for diagnostic purposes in pathology.[27] CAP convened an expert panel whose members were experienced in WSI use. The panel screened 767 articles on the subject of "digital pathology." After rigorous inclusion criteria were applied, 23 articles remained for thorough assessment regarding validation of WSI for clinical use. After draft guidelines were developed, they were posted online for a public comment period. Following revision based on feedback from the public comment period and input from other pathology professional societies, the workgroup settled on 12 guideline statements. These guideline statements included strength-of-evidence grades.

Among the highlights of the CAP WSI validation guideline is that validation of a WSI system should focus on its intended clinical use(s) (eg, primary diagnosis, frozen

sections, or immunohistochemistry review) and should emulate its real-world clinical environment. Whole slide imaging platforms are best validated as integrated systems, and it is not necessary to validate individual components such as a computer monitor. The guidelines recommend that at least 60 representative cases (irrespective of the number of slides per case) be examined in a validation study for any new clinical use, with at least a 2-week "washout" period. A washout period is the time between review of a glass slide with a traditional microscope and review of the same case using a digital slide (or vice versa). *Intraobserver* diagnostic concordance between glass slide and WSI diagnosis on the same slide is the important "performance characteristic" to assess. Importantly, the validation process should also confirm that all material on a glass slide is included in the digital scan.

Whether intraobserver or interobserver correlation for WSI versus glass slide diagnoses is more appropriate for WSI validation has been the subject of some debate. Intraobserver variation determines whether the same diagnosis is rendered on the same slide, when reviewed by WSI or light microscopy, by the same pathologist. This contrasts with interobserver variation, where one pathologist reviews the digital slide and another pathologist reviews the glass slide. The rationale for favoring intraobserver validation is that it removes sources of interobserver variation such as the application of diagnostic criteria, diagnostic thresholds, specific expertise, and pathologist experience from the equation. Any of these factors can influence the determination of the "correctness" of a diagnosis. In an intraobserver validation, it is irrelevant whether or not a diagnosis is considered "correct." The key question is whether the same pathologist makes the same interpretation, WSI versus glass, and the only variable introduced is the modality by which a case is reviewed. For the purpose of validation it is more important to evaluate the technology as opposed to the pathologist's diagnostic competency. Based on this rationale, the expert consensus was that intraobserver variation is favored for WSI validation.[1,27,30,31] Subsequent publications have confirmed that it is feasible and practical to perform WSI validation studies by using the CAP guidelines.[41]

A notable approach to WSI validation that appeared around the same time as the CAP guidelines was described by Bauer and colleagues.[30] The "noninferiority" design of this study accounted for the undeniable fact that intraobserver variation in pathology exists even for glass slide review at different times by the same pathologist. The study hypothesized that WSI review is not inferior to glass slide review in surgical pathology. Stated differently, the study sought to demonstrate noninferiority of WSI versus conventional microscope re-review of previously diagnosed cases. Intraobserver variation in routine surgical pathology was set at 4% for statistical and comparison purposes. Pathologists reviewed cases they themselves had reported 1 year prior to the study, using either a microscope or WSI. The study included 607 cases comprising 1025 parts. Major discrepancies occurred in 5 of 303 (1.65%) for WSI cases and 3 of 304 (0.99%) for glass, and minor discrepancies were found in 7 of 303 (2.31%) for WSI cases and 15 of 304 (4.93%) for glass. Whole slide imaging diagnoses were deemed to be more accurate, or "better" than the original glass slide diagnosis in some cases. The important conclusion of this study was that diagnostic review by WSI was not inferior to conventional microscope slide review ($P < .001$).

Completing an internal validation process should satisfy all users that WSI can be used to make accurate and complete diagnoses. It also provides an opportunity to identify histology-related issues that may require further attention to ensure optimal image quality, as well as allowing pathologists to identify potential limitations with WSI that may require ancillary procedures for digital sign-out (eg, special stains for *Helicobacter pylori*) or deferral to glass slides (eg, to examine slides requiring polarization).

Other Measures to Increase Pathologist Adoption of WSI

In addition to providing data in the form of literature and internal validation studies, there are a number of other approaches that can ease pathologists into using WSI.[1,42,43] For example, WSI has been used successfully to facilitate tumor boards and clinicopathologic review conferences.[12,44] Whole slide imaging facilitates the rapid creation of portable presentations and removes the need for managing individual photomicrograph collections. In academic centers, WSI enables the creation of interesting case archives (digital teaching sets), including material from consultation cases for which glass slides must be returned to the referring site. Whole slide imaging is also a useful platform for continuing medical education (eg, CAP's surgical pathology performance improvement program), facilitating central pathology for clinical trials, and to foster research collaborations across geographically dispersed centers.[42] In all of these ways, pathologists can become accustomed to reviewing slides by WSI in settings that do not bring any pressure to make clinical diagnoses.

When implementing any complex technology and information system, especially in busy, time-constrained environments, *training* can be easily overlooked. Training of pathologists is crucial to increasing pathologists' comfort with WSI technology and thereby reducing the potential for diagnostic error. Training is not the same as validation. Training in the context of WSI refers to instruction of each pathologist on how to use the system to efficiently and thoroughly review a virtual slide. The training of pathologists performing a validation study should be completed before starting the study and not included as part of the validation process.[27] To underscore this point, the CAP Laboratory Accreditation Program checklists require all laboratories using telepathology for clinical activities to provide separate documentation for training and validation.

Training with respect to incorporating WSI into clinical practice has 2 components. The first is training pathologists on how to access scanned slides and use the WSI software to review them. More comprehensively, and possibly more challenging, the second aspect of training involves the pathologist learning how to execute the entire workflow for intended uses of WSI in the department. Issues to be dealt with include knowing how and when WSI cases become available for a pathologist to review, how to find one's own WSI cases in the system, processes for deferring to glass slide review, and how reports will be created and distributed. Itemized checklists and sign-off sheets can be helpful in guiding training as well as providing documentation that training was completed. Training should ideally provide pathologists with access to the glass slides that they reviewed digitally, to allow them to evaluate similarities and differences as well as potential nuances related to interpretation by WSI.

Table 4. Potential Side Benefits of Whole Slide Imaging for Pathologists
Upgraded computers and monitors to read digital cases
Eliminating travel to cover service work at remote sites
Exposure to new technology and the opportunity to guide its safe implementation in the department
Innovative practice models including portability and flexible work schedules
Archiving of interesting cases for teaching and research
Enhanced revenue through expanded consultative practice
Leveraging algorithms for computer-aided diagnosis and enhancing workflow

Making "WSI life" easier for pathologists, in particular by attention to *workflow* components that are unique to WSI and "digital pathology," can reduce barriers to adoption.[45] In recognition of the importance of attention to process and workflow when contemplating WSI use, the American Telemedicine Association and the Canadian Association of Pathologists each recently published guidelines on implementing WSI for telepathology.[2,46] These guidelines discuss key elements of workflow unique to WSI-based pathology practice. For example, as in working with conventional glass slide cases, pathologists also need access to clinical information to interpret WSI cases; however, such information may not be readily available for WSI cases submitted from remote sites. Options for providing clinical information and other metadata include scanning and uploading paper documents, faxing, or allowing teleconsultants to have remote access to electronic patient records.

Pathologists will need a notification mechanism to know that a WSI case is ready for review. The typical prompt of glass slides appearing in a mailbox or on a desk is not there to alert the pathologist of the availability of cases that are ready to "sign out." Attention to mechanics and ergonomics of the WSI review workstation can help reduce physical pain, eye strain, fatigue, and possibly frustration with how digital slides are navigated.[47] Examples include large monitors or double monitors for viewing, accommodation of pathologist preference for input devices (eg, mouse, trackball), and control over the level of ambient light in the room.[48]

Whole slide imaging cases may take more time to review than routine glass slide cases, especially when a pathologist is relatively new to reviewing cases digitally. A number of studies[34,35,38–40,49–53] have shown either objectively or subjectively that more time per slide or per case for WSI compared to glass is necessary, with sometimes even up to 20% to 500% increase per case. Accounting for this increased time per case when assessing and determining pathologist workloads across a department raises issues of equitable workload distribution, TAT expectations, and productivity measures.

In addition, WSI may engender expectations of new service levels or access to pathologists that may impact pathologist time management. For example, expectations for shorter TAT may exist for WSI cases, since, once uploaded or scanned, they are "instantly available" at the reviewing (remote) site, as compared to the lag time inherent in physically sending glass slides. In addition, this apparent or presumed immediate availability, and elimination of time and distance considerations through WSI, may lead clinicians or referring pathologists to expect more ad hoc availability for real-time discussion mediated through

WSI technology. The accessibility of WSI systems over the Internet from any computer or mobile device may foster such expectations.

Finally, there are potential "side" benefits to pathologists of using WSI (Table 4). Deployment of a WSI system may result in upgraded computer monitors and other equipment for the pathologist. In settings where pathologists are called upon to travel to cover remote sites, use of WSI may eliminate wasted time, especially if such remote sites have only a low volume of work. Whole slide imaging provides exposure to new or "cutting edge" technologies, which may be of interest to some pathologists, as well as the opportunity to participate in innovative practice models. Whole slide imaging facilitates creating archives of interesting cases for documentation (eg, scanning of medicolegal cases), quality assurance, teaching, conferences, and research. There may even be opportunities to support more flexible work schedules, both in terms of time and place, through the use of WSI. Finally, potential may exist for increased revenue through an expanded consultative practice (eg, receiving consultation cases from sites that wish to refer digital slides by using their WSI systems[54]) or providing reference work (eg, performing immunohistochemical stains and hosting these slides online for referring pathologists to interpret, with the added option for them to seek further diagnostic consultation if needed).

WHAT TO EXPECT AFTER GOING LIVE: ONE INSTITUTION'S EXPERIENCE WITH FROZEN SECTIONS AND PRIMARY DIAGNOSIS

Going live with WSI after implementing and validating a system is exciting and rewarding for a pathology laboratory. Published information on what to expect during this important phase of the WSI life cycle, while somewhat sparse relative to validation studies, can be obtained from literature and presentations provided by a number of early adopters, including University Health Network (UHN) in Toronto, Ontario, Canada.[28,32] This section briefly describes UHN's experience on what can be expected when WSI is introduced into actual patient care situations for frozen sections and primary diagnosis. The authors recognize that UHN is not the only institution to have moved beyond validation studies with WSI. However, the UHN example was used to illustrate specific points during the "*Implementing Whole-Slide Imaging (WSI) for Clinical Use: What to Do and What to Avoid*" panel discussion for several reasons. The panel discussion (and this article) was not intended to provide an exhaustive review of telepathology and WSI, but rather to act as a forum for sharing the personal experience of the presenters (one of whom has served as the director of the UHN telepathology program since its planning phase in 2003). The information on the UHN experience shared with the course attendees provided a balanced overview of successes as well as setbacks concerning the performance of a WSI system after following the implementation process described in the previous sections.

UHN is a multisite health care institution in downtown Toronto, comprising Toronto General Hospital (TGH), Toronto Western Hospital (TWH), Princess Margaret Cancer Center, and Toronto Rehab Hospital. The pathology department is consolidated at the TGH site and operates on a subspecialty model. The department also has several partner sites that are located 40 to more than 400 miles from Toronto. To provide subspecialty pathology services to its

various partner sites, UHN would have to move glass slides and/or pathologists or implement telepathology. Since 2004, UHN has steadily expanded its use of WSI-based telepathology for clinical use to include frozen sections, consultation, quality assurance activities, and primary diagnosis between its partner sites. It is worthy to note that WSI is not used by all UHN pathologists, with many of the nonusers being reluctant to use the technology for reasons cited in Table 3.

Frozen Sections

The pathology department at UHN became fully consolidated by early 2006 with all pathologists based at TGH. Toronto Western Hospital is located approximately 1 mile to the west of TGH and the only site at UHN where neurosurgery is performed. The surgeons at TWH generate approximately 2 to 10 frozen sections per week, more than 90% of which come from neurosurgery cases. Following the consolidation of services, TWH was without an on-site pathologist, requiring a pathologist to travel to TWH to cover these intraoperative consultations. Three years before full consolidation at TGH, an implementation team was assembled and approximately 18 months was devoted to getting a telepathology system optimized for clinical use. Since this telepathology program was the first of its kind in Canada, the UHN implementation team covered a number of critical due-diligence items (Table 5). The frozen section telepathology program between TWH and TGH has no pathologist at the site where surgery takes place. As such, the intraoperative information given to a surgeon is based entirely on the review of scanned slides. The issue of whether frozen section diagnoses made solely on scanned slides represent primary diagnoses is a source of confusion for some pathologists. In fact, it may be a reason why some pathology practices have avoided using digital pathology for intraoperative consultations without also having an on-site pathologist present to review glass slides in conjunction with the digital review. There is no question that frozen section diagnoses can have profound impact on intraoperative surgical decision making. However, they are considered preliminary or working diagnoses pending subsequent examination of all surgically excised tissue after formalin fixation and paraffin embedding with or without ancillary techniques such as immunohistochemistry. Even if a frozen section is examined only by WSI, the diagnostic information provided to a surgeon is not a primary (or final) diagnosis.

UHN pathologists have remotely reviewed more than 4000 TWH frozen sections by WSI. The annual discrepancy rates comparing frozen section diagnoses to final permanent diagnoses range from 0% to 2%. Discrepancies to date have been interpretive in nature and none have been attributable to artifacts created by WSI. Annual deferral rates, where a pathologist defers a frozen section diagnosis to paraffin sections, are less than 2% and average TAT for single block frozen sections range from 14 to 16 minutes.[32]

It is important for a clinical telepathology service to have an ongoing quality management program that addresses technical performance of the system (eg, malfunction) and diagnostic performance of the pathologists using the system. Examples of quality metrics that may be used to assess diagnostic performance include number of misdiagnoses (eg, discordant glass versus digital diagnoses), delays in TAT, and deferral rates (eg, failure or inability to render a telepathology diagnosis).[2] UHN's WSI frozen section protocol includes a system test each morning, where a test slide is scanned to ensure proper scanner function and connectivity before frozen sections arrive. Four time points are documented for each TWH frozen section handled by telepathology: (1) when tissue was delivered to the surgical pathology laboratory, (2) when a frozen section slide was cut, stained, cover slipped, and scanned, (3) when the pathologist began review of the scanned slide, and (4) when the pathologist called a surgeon with a diagnosis. All time points are to be captured from the network computers to ensure consistency. This granularity is helpful for identifying the reason(s) for TAT delays, which is a required element for CAP laboratory accreditation.

There may be a need to rescan frozen section slides (or specific parts of slides as shown in Figure 8, A through C) to remedy occasional areas that are out of focus. This should occur infrequently if proper attention is paid to cutting the sections without tissue folds, placing the tissue on the center of the slide, then followed by appropriate staining and cover slipping. Having an experienced, highly skilled histotechnologist oversee this workflow is critical. Rare episodes of midcase technical failure have occurred, requiring a pathologist to physically go to TWH to read a frozen section by light microscopy. While this has occurred in only 0.2% of cases in 10 years, these episodes nonetheless highlight the need for a downtime protocol if frozen sections are to be read by telepathology in the absence of an on-site pathologist.

Primary Diagnosis

Primary diagnosis by WSI refers to final diagnoses made only by review of scanned digital slides, be they hematoxylin-eosin, histochemical, or immunohistochemical stains. These diagnoses become part of the patient's medical record and are used to make decisions on treatment. Two of UHN's partner sites, Timmins and District Hospital (TADH) and Lakeridge Health Oshawa (LHO), send a combined total of 300 to 600 glass slides per day to TGH for subspecialty reporting. The cases sent to TGH are those for which there are no on-site subspecialty pathologists to report them locally. A comprehensive prospective validation study of more than 1200 cases was completed over a period of 80 weeks by pathologists in 11 different

Figure 8. *Strategy for rescanning part of a frozen section slide to improve focus in a particular area. A, Rescanning a selected area (green box) to improve focus adds 1 to 2 minutes to frozen section turnaround time. B, Poorly focused area on the initial scan. C, Rescan of the area shown in (B) with sharp focus. This is easily accomplished through communication between the viewing pathologist and the on-site histotechnologist who is scanning the frozen section slide (hematoxylin-eosin, digital magnifications ×0.5 [A], ×3 [B], and ×3.8 [C]).*
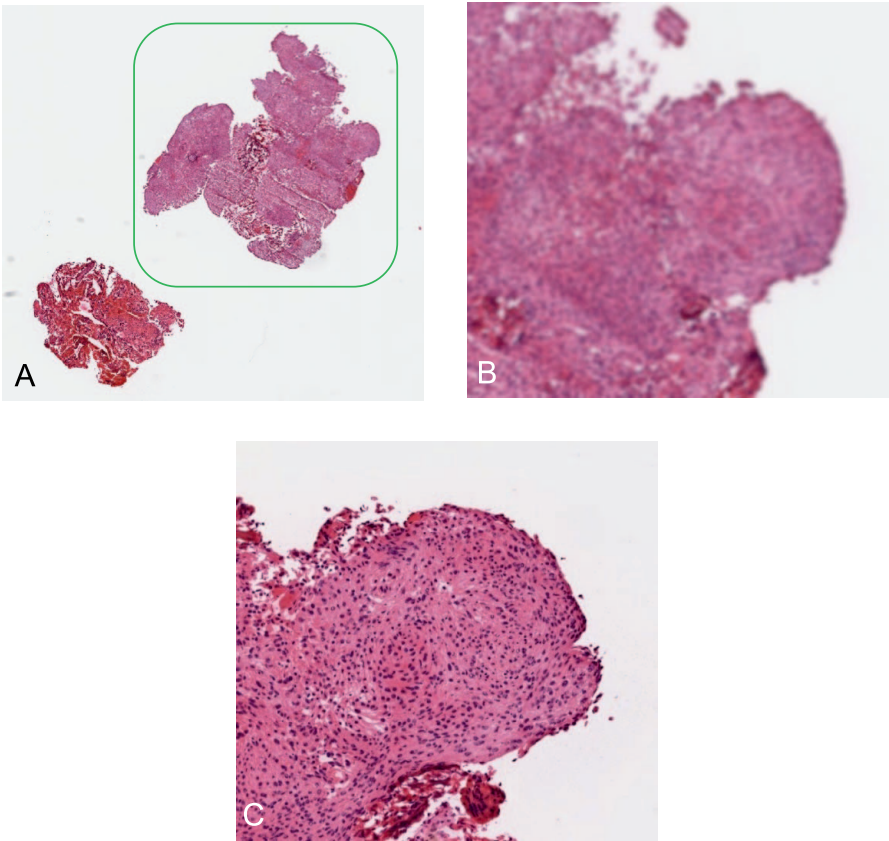
subspecialty areas.[55] The validation study included review of TADH and LHO cases sent to TGH for primary diagnosis. These cases were reviewed by WSI and light microscopy by the same pathologist as per the CAP WSI validation guideline.[27]

Primary diagnosis by WSI was phased in for specific subspecialty areas at LHO in October of 2012. All LHO slides from genitourinary, endocrine, liver, orthopedics, and head and neck cases were scanned at ×20 (0.5 μm/pixel resolution) using a Leica/Aperio ScanScope AT, with the intent of primary WSI sign-out. Importantly, pathologists could defer a diagnosis to glass slide review whenever it was required to make timely, confident, and complete diagnoses. To facilitate routine primary reporting by telepathology, the pathology department at LHO was incorporated into the UHN LIS, and advanced barcoding and tracking was implemented at LHO to allow scanned slides to be automatically linked to cases within the LIS. Whole slide imaging–LIS integration was felt to be an absolute necessity for primary digital reporting for managing workflow and for patient safety with respect to reporting diagnoses for the correct patient.

Since October 2012, greater than 6700 cases (representing more than 35 500 slides) have been scanned for primary diagnosis by WSI, greater than 90% of which have been signed out without deferral to glass slide review. These cases have included routine miscellaneous specimens, small biopsy specimens, multipart biopsy specimens, limited tumor excisions, and surgical resections of malignant disease. Figure 9, A through D, shows an example of a complex transurethral resection of bladder tumor specimen that was confidently and completely reported by WSI alone. The 3-year UHN experience of using WSI for primary diagnosis for LHO cases is the subject of a separate manuscript that is currently in preparation, although details on this specific project have been presented at several recent international pathology conferences.[56–58]

Even if pathologists are well trained and comfortable with making diagnoses by WSI, and histology has been optimized to allow for digital reporting, one should expect to have cases deferred to glass slide review. The most common reasons for deferring to glass slide review in the UHN experience are shown in Table 6. Seeking diagnostic reassurance on difficult or unusual cases, cases where there is a high likelihood they will be sent out for glass slide review by another pathologist, episodes of suboptimal IT performance, or slower digital workflow when pathologists have large numbers of cases to report account for most deferrals to glass slides.

| Table 6. Scenarios Where a Pathologist May Wish to Defer a Whole Slide Image (WSI) Diagnosis to Glass Slide Review |
| --- |
| Need for reassurance on difficult or unusual cases, unexpected diagnoses, and/or cases likely to be sent out for glass slide review by another pathologist |
| Suboptimal information technology performance or slow digital workflow, particularly if the pathologist has a large volume of cases to report |
| Suboptimal image quality in an area of potential diagnostic importance |
| Performing diagnostic activities that are currently not easily performed with WSI: counting mitotic figures on a per high-power-field basis |
| Confidently identifying microorganisms such as *Helicobacter pylori* |
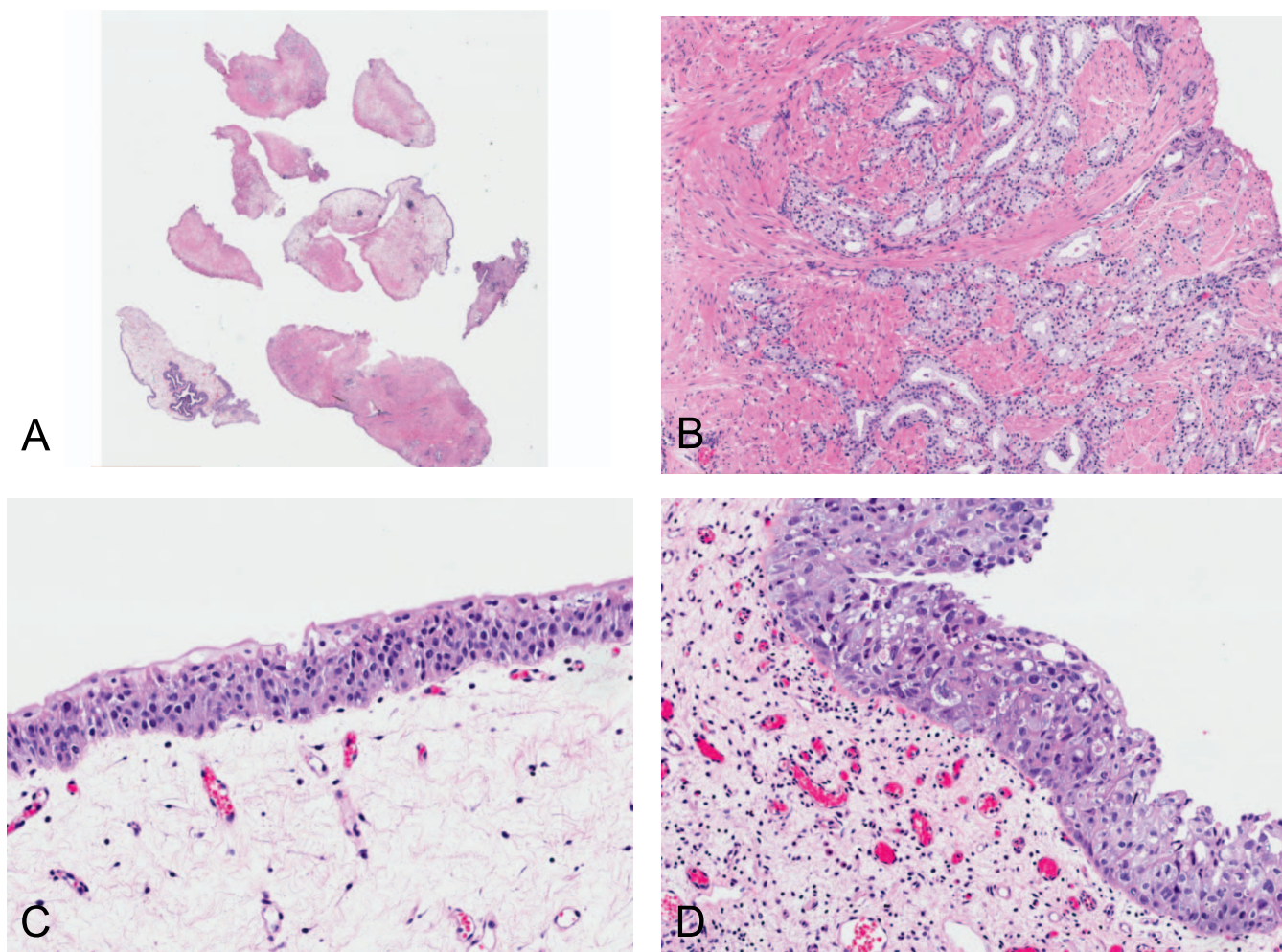
Figure 9. *Bladder transurethral resection specimen illustrating how complex cancer specimens can be accurately diagnosed and completely characterized by whole slide imaging. A, Overview image of the resected chips of tissue. B, Clinically unexpected finding of invasive prostatic adenocarcinoma infiltrating the smooth muscle of the bladder neck. C, Normal urothelium. D, Clinically expected urothelial carcinoma in situ (hematoxylin-eosin, digital magnifications ×0.5 [A], ×8.6 [B], and ×18 [C and D]).*

When introducing disruptive technology such as WSI into your primary diagnostic workflow, one should expect to encounter challenges. Issues experienced with the LHO initiative have come from 4 main sources: (1) IT infrastructure, (2) scanning throughput, (3) the WSI-LIS interface, and (4) the presence of a hybrid glass slide–digital slide workflow. Unacceptable lag and pixelation have resulted from episodes of viewer instability and/or higher than normal user traffic on the UHN or LHO networks. While infrequent, these episodes are disruptive and will be seen by some as a reason to avoid reviewing cases by WSI. The local privacy requirements of the UHN system are such that digital slides must be streamed from LHO as opposed to transferring digital files to a local server, although the latter option has been shown to markedly improve viewing performance.[59] While the scanner at LHO has a capacity of 400 slides, scanning times to date have averaged 2 to 3 minutes per slide. At this rate, 8 to 9 hours are required to scan 200 slides at ×20 (0.5 μm/pixel resolution). To increase the volume of slides scanned on a daily basis, LHO would need to move to round-the-clock scanning and/or purchase additional scanners. UHN has experienced episodes of WSI-LIS interface breakdown, many of which are attributable to barcode imperfections on the slides. Such slides are typically scanned without incident but will not cross the WSI-LSI interface to appear in the LIS. While occurring at a rate of at most 3 slides per month, these episodes are disruptive and are not always predictable by visually inspecting the barcodes ahead of placing slides in the scanner. UHN pathologists engaged in digital sign-out of LHO cases have a hybrid glass slide–WSI workflow, with most (>80%) of their workload being glass slides. Digital cases sit silently in an electronic worklist and must be actively sought as opposed to glass slide cases that are physically delivered to the pathologist. If pathologists do not monitor electronic worklists in the LIS, digital cases will languish on the worklist with associated TAT delays.

SUMMARY AND PEARLS OF WSI IMPLEMENTATION

The above overview was intended to provide guidance on the major issues to be considered by pathologists contemplating the introduction of WSI into clinical practice. Early efforts should be directed toward identifying initial clinical applications, assembling an implementation team, and identifying infrastructure and workflow requirements. A solid understanding of current-state glass slide workflow

and how this will change when WSI is introduced is essential. It is advisable to begin with a specific clinical application from which lessons will be learned that will facilitate subsequent expansion to new applications. Scanner selection should be based on intended use and budget, and careful attention should be paid to assessing image retention and archiving requirements as well as the need for WSI-LIS integration. Recognizing pathologist concerns over the use of WSI as a diagnostic tool, ensuring adequate training, and performing appropriate validation studies will help enhance the safe adoption of this technology. Consulting current guideline documents on the use of digital pathology as well as providing the "safety valve" of deferring digital cases to glass slide review will help to allay concerns of those new to WSI. There will be cases where deferral to glass slides is required; however, these should be infrequent. During the transition period from glass slide to WSI-based diagnostics, one should expect to encounter challenges associated with a hybrid glass slide–WSI workflow. With appropriate preparation and planning, WSI can be used for frozen sections, consultation, quality assurance, and primary diagnosis. Investing in WSI will also present laboratories with new opportunities for novel business use cases, as well as balancing workloads, supporting subspecialty practice, facilitating consolidation of services, fostering collaborations, and permitting computer-aided diagnosis.

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