

US Food and Drug Administration Approval of Whole Slide Imaging for Primary Diagnosis

A Key Milestone Is Reached and New Questions Are Raised

Andrew J. Evans, MD, PhD; Thomas W. Bauer, MD, PhD; Marilyn M. Bui, MD, PhD; Toby C. Cornish, MD, PhD; Helena Duncan, BBA, MJ; Eric F. Glassy, MD; Jason Hipp, MD, PhD; Robert S. McGee, MD, PhD; Doug Murphy, MT (ASCP); Charles Myers, MD; Dennis G. O'Neill, MD; Anil V. Parwani, MD, PhD; B. Alan Rampy, DO, PhD; Mohamed E. Salama, MD; Liron Pantanowitz, MD

• April 12, 2017 marked a significant day in the evolution of digital pathology in the United States, when the US Food and Drug Administration announced its approval of the Philips IntelliSite Pathology Solution for primary diagnosis in surgical pathology. Although this event is expected to facilitate more widespread adoption of whole slide imaging for clinical applications in the United States, it also raises a number of questions as to the means by which pathologists might choose to incorporate this technology into their

clinical practice. This article from the College of American Pathologists Digital Pathology Committee reviews frequently asked questions on this topic and provides answers based on currently available information.

(*Arch Pathol Lab Med.* 2018;142:1383–1387; doi: 10.5858/arpa.2017-0496-CP)

On April 12, 2017, the US Food and Drug Administration (FDA) announced the approval of the first whole slide imaging (WSI) system for primary diagnosis in surgical pathology.¹ This marked a significant milestone in the evolution of digital pathology, as prior to this pioneering event, lack of FDA approval was frequently cited as a major barrier to the adoption of WSI for clinical purposes.² The FDA announcement applies specifically to the Philips IntelliSite Pathology Solution (Philips Digital Pathology Solutions, Best, The Netherlands) for the review and interpretation of digital anatomical pathology slides prepared from formalin-fixed, paraffin-embedded tissue. The studies completed by Philips as part of its application to the FDA demonstrated 2 critical points that should bolster confidence with respect to using WSI for primary diagnostic work. First and foremost, its clinical trial demonstrated noninferiority of WSI to glass slides in terms of diagnostic concordance.³ Based on its findings, the FDA was thus satisfied that the risk to benefit ratio associated with the use of WSI is similar to that of conventional light microscopy. Secondly, this vendor's supporting technical precision studies demonstrated reproducibility of WSI when a single glass slide was scanned repeatedly with the same scanner or by different scanners of identical type. The FDA announcement additionally specified that pathologists must keep their microscopes for situations where, in their clinical judgment, it would be best to defer to glass slide review. Although FDA approval for primary diagnosis represents removal of a significant barrier to the widespread adoption of WSI, it also raises a number of questions concerning the past and future journey to regulatory clearance for digital pathology.⁴ This article addresses many of these questions and evaluates the impact of FDA clearance for WSI of primary diagnosis on

Accepted for publication March 22, 2018.

Published online April 30, 2018.

From the Laboratory Medicine Program, Department of Pathology, University Health Network, Toronto, Ontario, Canada (Dr Evans); the Department of Pathology and Laboratory Medicine, Hospital for Special Surgery, New York, New York (Dr Bauer); the Department of Anatomic Pathology, H. Lee Moffitt Cancer Center, Tampa, Florida (Dr Bui); the Department of Pathology, University of Colorado Denver, Aurora (Dr Cornish); Economic and Regulatory Affairs, College of American Pathologists, Washington, DC (Ms Duncan); Affiliated Pathologists Medical Group, Rancho Dominguez, California (Dr Glassy); the Medical Brain Team, Google, San Francisco, California (Dr Hipp); Covance, Indianapolis, Indiana (Dr McGee); the Surveys Department, College of American Pathologists, Northfield, Illinois (Mr Murphy); the Department of Pathology, Emory University Hospital, Atlanta, Georgia (Dr Myers); the Department of Pathology, Manchester Memorial Hospital, Manchester, Connecticut (Dr O'Neill); the Department of Pathology, Ohio State University Wexner Medical Center, Columbus (Dr Parwani); the Department of Pathology, Dell Medical School, University of Texas at Austin (Dr Rampy); ARUP Laboratories Incorporated, Salt Lake City, Utah (Dr Salama); and the Department of Pathology, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania (Dr Pantanowitz).

Dr Bauer is a consultant to Leica Biosystems. Dr Cornish is on the Pathology Imaging Advisory Board with Leica Biosystems and has US patent 9,214,019, "Method and System to Digitize Pathology Slides in a Stepwise Fashion for Review." Dr Hipp is a contractor for Google. Dr Pantanowitz is a consultant for Hamamatsu and is on the Medical Advisory Board for Leica Biosystems. The other authors have no relevant financial interest in the products or companies described in this article.

Ms Duncan and Mr Murphy are employees of the College of American Pathologists.

Corresponding author: Andrew J. Evans, MD, PhD, Department of Pathology, University Health Network, Toronto General Hospital, Eaton Wing, Room E11-223, 200 Elizabeth St, Toronto, ON M5G 2C4, Canada (email: andrew.evans@uhn.ca).

the digital pathology field, and on how pathologists may begin to incorporate WSI into their clinical practice.

WHY DID FDA APPROVAL TAKE SO LONG?

The specifics of the FDA regulatory pathway for WSI were recently reviewed.⁵ It is important to note that the FDA regulates vendors and claims they make about products. The FDA does not regulate pathologists. In order to protect the safety of all stakeholders, especially patients, FDA clearance is required for all medical devices that are to be promoted and sold in the United States. The FDA accordingly classifies medical devices based on perceived risk as well as regulatory requirements in the form of suitable controls. Devices deemed to be of highest risk that also lack general controls based on a previously approved predicate device are considered class III. Technically speaking, class III devices must follow a premarket approval (PMA) pathway that requires a clinical trial. Devices that successfully navigate the PMA pathway are therefore approved. Moreover, the manufacturer of the device must meet rigorous technical performance and manufacturing standards. By contrast, class II devices are considered moderate to high risk, have existing general and special controls, are substantially equivalent to another legally marketed device, and are cleared through the less resource-intensive 510(k) pathway.

Formal engagement between the FDA and WSI stakeholders began in October of 2009 when the FDA convened a public advisory panel in Gaithersburg, Maryland. The panel heard depositions from vendors, scientists, and pathologists (including the College of American Pathologists [CAP]) concerning the value proposition of WSI in patient care, approaches to validating WSI for diagnostic purposes, and how the technology was being used in countries other than the United States, as well as known risks of using WSI for clinical work and risk-mitigation strategies. Following the 2009 advisory panel, the FDA was essentially silent on WSI until October 2011, when it was announced that WSI systems should be considered class III devices requiring vendors to follow a PMA process. This was followed by predictions that the earliest approval would come in 5 years,⁶ which turned out to be accurate.

The FDA had no initial guidance for vendors on either technical performance standards or clinical trial design. The agency released draft guidance for vendors on technical performance assessment in 2014, with the final version being released in 2016.⁷ In 2012, a limited number of WSI vendors had begun independent discussions with the FDA on their PMA clinical trial design. This dialogue followed a presubmission process whereby vendors submitted potential clinical trial designs to the FDA for constructive feedback. Vendors requested face-to-face meetings with the panel and/or teleconferences to move the presubmission process forward. Issues central to the clinical trial design included the number and mix of cases to be assessed by WSI and glass slides, the number and type of pathologists reading those cases in the clinical trial, and the sources of the cases to be used (eg, academic centers versus community hospitals versus reference laboratories). The FDA was concerned about minimizing bias toward straight-forward diagnoses (or a limited spectrum of diagnoses) in the study set and specifically requested the inclusion of cases recognized as being challenging. The final PMA trial design was not officially announced until 2015, roughly 3 years after the first vendor engaged the FDA. The approved trial

design called for approximately 2000 retrospective cases. This design further stipulated that there were to be 4 reading sites, each of which would contribute approximately 500 of its own cases. Each reading site was to have its own scanner and to provide 4 pathologists to read its cases by WSI and as glass slides, with a suitable washout period between modalities. Study diagnoses made by WSI and glass slides were to be compared with each other and with ground truth diagnoses established by an expert panel or the original diagnosis at the time the case was signed out. Interobserver variability within and between diagnostic modalities could also be assessed in this design. The primary endpoint was the demonstration of diagnostic noninferiority of WSI to glass slides using a noninferiority margin of 4% or less, matching what had been proposed in the literature.⁸ As long as the WSI discordance rate compared with ground truth was not more than 4% greater than that for glass slides compared with ground truth, WSI would be considered noninferior to glass slides.

The expense, time requirements, and initial lack of guidance from the FDA were a disincentive for many vendors seeking approval for WSI via the class III/PMA route. An initiative led by the Digital Pathology Association (DPA) was instrumental in breaking this regulatory logjam. The DPA is a nonprofit organization comprising pathologists, scientists, technologists, and industry representatives dedicated to advancing the field of digital pathology by facilitating education and awareness of digital pathology applications in health care and life sciences. A regulatory task force within the DPA initially began collegial dialogue with the FDA in 2014. These discussions were intended to provide clarity on digital pathology regulations, identify risks of using WSI for diagnostic purposes, and provide risk-mitigation strategies. The DPA-FDA dialogue focused on a provision in the FDA Modernization Act of 1997 allowing vendors seeking clearance for devices deemed not substantially equivalent to previously approved devices to submit a *de novo* application. A successful *de novo* application would result in that vendor's system becoming a predicate device for all other WSI systems, downgrading WSI devices to class II and encouraging other vendors to approach the FDA for clearance by the 510(k) route.

EXACTLY WHAT DID THE FDA APPROVE AND WHAT ARE THE IMPLICATIONS?

The FDA considers WSI systems to be made up of 2 subsystems: (1) the image acquisition component (ie, the scanner) and (2) the workstation (ie, the image viewing software, computer, and display). The FDA also considers this entire digital pathology system to be a closed unit. Hence, an approved system becomes locked down, precluding the substitution of other nonapproved components. Indeed, substituting monitors, scanners, or viewing software, including viewing images in other formats, such as Digital Imaging and Communications in Medicine format, is currently considered off-label use. In so doing, the FDA has unintentionally created a temporary monopoly for one vendor in the digital pathology space. As a general guide for pathologists seeking to compare WSI systems, all slide scanning on the Philips IntelliSite Pathology Solution is performed at $\times 40$ with a resolution of $0.25 \mu\text{m}/\text{pixel}$ and a scanning speed of 60 seconds for a $15 \times 15\text{-mm}$ scan area. File sizes at this resolution vary depending on the scan area, but are in the range of 1.3 to 1.5 GB for $15 \times 15 \text{ mm}$. The

recommended monitor size is 21 inches or larger with a resolution of 1920 × 1200 or greater. The recommended connectivity is 1 GB/s, with a minimum requirement of 100 MB/s.

The FDA announcement has several positive implications. The benefits of FDA approval to the field of digital pathology can be considered from short-term and longer-term perspectives. The most significant short-term benefit is the adoption of WSI for primary diagnosis by laboratories in the United States. Those institutions that transition to using WSI for primary diagnosis will likely soon join laboratories in Canada,^{9,10} Europe,^{11,12} and Singapore^{13,14} that have been doing this for several years. The early experience from these laboratories indicates that, with proper preparation and planning, at least 95% of cases can be reported digitally without the need to defer to glass slides. The corollary is that review of glass slides with a light microscope will still be required in a small number of cases, as per the April 2017 FDA approval announcement. Cheng et al¹⁴ in Singapore implemented WSI with a primary focus on the reporting of small biopsies. In addition to workflow benefits and minimizing (if not eliminating) the chance of valuable biopsy slides becoming lost or damaged, this laboratory found the implementation of WSI was associated with a need for continual service management. Specifically, the implementation of WSI was not a one-time event, but required ongoing support from an interdisciplinary team comprising pathologists, technologists, institutional information technology personnel, and the vendor. The success of the program has required maintained attention to preanalytical (eg, slide quality), analytical (eg, scanning), and postanalytical (eg, pathologist interpretation) variables and laboratory accreditation issues associated with the use of digital pathology for diagnostic purposes. The experience of the Singapore group is similar to that of Thorstenson et al¹² in Sweden and University Health Network in Canada, where WSI was introduced in 2012 for primary diagnosis in particular subspecialty areas at a partner site east of Toronto.^{9,10} The University Health Network experience highlights the disruptive effect of a hybrid glass slide–WSI workflow with respect to getting pathologists to adopt the use of WSI for making diagnoses.¹⁰ Publications on the experience of laboratories in the Netherlands that have recently transitioned to complete digital reporting will no doubt provide valuable information on the impact of this technology on clinical practice.¹¹

Just how many pathology laboratories will transition and how quickly those laboratories will adopt WSI for routine diagnostic use will depend on the strength of their business case for adopting WSI. Individual laboratories will have to weigh the value proposition and potential return on investment for moving to WSI against the cost of implementing and maintaining these systems. The FDA approval addresses only one (ie, the regulatory hurdle) of several long-standing barriers to digital pathology. Transition cost, other information technology issues (eg, data storage), and pathologists' mindsets (eg, technophobia of WSI) are still formidable. Overcoming these other barriers will certainly require more time. As more laboratories validate and implement WSI for primary diagnosis across diverse clinical practice settings in the United States, the collective experience with digital reporting by WSI will be greatly enhanced. The body of literature on clinical applications of digital pathology can also be expected to grow, helping to improve guidelines and refine best

practices, as well as to reduce fears or misconceptions about using WSI for primary diagnosis. It is not the intent of the authors to claim that WSI is superior to light microscopy with respect to diagnostic accuracy. The FDA approval announcement specifically indicates that WSI is "non-inferior" to light microscopy.^{1,3} However, a WSI system that is fully integrated into a laboratory offers many benefits over light microscopy. These include, but are not limited to, improvements in patient safety through reduced slide misidentification errors, reduced risk of slide loss or damage, improved system-wide workflow through better workload allocation, case tracking, and reduced time to transfer slides to pathologists, allowing more rapid diagnoses on urgent cases. Digital pathology also offers faster access to external second opinion and a flexible platform for mobile reporting, as well as improved opportunities for teaching and mentoring, not to mention ergonomic advantages over the light microscope.¹⁵

The successful de novo application also paves the way for additional FDA-cleared WSI systems from other manufacturers. This should create more product choices for laboratories, encourage improvements in WSI technology, and perhaps ultimately lower the cost of these systems as vendors compete with each other to sell their products. This will undoubtedly cause the FDA to address the issue of plug-and-play digital pathology systems, as multisite laboratories will seek scanner-agnostic viewing systems and will not want to be forced into buying only one approved WSI platform. The current locked-down regulatory position will be difficult to reconcile if appropriately validated, non-FDA-approved or non-FDA-cleared WSI components have already been deployed within a given pathology network. Currently, there are no regulatory barriers to using nonapproved WSI systems for frozen sections or teleconsultation. Laboratories using WSI for uses other than primary diagnosis (eg, remote frozen section coverage) should still ensure that case-specific validation has been performed, documented, and approved internally for intended clinical use as per the CAP checklists. Quantitative image analysis of immunohistochemical biomarkers can be performed using either an FDA-cleared platform or a non-FDA-cleared alternative such as a laboratory-developed test, as long as the proper validation, quality control, and quality assurance requirements are fulfilled following the CAP checklists to deliver accurate, precise, and reproducible results. Using nonquantitative image analysis for immunohistochemical or special histochemical stains or digital reading of these slides represents another clinical use of WSI, but is not deemed to be primary diagnosis.

One potential longer-term benefit of FDA approval may be cultivating the development of machine-learning algorithms, once more laboratories have implemented and optimized WSI for standard visual interpretation of scanned slides and have amassed large WSI data sets. Although it may take time to develop and validate artificial intelligence systems specific to pathology, these computer-aided diagnosis algorithms nonetheless hold great promise. One example of computer-aided diagnosis to improve efficiency and quality is automating the screening and triage of cases before pathologists review them. As a result, we are witnessing several new start-up companies entering the digital pathology market. Machine learning will no doubt directly tackle the current issue of WSI being thought of as "too slow" and "not as fast as glass" for routine diagnostic

use, while at the same time improving precision and accuracy by decreasing the subjectivity inherent in histopathologic interpretation by humans. With the forthcoming era of computational pathology, it is important to remember that pathologists, not computers or software, make diagnoses. Machine-learning technology will hopefully augment the way we practice, and not be used to replace pathologists. Pathologists must take the lead in developing these algorithms as well as demonstrating the value they can add in terms of quality, efficiency, and improved patient outcomes. If we as a profession do not seize the day on this front, others will.

DOES FDA APPROVAL OBTAIN THE NEED FOR LABORATORIES TO INTERNALLY VALIDATE WSI FOR CLINICAL PRACTICE?

Laboratories involved in the CAP laboratory accreditation program that are seeking to implement WSI for any clinical application are still required to perform their own validation studies specific to the intended use of the technology.¹⁶ The CAP is currently preparing to update its original 2013 guidelines for validating WSI for clinical purposes. Although the clinical trial conducted by Philips included approximately 2000 cases, only small numbers of certain cases (eg, soft tissue tumors) in surgical pathology were represented in its study set.³ Therefore, it will be important for laboratories to validate that this technology performs as well as intended for their unique pathology practice setting. In addition to being a CAP laboratory accreditation program requirement, self-validation studies are important for several other reasons. When performing a validation study, laboratories are often able to identify other (eg, histology-related) issues specific to their laboratory that may need to be addressed in order to optimize workflow and/or image quality for diagnosis by WSI. For example, no digital image can be better than the quality of the original microscope slide. Similarly, the operator of the scanner may need to be sure that all of the tissue on the slide is included in the scanned image. Although the technology behind scanner design is intended to insure optimum image quality, performance of a validation study can help a laboratory identify issues related to glass slide preparation and quality that will optimize scanning workflow. These studies may also help pathologists navigate their learning curve with this technology, identify situations where they may wish to defer to glass slides, or anticipate when ancillary stains may be needed up front in instances where certain types of challenging cases will be reported digitally. The CAP Digital Pathology Committee acknowledges that there are recognized limitations for WSI. The recognition of *Helicobacter pylori* is challenging on hematoxylin-eosin slides scanned at $\times 20$ -equivalent magnification (0.5 μm /pixel resolution), especially when the number of organisms is small.^{17–19} The identification of small structures such as *H pylori* or acid-fast bacilli on WSI can be further complicated by artifacts such as tissue folds and air bubbles under coverslips. The inability to recognize polarizable material represents another limitation of WSI systems. However, these limitations can be managed. Hematoxylin-eosin slides requiring the identification of microorganisms can be scanned at a minimum of $\times 40$ magnification (at least 0.27 μm /pixel resolution). Pathologists can consider the use of up-front special stains and/or z-stacking of images to enhance the detection of specific microorganisms on scanned slides. Particular

attention should be given to preimaging steps such as tissue processing and microtomy to minimize artifacts known to adversely affect image quality. Finally, pathologists should ultimately exercise sound professional judgment on a case-by-case basis and defer to glass slide review when required.

The examination of cytology specimens by current-state WSI systems is challenging, as it requires multi-planar scanning with z-stacking of images.²⁰ The Philips system approved by the FDA does not offer z-stacking capabilities. As such, the examination of cytology material will never be included as an intended use for this particular system and was not included in its FDA approval. The FDA approval of digital pathology systems for primary diagnosis in cytopathology awaits the submission of applications to the FDA from vendors offering z-stacking capabilities and/or hybrid WSI–video microscopy devices. This creates a unique opportunity for vendors in the digital pathology space. It is also worth noting that the same issue applies to diagnostic hematology, where oil immersion is necessary. This specific intended use will also require regulatory approval.

DOES FDA APPROVAL ALLOW PATHOLOGISTS TO REVIEW AND REPORT CASES FROM HOME OR ANY LOCATION OTHER THAN THEIR OFFICE?

The current answer to this question in the United States is no, unless the pathologist has a Clinical Laboratory Improvement Amendments (CLIA) license for the pathologist's home or remote WSI workstation.²¹ Pathologists in the United States may be familiar with remote electronic sign-out of pathology reports from home, using a virtual private network to link with their laboratory information system, without the need for a CLIA license (eg, after glass slides have already been reviewed in their office and are not reviewed further at home). The primary diagnostic interpretation is not being made at home in this situation. In the United States, pathologists are required to make primary diagnostic interpretations while viewing slides in a CLIA-certified location regardless of the diagnostic modality used (ie, glass slides or WSI). According to the current CAP checklists, pathologists are at least able to engage in "infrequent" sign-out in a non-CLIA setting; however, a hard number, frequency, or percentage of cases qualifying as infrequent has not been officially defined. For the foreseeable future, pathologists considering primary reporting of WSI cases from non-CLIA-certified locations may not be able to bill for their services and potentially risk sanctions if they are inspected. This may leave pathologists asking how radiologists in the United States are able to report digital studies from home. The answer is that CLIA does not apply to radiology. To the best of our knowledge, CLIA does not apply to the interpretation of frozen sections and would not apply to the use of WSI telepathology for this purpose. It is, however, worth noting that CLIA originally became law in October of 1988. Hence, its detailed regulations were formulated well before the digital era, making it difficult to extrapolate those rules to contemporary practice involving WSI.

Under the terms of current FDA approval, the pixel pathway of an approved WSI system cannot be broken. For the immediate future, pathologists will not be able to substitute different monitors into the FDA-approved system whether the pathologist is reporting cases from the office or

at home. Thus, the minimum monitor specifications outlined above would apply regardless of where a pathologist is making diagnostic interpretations. Pathologists engaging in remote reporting of this nature should also be aware of privacy and security issues for best clinical practice in telepathology.²²

CONCLUSIONS

Although FDA approval has raised many questions and does not address all barriers to WSI, the April 12, 2017 announcement represents a huge vote of confidence for digital pathology and will undoubtedly facilitate the evolution of this technology. The aforementioned challenges that have arisen on the heels of the FDA announcement will hopefully be addressed by organizations like the CAP and DPA, with support from the growing number of laboratories that successfully incorporate WSI into clinical practice and their vendor partners. Such coordinated efforts to advance the responsible use of WSI and the development of associated artificial intelligence systems for clinical applications will help pathology strengthen its cornerstone role in contemporary medical practice.

All authors are current or past members of the College of American Pathologists Digital Pathology Committee (Dr Evans, chair, and Dr Glassy, past chair). Comments and/or questions on this article can be sent to the College of American Pathologists Digital Pathology Committee at digpath@cap.org.

References

1. US Food & Drug Administration. FDA news release: FDA allows marketing of first whole slide imaging system for digital pathology. <https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm552742.htm>. Accessed August 25, 2017.
2. Parwani AV, Hassell L, Glassy E, Pantanowitz L. Regulatory barriers surrounding the use of whole slide imaging in the United States of America. *J Pathol Inform*. 2014;5:38.
3. Mukhopadhyay S, Feldman MD, Abels E, et al. Whole slide imaging versus microscopy for primary diagnosis in surgical pathology: a multicenter blinded randomized non-inferiority study of 1992 cases (pivotal study). *Am J Surg Pathol*. 2018;42(1):39–52.
4. Kaplan KJ. What does FDA approval mean for the digital pathology market? part 1. Tissuepathology.com Web site. <http://tissuepathology.com/2017/05/15/what-does-fda-approval-mean-for-the-digital-pathology-market-part-1/#axzz4qnSRicY>. Published May 15, 2017. Accessed February 16, 2018.

5. Abels E, Pantanowitz L. The current state of the regulatory trajectory for whole slide imaging devices in the USA. *J Pathol Inform*. 2017;8:23.
6. Titus K. Regulators scanning the digital scanners. *CAP Today*. http://www.captodayonline.com/Archives/0112/0112a_regulators.html. Published January 2012. Accessed August 25, 2017.
7. US Food & Drug Administration technical performance assessment of digital pathology whole slide imaging devices. <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM435355.pdf>. Accessed August 25, 2017.
8. Bauer TW, Schoenfeld L, Slaw RJ, et al. Validation of whole slide imaging for primary diagnosis in surgical pathology. *Arch Pathol Lab Med*. 2013;137(4):518–524.
9. Evans AJ, Asa SL. Whole slide imaging telepathology (WSITP) for primary diagnosis in surgical pathology: a comprehensive validation study at University Health Network (UHN). *Mod Pathol*. 2012;25(suppl 2):391A.
10. Evans AJ, Salama ME, Henricks WH, et al. Implementation of whole slide imaging for clinical purposes: issues to consider from the perspective of early adopters. *Arch Pathol Lab Med*. 2017;141(7):944–959.
11. Stathonikos N, Veta M, Huisman A, van Diest PJ. Going fully digital: perspective of a Dutch academic pathology lab. *J Pathol Inform*. 2013;4:15.
12. Thorstenson S, Molin J, Lundström C. Implementation of large-scale routine diagnostics using whole slide imaging in Sweden: digital pathology experiences 2006–2013. *J Pathol Inform*. 2014;5(1):14.
13. Cheng CL, Azhar R, Sng SH, et al. Enabling digital pathology in the diagnostic setting: navigating through the implementation journey in an academic medical centre. *J Clin Pathol*. 2016;69(9):784–792.
14. Cheng CL, Tan PH. Digital pathology in the diagnostic setting: beyond technology into best practice and service management. *J Clin Pathol*. 2017;70(5):454–457.
15. Williams BJ, Bottoms D, Treanor D. Future-proofing pathology: the case for clinical adoption of digital pathology. *J Clin Pathol*. 2017;70(12):1010–1018.
16. Pantanowitz L, Sinard JH, Fatheree LA, et al. Validating whole slide imaging for diagnostic purposes in pathology: recommendations of the College of American Pathologists (CAP) pathology and laboratory quality center. *Arch Pathol Lab Med*. 2013;137(12):1710–1722.
17. Hartman DJ, Pradhan D, Pantanowitz L, Duboy L. How does digital magnification on different whole slide scanners affect the assessment of gastric biopsies for *Helicobacter pylori*? *J Pathol Inform*. 2016;7:S31–S32.
18. Snead DR, Tsang YW, Meskiri A, et al. Validation of digital pathology imaging for primary histopathological diagnosis. *Histopathology*. 2016;68(7):1063–1072.
19. Thrall MJ, Wimmer JL, Schwartz MR. Validation of multiple whole slide imaging scanners based on the guideline from the College of American Pathologists Pathology and Laboratory Quality Center. *Arch Pathol Lab Med*. 2015;139(5):656–664.
20. Hanna MG, Monaco SE, Cuda J, et al. Comparison of glass slides and various digital-slide modalities for cytopathology screening and interpretation. *Cancer Cytopathol*. 2017;125(9):701–709.
21. Clinical Laboratory Improvement Amendments (CLIA). Centers for Disease Control and Prevention Web site. <https://wwwn.cdc.gov/clia/Regulatory/default.aspx>. Accessed February 13, 2018.
22. Pantanowitz L, Dickinson K, Evans AJ, et al. American Telemedicine Association clinical guidelines for telepathology. *J Pathol Inform*. 2014;5(1):39.