J Pathol Inform

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Editorial

Regulatory barriers surrounding the use of whole slide imaging in the United States of America

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Received: 02 July 2014 Accepted: 07 August 2014 Published: 21 October 2014

This article may be cited as:
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.

Available FREE in open access from: http://www.jpathinformatics.org/text.asp?2014/5/1/38/143325

The last decade has seen significant technology advances in the evolution of whole slide imaging (WSI) with the ability to rapidly digitize large numbers of slides automatically and at high resolution. Many applications have emerged and, as a result, WSI is increasingly being used in both clinical and research areas.[1-4] One of the major barriers that has halted the widespread use of this technology in the United States has been regulatory issues, particularly the impact of classifying WSI devices as Class III by the U.S. Food and Drug Administration (FDA).

Whole slide imaging technology provides pathologists with an ability to archive, review, analyze and share their digital slides. There are a wide range of WSI devices available that are being marketed at various cost points. Many pathologists have acquired or are considering the acquisition of one or more of these WSI scanners. One of the key advantages of WSI is that it offers the pathologist remote access to the entire slide. Other advantageous features include automated scanning of large numbers of slides, easy acquisition of high resolution digital images that simulate microscopy, capability to simultaneously view multiple, synchronized images, interactive medium for education using annotated digital slides, and the availability of value-added software for teleconferencing, image management, and image analysis. Those pathology practices that are using WSI scanners now have the ability to establish additional outreach services via telepathology, digitize slides for quality assurance purposes (e.g. overeads, proficiency testing), education (e.g. digital teaching sets, tumor boards), and documentation (e.g. archiving consult and medicolegal cases). The use of WSI technology is not only useful for pathologists but also for the many patients who now have an opportunity for their cases to be reviewed by recognized experts providing avenues for improved diagnosis and quality assurance. WSI has already been shown to have had a positive impact on education, quality assurance, and patient care.[5,6]

Whole slide imaging has also seen widespread use in research, especially in the arena of experimental image analysis. Because advanced WSI scanners are able to work with both transmitted light and fluorescent modes, it is possible to use WSI for immunohistochemistry, immunofluorescence, and fluorescence *in-situ* hybridization. These research applications have the potential to provide useful diagnostic assays, particularly in the field of companion diagnostics. Additional opportunities for improved patient care come from the ability to globally share cases. More recently, we have seen the emergence of several vendor/private and institutional digital pathology networks developed around this technology. Several anatomical pathology practices currently using WSI have invested significant

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DOI: 10.4103/2153-3539.143325

effort to integrate their digital slides with the laboratory information system, and have initiated a digital workflow towards supporting a "slideless" laboratory.[7] It is technically feasible to use WSI for routine pathologic diagnosis if the images are an accurate representation of the scanned glass slide. Several studies have shown that when those conditions are met, there is little to no statistical difference between a diagnosis rendered via WSI as opposed to one rendered via conventional microscopy with a glass slide.[8] Some investigators note, however, that a review of a WSI may take participants longer than a review of a glass slide, while others point out that WSI without z-stacking may not always be suitable for cytopathology and hematopathology.[2,3]

Pathologists in some European countries and Canada have been able to advance their clinical efforts with WSI, because they have been using WSI for initial (aka. Primary) diagnosis (i.e. signing out cases based solely on the review of the digital slide).[9-12] Ironically, in the USA where much of the pioneering work in WSI has occurred,[13] the events surrounding the use of WSI for primary diagnosis have been slow in evolution. In the U.S. the FDA have approved a number of specific and limited applications of WSI for care such as the use of automated cell-locating devices and quantification of immunohistochemistry results (via a 510 K approval process) (e.g. HER2). These specific applications have a defined scope, and are equivalent to prior practices and overall offer advantages with minimal safety risk.

However, the progress toward widespread use of WSI for primary diagnosis has been dampened and significantly delayed largely due to regulatory issues surrounding the use of this technology, particularly the classification of WSI devices as Class III devices by the FDA. Microscopes are Class I subject to specific limitations while WSI, which utilize a microscope as one of its components is classified as Class III. Pathologists remain confused and are unclear if WSI scanners can still be used for primary diagnosis if they are validated as a laboratory developed test (LDT). In the United States, the FDA typically allows LDTs to enter the market without prior approval from the Agency (http://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm212830.htm). Prior to this announcement, WSI system vendors were hoping that the FDA would declare WSI systems as Class II (moderate risk devices that already have a predicate device on the market) or as Class I (no pre-market notification required). The FDA utilizes the Class III categorization to label devices that pose the "highest risk"period Class III devices are, therefore, the most highly regulated of all medical devices, requiring not only general controls (e.g. quality system regulation and good manufacturing procedures), but also premarket approval (PMA). As a result, individual WSI systems now have to be rigorously validated for every intended use – and it is not yet known how narrow or broad an intended use can be. These validation studies may be too expensive and too difficult for smaller companies to perform, and some have thus chosen not to pursue approval or marketing in the USA. For companies that have the resources, a large amount of invested time will be required to accomplish this. However, even those companies with the resources and desire to pursue a PMA, they too, have been held back as the FDA has not publicly issued any specific guidance with respect to clinical validation performance standards. There is a critical need by the regulatory agencies to issue detailed guidelines clarifying the design of a PMA study and/or what type and extent of evidence is needed to achieve a down-classification of the WSI device to Class II. As a result of this lack of direction and related regulatory issues, progress with WSI technology in the USA may be abandoned or placed on hold as vendors continue to navigate these regulatory hurdles. On the basis of the seemingly lack of progress of PMA approval of WSI devices in the USA, we estimate that the first FDA-approved WSI systems for primary diagnosis are at least 2 years away and to get this approval it is most likely going to cost the industry millions and millions of dollars. In the interim, improvements in rapid access to subspecialty experts and the resulting diagnostic quality gains is on hold in the USA. It should be noted that these WSI devices are innovations which are capable of advancing care and enhancing productivity and reducing costs, unfortunately, as a result of these regulatory hurdles, efforts to advance their use in the USA continues to languish or are deferred to other countries to take the lead. It should be noted that the FDA regulates device manufactures, not clinical laboratories and not individual physicians. The FDA has the authority to exercise enforcement of federal regulations over device manufacturers that inappropriately market a device (including *in vitro* diagnostic devices and tests) as a medical device without approval. Marketing a device includes its promotion and advertising and even labeling of the device itself. Manufacturers can legally market a device in two ways: (1) as an '*in vitro* diagnostic device'(IVD) or (2) 'research use only (RUO)' device; the latter to be used for research purposes only. The FDA ensures that manufacturers abide by the proper labeling and marketing of both IVD and RUO devices. Recently, the FDA tried extending their jurisdiction of this enforcement in a draft public guidance. In this draft proposal, the FDA was trying to prevent manufacturers from selling RUO products (that are legally marketed as such) to customers if they knew the customers' intentions were to improperly use the device beyond RUO. RUO products in laboratories have long been used by laboratorians to develop their own LDTs, many of which help the public get access to important diagnostic tests. However, the RUO provisions by the FDA sought to

limit the use of RUO through policing of manufacturers, thereby secondarily restricting how a laboratory performs testing. For this reason, this draft guidance was the subject of much debate between reagent or device vendors and the FDA. Manufacturers along with the help of various members of Congress have introduced legislation that would aim to help secure the availability of LDTs and prevent the FDA from seeking to regulate their use through manufacturers (House Resolution 3003 – Medical Testing Availability Act). As a result of the public backlash, the FDA retracted the provision to bar companies from selling products to labs that intend to use medical devices beyond the scope of its labeled use (Regulatory Affairs Professionals Society , November 2013 FDA Removes Controversial Provision from Final Guidance on IVDs. http://www.raps.org/regulatoryDetail.aspx?id=9686). (accessioned on August 6, 2014).

All of this is relevant to WSI because it is clear that the FDA does not have the authority to regulate laboratories. However, it appears that they are attempting to do so through regulating WSI manufacturers, creating a long and bumpy road ahead for labs who would like to use WSI for clinical diagnostic work. Even though laboratories are not regulated by the FDA, they must abide by other governing regulatory bodies such as CLIA and the College of American Pathologists (CAP) accreditation programs, not to mention the individual medical licensing of the physician. As such, although the FDA's decision to regulate WSI as a class III device will certainly impact the ability of manufacturers to 'market' their WSI systems, this should not and does not impact a laboratory's ability to use these devices according to its own medical and professional obligations.

On the bright side, efforts by both industry and academia to deal with the issue of WSI validation are ongoing.[2-4] On the industry side, several vendors are continuing to work with the FDA on PMA and device validation. Organizations such as the CAP, Digital Pathology Association (DPA), and American Telemedicine Association are advocating the use of this promising technology to advance patient care and provide rapid access to expert opinions. The CAP has been a strong advocate of digital pathology and despite the lack of guidance from the FDA, has continued its march forward toward helping pathologists adopt WSI technology. The CAP took a positive step in the right direction when they convened an expert panel which was tasked to develop guidelines for the validation of WSI for diagnostic purposes.[8] These guidelines, which are based on scientific evidence and expert opinion, will allow pathologists to now move closer towards actually using validated WSI technology in a safe manner to improve patient care. The DPA has continued its efforts to bring industry leaders and key opinion leaders together with the FDA and other regulatory agencies via dissemination of sentinel white papers and panel discussions at their national meetings. The FDA has been receptive to input from the DPA and other professional organizations. It should be noted by both laboratories and pathologists that a WSI manufacturer's claims when cleared by FDA do not alleviate the requirement by the labs to carefully design protocols to implement, validate, test and train users on the appropriate and safe use of these WSI systems for patient care. This is true for any instrument or test in our laboratories which are either FDA-cleared or lab-developed tests.

In summary, it is clear that WSI is a key enabler of improved patient care and provides pathologists with the ability to share cases with experts. These WSI devices are reliable, provide portability, ease of sharing, and retrieval of archival digital images. Even more powerful is the ability to couple these images with computer-aided image analysis tools. WSI has proven benefits for remote consultation, as it is easier to move an image than it is to move a pathologist or patients' glass slides. While pathologists in other countries have already received approval to use WSI for routine diagnostic use, (http://www.cap.org/apps//cap.portal?_nfpb = true and cntvwrPtlt_actionOverride=%2Fportlets%2FcontentViewer%2Fshow and _windowLabel = cntvwrPtlt and cntvwrPtlt%7BactionForm.contentReference%7D = cap_today%2F0613%2Fmiles_away.html & _state = maximized and _pageLabel = cntvwr) regulatory barriers in the United States of America are preventing patients from reaping similar benefits from this promising and ground-breaking technology. There is an immediate need to overcome regulatory barriers and guide WSI device manufacturers, allowing pathologists to be equipped to utilize WSI and further develop this technology. Some specific actions by the FDA may be to reconsider the class III designation and/or issue reasoned and reachable guidance to the vendors as to the kind of studies that are needed to meet the requirements for approval. The authors of this editorial call for urgent resolution and clarification to the murky regulations currently hampering WSI before the digital pathology candle burns out.

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