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Editors

Digital Pathology

Historical Perspectives, Current Concepts & Future Applications

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Chapter 1
Introduction

Keith J. Kaplan

Healthcare, an information-based industry, is in a state of transition. The current focus of attention on health information is taking place in an environment in which better access to effective healthcare has been identified by governmental leaders as a societal goal. In several countries, including the U.S., governments are funding programs to develop comprehensive patient electronic health records.

This reflects recognition of the critical importance of information management in almost every aspect of the healthcare enterprise, ranging from individual patient care to disease prevention and public health. The ultimate goal of creating large information systems to permanently archive cradle-to-grave electronic patient health records is regarded as technically feasible as well as achievable in the foreseeable future. Such patient electronic health records would contain plenary data sets, including the digital images of all imaging studies ever performed on the patient, securely archived but readily accessible, on-line, to patients and their designated service providers.

The electronic patient health record concept can be taken even further by expanding its scope to include patient healthcare-related education information. This might be accomplished by appending a personal electronic health education portfolio to each electronic health record.

Tools would be developed to assist patients in navigating between the information in their linked electronic health records and their personal health education portfolios. Using mass customization techniques, patient information could be continuously updated on an individualized basis. Another futuristic concept is the development of on-line patient self-evaluations.

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Patient proficiency testing could be used to evaluate the patient's current capacity for self-help to manage his/her own healthcare in light of his/her health status, environment, and other relevant information.

The creation of such comprehensive electronic health records would eventually have implications for all facets of the healthcare industry, including the practice of pathology. For pathology to fully participate in the digital revolution in healthcare, pathology imaging will have to be in digital formats. It is anticipated that whole slide images (WSI), as described in this book, will be a key component of laboratory reports in electronic health records and will be universally retrievable by patients' healthcare providers.

A goal of healthcare planners is to have pathology picture archiving and communication systems (PACS)–telepathology systems, as well as the information systems of all other medical specialties, linked by telecommunications to networks of information systems that archive comprehensive patient electronic health records. Thus, whole slides would become an integral component of electronic health records as part of laboratory reports. The new generation of whole slide processors will be critically important because they will enable pathology laboratories to go fully digital without interfering with a laboratory's workflow or throughput, for the first time.

The medical specialty that generates the largest number of digital images today is radiology. Remarkable progress has been made in taking radiology departments filmless and fully digital over the past two decades. In radiology, going fully digital means that all imaging processes are in digital formats, from the point of image acquisition to image storage. Radiology PACS are regarded as standard equipment at larger institutions. The benefits of having a radiology PACS are numerous and include making radiology studies immediately available on hospital wards and in decentralized doctors' offices. It permits the simultaneous access of physicians to the results of studies carried out by various imaging modalities (i.e., CAT scans, MRIs, PET scans, etc.). The radiology PACS is a critical component of the infrastructure for many digital teleradiology services.

Going fully digital has a somewhat different connotation for the field of pathology. Whereas a radiology image can be recorded directly on an electronic sensor, a pathology specimen mounted on a glass slide is a physical object. It is unlikely that pathology laboratories would be able to go fully digital in exactly the same way as radiology departments, although some work is being done on the direct imaging of paraffin-embedded tissue blocks. It is reasonable to expect that glass slides will remain part of pathology practices into the foreseeable future, although pathologists might stop looking through light microscopes when WSI microscopy becomes routine.

Once pathology glass slides of histopathology sections, cytopathology preparations, blood smears, microbiology stains, etc., are routinely archived in pathology PACS–telepathology systems, the range of telepathology services can be expanded.

For example, at institutions equipped with pathology PACS–telepathology systems, patients could potentially gain access to immediate second opinions on their cases on-line from experts. This type of service is currently available at a few institutions on a rather limited basis.

In addition, pathology reports of patients with specific diseases could be re-reviewed as new concepts of the disease are validated and new therapies are introduced. With the widespread introduction of new data mining services, old pathology reports would become living documents, available for reassessment and forming the basis for new actions that could benefit patients later in life. It has been estimated that 200,000,000 paraffin blocks of surgical pathology cases, and their corresponding glass slides, are currently in storage at laboratories in the U.S. [1].

Digital pathology systems offer pathologists an alternate, emerging mechanism to manage and interpret information. They offer increasingly fast and scalable hardware platforms for slide scanning and software that facilitates remote viewing, slide conferencing, archiving and image analysis. Deployed initially and validated largely within the research and biopharmaceutical industries, WSI is increasingly being implemented for direct patient care. Improvements in image quality, scan times and image-viewing browsers will hopefully allow pathologists to more seamlessly convert to digital pathology, much like our radiology colleagues have done before us. However, WSI creates both opportunities and challenges. While niche applications of WSI technology for clinical, educational and research purposes are clearly successful, it is evident that several areas still require attention and careful consideration before more widespread clinical adoption of WSI takes place. These include regulatory issues, development of standards of practice and validation guidelines, workflow modifications, as well as defining situations where WSI technology will really improve practice in a cost-effective way. Current progress on these and other issues, along with improving technology, will no doubt pave the way for increased adoption over the next decade, allowing the pathology community as a whole to harness the true potential of WSI for patient care. The digital decade will likely redefine how pathology is practiced and the role of the pathologist.

This book provides an overview and reference framework to help pathologists and laboratory professionals with the implementation of digital pathology in their clinical laboratories. The appropriate use cases, role in medicine, education, business models, consultations and regulatory requirements among others topics applying to digital pathology will be discussed.

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Chapter 2
Use Cases for Digital Pathology

Wenyi Luo and Lewis A. Hassell

Introduction

Perhaps one of the biggest challenges for pathologists today is managing the huge amounts of data which are generated daily. Although glass slides are highly efficient ways to convey the information needed to make the initial diagnoses, they are often inefficient, expensive, and time-consuming when it comes to physical management, consultation, education, and research. Digital Pathology (DP) is an environment for the management and interpretation of pathology information that is enabled by the digitization or other electronic transformation (imaging) of a glass slide. It provides a potentially more efficient and cost-effective means of presenting, transmitting, archiving and transporting pathology information. Whole slide imaging (WSI) is now the primary means of digital pathology image capture although other methods such as single field-of-view-based approaches—e.g. a digital camera on a microscope or streaming video with or without robotic microscopy, are also considered part of digital pathology and may be preferred for specific applications. In this chapter, we will provide some use cases to demonstrate a variety of ways that digital pathology can be used to facilitate pathology practice and education. Specific research applications will only be discussed cursorily.

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Making a Tissue Diagnosis

The paramount task of pathologists is to make tissue diagnoses that will inform patient care. Almost all pathologists today grew up making diagnoses by examining the glass slides under the microscope, yet digital pathology is gradually making its way into our daily work. It may be just the abandonment of film for gross photography, or the incorporation of fixed digital microscopic images in a presentation, but there is hardly a pathologist today who does not use digital images in some form (CAP survey 2014, personal communication).

In our institution, several variations of digital pathology are employed, ranging from WSI in selected tumor boards to streaming video telecytology for adequacy assessment. The adoption of these means has been highly individual user and context based (for example, some tumor boards do not use WSI still, due to user preference and pacing or logistical issues.) We have also used DP for consultations within and outside our department, for both routine and frozen section (FS) cases and to archive unique materials. We also employ extensive educational uses as well [1, 2]. Despite the fact that digital pathology has not yet been approved by the Food and Drug Administration (FDA) for primary diagnosis [3], the feasibility of using digital pathology in daily surgical pathology practice is being evaluated and validated by many practices for a variety of applications, including initial diagnosis [4–6]. The concordance rate of light microscopy and whole slide imaging is 94 % in dermatopathology [4], 95 % in gastrointestinal tract pathology [7], 93 % for breast pathology [8] and 95–97.7 % in two studies composed of mixed cases [9, 10]. The discordance is mostly caused by a lack of experience with the use of digital pathology or technical difficulties such as scanning at a fixed 20× magnification. Other limitations also include difficulties of viewing nuclear details, polarizable foreign material or identifying the presence of microorganisms. Whole slide imaging is also well suited to decrease the inter-observer variation in issues such as Gleason grading of prostate cancer [11].

Digital pathology using WSI is widely employed for consultation, both intra-institutional and at long distances between practices. Validation of this method has been performed by multiple institutions, and several software platforms exist to facilitate this kind of linkage of expertise. The FDA has determined that they will not regulate uses in this realm. We'll discuss this use case more below.

Although there are a variety of technologies available for telecytology, real-time image transmission involving an image stream, sent immediately upon acquisition, and continually updated as the specimen is reviewed, is particularly suitable for adequacy assessment. Such system usually enables the observer to control the review or instruct the on-site microscope operator to perform certain actions including changing the field of view, the magnification, or fine focusing to allow for an unbiased review [12]. Significant advantages may be offered by whole slide imaging since it enables the viewers to review the entire slide with a resolution similar to a standard light microscope though it comes with some cost and its application in telecytology has not been widely evaluated yet [13]. So-called *z-sacking* technology considered crucial for cytologic evaluations is not yet well automated for mobile, point of care-type scanners.

Undergraduate Pathology Education

Digital pathology is playing a major role in undergraduate pathology education. Over 60 % of the medical schools in the United States use digital slides exclusively (http://www.cap.org/apps/docs/education/OnlineCourseContent/2010/ET/RoleDigPath/player.html, accessed 5 Nov 2014). It is also widely adopted in dental schools, veterinary schools and many other fields.

Virtual or digital slide box is one type of internet-based pathology learning system offering a collection of hundreds of high resolution scanned slides organized by organ systems. These usually have accompanying text and references and allow users to magnify a part of the picture to mimic the function of a microscope. Many medical schools have their own virtual slide boxes adapted to their specific needs. Some of them offer additional utilities such as a question and answer format, interactive annotations and video panning. Some of them are capable of switching between learning mode and test mode for added flexibility.

The Virtual Slidebox created by Dr. Fred R. Dee at the University of Iowa is a prototype for the system above mentioned [14]. Pathology education based on digital slides has been shown to increase the time students spend studying slides, lower barriers to access, and result in better or at least no change in performance on examination. (http://www.cap.org/apps/docs/education/OnlineCourseContent/2010/ET/RoleDigPath/player.html, accessed 5 Nov 2014 [15]) The evidence suggests that pathology education based on digital slides is at least comparable to the education based on real slides [16]. A similar study using digitalized slides with a higher magnification (up to 1000×) demonstrated additionally that a majority of the students favored digital slides over traditional slides. They felt that digital slides were an effective learning tool, enhanced learning, were easy to use, and promoted collaboration and discussion. Also, students using digital slides tended to view their performance, instructor feedback, and their learning environment more positively than students using traditional slides [17]. Use of virtual slides is also much more efficient for faculty, with a reported tenfold decrease in requisite faculty resources needed (University of Barcelona, personal communication).

Pathology Residency Education

In the past decade, the Accreditation Council on Graduate Medical Education (ACGME) has shifted the emphasis in graduate medical education to one which focuses on specific areas of competency essential to practice medicine, specifically these six areas: patient care, medical knowledge, communication skills, professionalism, practice-based learning, and system-based practice. Some competency statements in each core competency can be directly linked to digital pathology-enabled or measureable skills [18]. Digital pathology, by incorporating electronic tracking of examination time, observed area, and magnifications used, for example, could provide quantitative metrics to assess a resident's habit of examining a slide and

skills to find diagnostic features, which are all part of patient care competency. A well-organized collection of digital slides can also serve as an atlas of review cases supplemental to textbooks to increase residents' exposure to a wider array of diseases and to solidify their medical knowledge. Meanwhile, digital slides serve as a means of review for board exams and offer a means for consistent measurement of the diagnostic skill progress. In addition, a digital pathology workflow potentially enables assessment of residents' communication skills by capturing residents' sign-out and comparing it to attendings' sign-out, and by observing their ability to appropriately select and present areas of significance during meetings or remote conferences. Practice-based learning requires residents to use current and archived case material to guide, study, and expand knowledge and identify gaps in their abilities and knowledge from quality assurance data trends. Digital pathology allows for the side-by-side comparison between a historical slide and a current slide and real-time monitoring of the accuracy of the diagnosis therefore helping residents to meet these competencies. Additionally, digital pathology breaks the barriers to both informal and formal consultation and promotes standardization of diagnostic criteria to facilitate systems-based practice. Moreover, since digital pathology enables creation of a virtual pathology laboratory, simulation-based education becomes possible, allowing significant reduction in training costs for both trainees and faculty [19]. (How are we part of the problem-and the solution? *CAPConnect*, 2014 Oct 24, http://community.cap.org/2014/10/how-are-we-part-of-the-problem-and-the-solution/, accessed 3 Nov 2014).

The user interface is considered a critical factor for adoption of whole slide imaging in residency education since pathology residents who have mastered the utility of the microscope and glass slide recognize how readily tremendous amounts of information are conveyed efficiently through that medium. Many current digital pathology configurations are haunted by cumbersome and slower user interfaces which are quickly recognized as being inefficient compared to glass slides. Strategies to remedy this are being developed but substantive improvement will be highly dependent on the development of key aspects of the accompanying information technology tools [20].

Continuing Medical Education

Digital pathology is now a significant part of postgraduate education. Digital slides are now ubiquitously used in pathology meetings covering anatomical pathology topics, including the conferences by esteemed pathology societies such as United States and Canadian Academy of Pathology (USCAP) and College of American Pathologists (CAP). As noted above, all the tumor board materials in our institution are presented with either digital photographs or whole slide imaging. Unlike real slides which need to be searched and retrieved each time before conference and are subject to loss and damage, digital slides are easily archived and readily retrievable and well suited for discussion of patients undergoing serial biopsies who may

benefit from comparative continuing monitoring. An obvious shortcoming of traditional real slide-based meetings is that their duration is usually limited and fields of view may be biased according to the pre-conference understanding of the issues associated with the case. Whole slide imaging allows pathologists and clinicians to revisit the pathology slides at their convenience. Features or details that may not be well perceived or omitted are better appreciated and new or modified diagnoses may be rendered in asking and answering clinical questions in real time. Digital pathology thus engages interactions within and beyond the meeting room and facilitates ongoing virtual meetings.

Digital pathology is transforming the ability to create enduring educational materials. Both USCAP and the CAP have provided unknown challenges in the format of WSI to members accompanied by detailed expert explanations. The Digital Pathology Association (DPA) website lists all the online whole slide imaging databases and provides links to these. It includes many sizable collections including the Juan Rosai Collection of Surgical Pathology Seminars from 1945 to present. None require membership and are freely available to the public. Similarly, most pathology textbooks are now offering online access to digital materials in the form of digital images (primarily fixed fields) which are used to demonstrate pathological features in a more cost-effective way than the paper based volumes. These digital images offer a richer reader experience and allow students additional study materials and educators the images that can be directly used in teaching sessions. Beginning in January 2011, *Diagnostic Pathology* has offered authors the opportunity to publish whole slide images. Over 50 % of their authors have accepted the opportunity with suitable articles [21]. In 2014 *Archives of Pathology and Laboratory Medicine* also started publishing digital slides for selected articles [22]. These digital images offer a more complete microscopy context and greater information that is more applicable to real-world experience. Users can use them as a source of future references when they meet similar cases in practice and comparison as the diagnostic criteria evolve. The durability of such postings however has not been fully established. Inasmuch as costs may be one barrier to more journals adopting this tool, studies validating the educational value which are achieved when these materials are referenced could be of value in moving others to adopt this method.

Proficiency Testing and Qualifying Exams

DigitalScope, a robust whole slide imaging display tool capable of serving many simultaneous viewers, is currently used by the CAP in proficiency testing for hematology, parasitology, bacteriology and andrology, with other disciplines under study or development. It allows for magnification from 5× to 100×. Individual objects on hematology and parasitology slides are labeled with numbers to allow test takers to look at the same object in the same order. This solves the intrinsic limitations of previous real slide-based and fixed image proficiency tests and allows better assessment of true proficiency in the live environment.

A significant portion of microscopic materials presented on the American Board of Pathology exams has been based on digital slides since 2005. Based on that, the Pathology Resident Wiki, an online encyclopedia targeted at pathology residents, has compiled a list of links to digital images which are organized by organ systems and can be readily used for board review purposes (http://pathinfo.wikia.com/wiki/Pathology_Resident_Wiki, accessed 5 Nov 2014). Digital slides may also be potentially used in other types of exams including but not limited to competency assessment, pre-employment evaluation [23], and validation of frozen section or immunohistochemistry interpretations when combined with new modalities, although the experiences in these areas have not been abundant.

Consultation

Digital pathology is being used in consultation in two major settings: intra-procedure consultation and consultation on permanent sections. In terms of format, digital consultation can be classified as local when that consultation is performed between colleagues in the same practice but at a different site, and remote consultation when a distant consultation outside the practice is involved to give expert opinions. Local consultation can be used in intra-operative consultation to enhance access to specialists or expand the range of coverage offered to rural sites. Local digital consultation can easily engage two or more pathologists simultaneously in the same case for instant quality assurance. Digital Pathology also facilitates subspecialist practice by enabling convergence of difficult cases from the same organ system to subspecialty-trained pathologists.

Telepathology-based consultation can be used for intraoperative frozen sections, but the added time may bump up against the time expectations of routine frozen section. Its use is also hampered by the need for video-assisted gross examination and clean flat sections that can provide high image quality. However, a recent study on virtual slide telepathology with scanner systems for intraoperative frozen section consultation [24] demonstrated that although the time needed for each case is 35.6 ± 1.65 min, the average time spent on each frozen section is only 10.58 ± 8.19 min. 98.59 % of all intraoperative frozen sections were accurately diagnosed in the initial telepathological assessment. This study supported the use of digital pathology in intraoperative frozen section.

A separate validation study on the use of digital pathology in consultation was also performed to address the concern that consultation cases are fundamentally more difficult than the cases used for validation of digital pathology in primary diagnosis and validation results for primary diagnosis might not be valid for consultation cases. One study involving 217 consultation cases evenly distributed between organ systems and 26 pathologists demonstrated only 0.92 % major discrepancies. These discrepancies included atypical versus nonatypical endometrial hyperplasia in one case and reactive squamous changes versus carcinoma [25]. Therefore, digital pathology can be effectively used in remote consultation. Appropriate training and institutional validation are still needful however.

Quality Control and Quality Assurance

Digital pathology has great potential in quality control of diagnostic pathology by integrating the quality control process into the daily workflow. Since whole slide imaging can be accessed remotely, a just-in-time consultation or review with colleagues can be conducted in real time. The time for physical transfer for quality review is eliminated and the turnaround time is shortened. In fact, real-time consultation can be employed at any point in the diagnostic process from gross evaluation, frozen section interpretation, ancillary testing, or final review. Digital pathology breaks the institutional and national boundaries and facilitates collaboration on challenging cases.

The quality of the technical components (staining consistency, sectioning, etc.) can also be assessed with tools of digital pathology. Current quality assessment of the section or staining quality is based on pathologists' continuous evaluation of the sections or staining of the same specimen. It is subjective and prone to significant inter-observer and temporal variation. However, a more objective assessment can be achieved with digital pathology by comparing current section or staining results with previous ones using certain measurable parameters to insure consistent performance. Even just subjective visual trending over time can be more readily displayed and detected using side-by-side arrays of QA slides or stain controls.

Digital pathology lowers the barriers to accessing prior slides (assuming they have been scanned) for comparison purposes, enabling better continuity of care. It may also reduce the need for expensive stains often used to "prove" a new case is the same as the prior diagnosis. But the number of institutions in a position to take advantage of this benefit is limited due primarily to decisions regarding which cases are scanned and how long images are retained.

DP offers the potential for prospective inclusion of quality control materials into the diagnostic workflow. Due to the fact that current quality control of diagnostic pathology is mostly based on retrospective assessment, a diagnostic pathologist can continue to make potentially erroneous diagnoses for months before a higher than acceptable error rate is detected by retrospective review methods. Digital pathology allows for insertion of quality control materials blindly into the daily workflow so that the everyday diagnostic work of the pathologists can be evaluated in an ongoing and prospective manner. This "random insertion" functionality, on the other hand, offers a potentially meaningful way of conducting performance improvement or proficiency testing [26]. It helps avoid the inherent limitation that these test materials are often treated mentally differently allowing the assertion that test results lack correlation with daily diagnostic performance.

Advanced Image Analysis

Computer-assisted diagnosis based on automated image analysis is the ultimate goal of digital pathology. The basic idea of automated histopathologic image analysis is to use a series of mathematical algorithms to process images that enables the segmentation of picture elements into regions of interest based on their color, texture, and/or context [27].

Today automated image analysis is still in its childhood. Many image analysis software tools can perform quantification of immunolabeled cells or areas and are currently used in certain applications such as human epidermal growth factor receptor 2/neu quantification, estrogen receptor and progesterone receptor applications. A method to obtain stain distribution across a pathology slide was recently proposed [28]. It has been used experimentally to detect macrophage infiltration in a cardiac transplantation rejection animal model and facilitate the nuclear grading of clear renal cell carcinoma [29] successfully.

The higher level of utilization would be identification and quantification of histological features to facilitate diagnosis or even make an automated diagnosis. For example, a tool which reliably quantifies the metastatic tumor cells in a lymph node could significantly speed up the sign-out of breast lobular carcinoma and melanoma cases when metastases to the lymph nodes are very subtle and easily missed, or in head and neck malignancies where more than one hundred lymph nodes can be isolated. The realization of these will ultimately depend upon the progress of artificial intelligence in pattern recognition and establishment of diagnostic algorithms [30]. A commercial pattern recognition software has been evaluated for its ability to identify lung metastases and compared to manual methods. The software was able to differentiate metastatic carcinoma and lung in all tissue sections, and sensitivity reached up to 98 % and specificity to 97 % [31]. The limitation of the software is obvious: it took 4–8 h to train it and 40 min to find metastases on each unknown testing slide; the sensitivity and specificity are significantly decreased when a more complicated scenario such as teratoma is encountered. Therefore, automated diagnosis would only be possible when more sophisticated pattern recognition technologies are developed.

Optimized Archive Management

Digital pathology provides an optimized means of archiving pathology information. Rather than sequestering valuable slides in stacks on the pathologist's floor, slides are maintained in searchable electronic storage media and thus continuously available for teaching and patient care by multiple users. The risks of breakage, faded stains (especially for immunofluorescence for example), loss or misfiling are replaced by presumably lower system IT failures, hard drive meltdowns or power outages [32]. DP reduces tissue consumption so that tissues can be preserved for additional diagnostic studies or research. More remote consultations are expedited and made simple. Simultaneous consultation by multiple pathologists at a distance is also made possible. In addition, digital pathology is particularly advantageous for archiving materials which are unique or of limited availability such as medical-legal materials or incoming consults. Losses due to physical damage or misfiling are eliminated and availability of borrowed materials is enhanced. All of these facilitate the business purposes of a pathology service, while also advancing education and patient care quality.

A primary consideration when planning digital archiving however is creation of a strong information technology support system, a robust backup strategy, and readily expandable storage. As the diagnostic equivalency of whole slide images to glass slides is being established, both storage methods need to be maintained and the redundant storage may actually increase the resources spent on slide archiving [27].

Other Business Uses

DP can also create added business value by offering direct links with clinicians and patients. Some practices have employed QR codes linked to the case slide within patient reports allowing for clinician review with their patients, or simultaneous conversation with the sign-out pathologist. Patients wishing to maintain copies of their medical materials can more easily obtain digital files to transport for second opinion elsewhere. While such marketing efforts may not be key initial attractants for new business, these kinds of linkages create "stickiness" in terms of ongoing business arrangements. The marketing value of DP may also be seen on the educational side of things, where resident relative rankings of programs sometimes hinges on whether or not they will be adequately prepared to enter the DP age prepared from extensive experience, or trying to quickly catch up.

Provision of imaged slides for use in bio-banking, clinical trials enrollment and other pertinent clinical and non-diagnostic business areas can also be accomplished more readily using WSI [33].

Medical Research

Image-based cell counting has long been used in basic medical research to quantify cells which express certain fluorescent proteins or cells that are labeled with colorimetric dyes for cell viability analysis. All automated methods are based on pure cell cultures and merely involve complicated pattern recognition algorithms as for pathology slides.

Digital pathology and image analysis also has potential use in tissue biomarker research, which is critical for personalized medicine. Development of new drugs for novel targets present in different quality and quantity in different individuals requires the concurrent development of "companion biomarkers" which identify specific patient populations who will potentially benefit from the new drugs. Digital pathology has significant roles across the entire development process of a new drug which include but are not limited to biobanking, analysis of biomarkers in tissue microarrays, and remote review for trial and therapeutic arm selection [34]. DP coupled with image analysis tools may supplant the needs for more expensive bio- or molecular markers which may be found to have morphologic correlates, for example.

DP also potentially changes the paradigm for research review and reporting. Traditional ways of presenting research results have employed "representative" images entirely based on the choice of the authors, and therefore biased and potentially misleading. No matter how stringently criteria are applied, investigators have the intent to choose the images that support their hypotheses and desired outcomes either consciously or subconsciously. Whole slide imaging has the advantage of offering more objective evaluation of the research materials and primary morphologic data in the form of WSI (data transparency) but also retains the flexibility of allowing authors to annotate areas of interest to demonstrate their points.

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Chapter 3
Role in Medicine for Digital Pathology

Bernard Têtu and Lewis A. Hassell

Introduction and Historical Background

Digital pathology (DP) has been implemented around the world mostly for education, clinical pathological conferences, quality control and research. Its introduction into diagnostic activities such as intraoperative consultations (frozen sections) and expert opinions (secondary consultation) is increasing steadily. The adoption for primary diagnoses and telepathology on a routine clinical basis is also increasing but at a slower pace. The College of American Pathologists (CAP) defines telepathology as "… the practice of pathology, in which the pathologist views digitized or analog video or still image(s), and renders an interpretation that is included in a formal diagnostic report or documented in the patient record" [1]. Prior to 1990, different experiences using either static image or dynamic-robotic telepathology systems were independently attempted to provide diagnostic services. Dr. Ronald Weinstein was the very first pathologist to experience telepathology as part of a multiservice between the Logan Airport and the Massachusetts General Hospital in 1968 using an analog technology [1, 2]. In 1986, a telepathology system combining a color video and a robotic microscope was used successfully between El Paso, TX and Washington, DC. This same year, the term telepathology was introduced [2]. In Europe, the very first telepathology experience for frozen sections was performed

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in Norway, using a dual static/dynamic system between two cities situated 420 km apart [3]. Since then, telepathology has been developed primarily to provide diagnostic service to remote regions experiencing a shortage of pathologists or to support sites in the third world, mostly in Africa, [4]. The 1990s was a decade of major digital technological breakthroughs with, for example, the introduction of automated slide scanners with image analysis algorithms for cervical cytology smears screening [5]. 1990s and 2000s were decades of intensive development of international teleconsultation platforms. The most popular were the AFIP system in Bethesda, USA, the iPATH in Basels, Switzerland, and the UICC-TPCC in Berlin [6]. More recently, an international Virtual Pathology Institute (VPI) has been created in Germany [6], a DP consultation portal (https://pathconsult.upmc.com/) has also been developed at the University of Pittsburgh Medical Center [7] as have similar brokered consultation services offered through DP companies and, in 2011, the European telepathology forum called Medical Electronic Consultation Expert System (MECES) was launched, taking advantage of the experiences of iPATH and UICC-TPCC in combination [5]. Important improvements in the quality of the images and reduced scanning times have become available in the 2000s. Since the introduction of this technology, a large number of studies clearly demonstrated that the quality of the virtual images were not inferior to the microscope [8], which paved the way to the expansion of telepathology for clinical use. Canada has been a leader in the development of patient-centered telepathology networks [9, 10], in good part because of the geographical challenges but also thanks to the initiative of a few leading pathologists and the availability of public financial support. New algorithms using the digital technology such as those allowing quantitative analysis of immunohistochemical cancer markers for estrogen receptor, progesterone receptor and HER2 were also developed in the 2000s [5]. Finally, the 1990s and 2000s are the decades of development of national and international Societies and Meetings focusing on DP. In 1992 the first European conference on telepathology took place in Heidelberg and the first international meeting on telemedicine in Tromso, Norway [5]. Later, several societies and companion meetings were created namely Pathology Visions (originally under the sponsorship of Aperio, and later the Digital Pathology Association), the International Academy of Digital Pathology, the European Congress on Digital Pathology, European Congress on Telepathology and International Congress on Virtual Microscopy, to name only a few of them.

Out of all this, several critical roles can be seen emerging in medicine. Herewith we summarize the key points of each of these.

Applications of Digital Pathology

Education

DP has made a profound impact in medical education at all levels. This began with activity from many institutions looking for ways to exploit this new technology to their advantage. As computer networks and laptop computers became more commonplace,

the need for floor-space-occupying microscopy labs held at fixed times and using glass slides in varying states of cleanliness and completeness was viewed as less and less of a priority. The shift from glass to virtual slides or whole-slide images (WSI) in basic histology and pathology courses in medical, dental, veterinary and other health sciences has been dramatic and is nearly complete. Since Fred Dee reviewed the landscape in 2009 [11], the pace of the transition has not abated. Current US medical school graduates entering pathology training almost uniformly have been tutored using digital rather than glass slides, and an increasing number of international graduates as well as trainees in other disciplines. The transition has been accelerated by several factors highlighted in Table 3.1.

In the post-graduate realm, WSI have many advantages as well, such as in the creation of teaching libraries, documentation of resident competencies, and hastening skill acquisition in slide examination [12–15]. Training residents in specific disciplines, stain interpretation and other activities are enhanced with this tool [15]. WSI also offer the same access advantages to programs with multiple sites of resident activity and teaching conferences at a single site.

Post-graduate medical education paradigms are also enhanced and altered by the ready adoption of WSI. On-line slide libraries are useful to students, residents and practitioners alike (see https://digitalpathologyassociation.org/whole-slide-imaging-repository for comprehensive listing). WSI are extensively used by certifying boards in the US and elsewhere, further indicating the utility of these in the educational assessment realm. Furthermore, several journals have added WSI access capabilities to their publications to enhance learning [16] and research value.

Table 3.1 Pros and cons of glass vs. digital slides in education environment

	Glass slides-fixed microscope	Virtual slides-anywhere viewing
Advantages	• Existing infrastructure • Carry-over skill to practice	• Faculty time saver • Annotate-able • Rare features made widely viewable • Adaptable to group or individual study • Access anywhere, anytime • Computer interface less intimidating • Makes lab-space multiuse • Adapts to testing easily • Thumbnail view for orientation
Disadvantages	• Faculty-time intensive • Slides maintenance • Feature selection limited by need for many cuts • Student time demanding • Microscope use learning curve • Physical storage space	• Investment in software and equipment • Diminished faculty contact to model pathology • Device and network speed may lead to slow slide loading, frequent pixilation • File compatibility and viewer issues

Research

DP brings a new set of tools to the research realm. From the studying of the fundamental manner in which a diagnosis is determined to extracting new lines of data from multispectral analysis of imaged slides, DP is yielding a rich array of new knowledge. The adoption of DP for just conventional veterinary microscopy has had a profound impact on pharmaceutical work by allowing the electronic linkage of study sites and expertise, supplanting the need for moving people or samples between data collection centers. The quantitative image analysis tools that can be applied to digital images have further expanded the field and entered routine clinical care in many niches. Image search algorithms, rare event identification routines, stain quantization and similar options all now combine to offer the researcher using tissue analyses a new armamentarium.

Tumor Boards and Patient Education

Multidisciplinary patient conferences such as tumor boards benefit from inclusion of pathology materials, in the form of digital slides, accessed live in much the same manner that radiologic imaging or endoscopic data is often reviewed in these settings [17, 18]. Some technologic barriers, such as loading speeds still can pose a challenge in some fast moving conferences, but the ability to visually demonstrate microscopic anatomy and relationships in these settings enhances team-based care and builds confidence in the pathologist, as shown in Table 3.2. Likewise, digital

Table 3.2 Tumor board presentation of pathology materials comparison

	Glass slides	Digital slides (WSI)	Fixed digital images
Advantages	• Primary data • Cheap • On-the-fly questions can be answered	• Superb low-power images • On-the-fly questions can be answered • Quickly move between slides	• Control of fields shown • Presentation speed fast
Disadvantages	• Filing/refilling • Microscope with video camera required • Physical movement • Low power images often not high quality	• Slides must be scanned in advance • Pixelation	• On-the-fly questions cannot be easily answered • Preparation time increased • Low power images more difficult to demonstrate

slides open the opportunity for inclusion of links to these in patient reports which can either be shown directly to the patient, or accessed in a virtual conference format. Some evidence suggests that these kinds of educational efforts improve patient compliance and outcomes (J. Hunt, personal communication.)

Clinical Work

The penetration of DP into day to day clinical care of patients has no doubt been slower than device manufacturers would have hoped, impeded by some of the regulatory barriers, and the variations in the degree to which economic or workflow advantages have been demonstrated or apply to a given setting. Food and Drug Administration (FDA) approval of various quantification algorithms for prognostic marker reporting has allowed this DP tool to become standard practice in most clinical centers. In some settings such as consultation with disseminated specialists (e.g. Clarient's model, see http://www.clarientinc.com/about-us/clarient-pathology-services.aspx, accessed 4 Nov 2014), DP is also routine. Opening timely access to remote technical services for immunohistochemistry (IHC) or other specialized stains has been similarly readily adopted as a DP business solution. A similar early adoption scenario has been followed for frozen section coverage of sites not continuously staffed by an on-site pathologist [19]. These now form the foundation on which telepathology using WSI is now practiced in several locations [20]. Practice guidelines for telepathology and validation guidelines for the use of WSI now exist to guide broader adoption [21–23], in advance of regulatory approval for primary diagnosis in the US though such approval does exist for Canada [23, 24]. Several compelling use cases also exist for cytopathology [25].

Technologies

Static (Store and Forward) Image Telepathology

Static image telepathology means the capture and storage of still images, whether microscopic or macroscopic, using either a microscope or a macroscopic platform with transmission of the captured images to a remote recipient. This is the most simple and certainly the cheapest modality to transmit images. Despite these clear advantages, only part of the whole slide is captured and the major limitation is the representativeness of the captured field which is dependent on the operator. Advantages and disadvantages of this form of telepathology are presented in Table 3.3.

Table 3.3 Comparison of technologies used for telepathology (adapted from Pantanowitz et al. [7])

	Static	Streaming	WSI
Advantages	• Low cost • Vendor independence • Technical simplicity • No special software required to view images • Small manageable files • Systems easy to maintain	• Real-time transmission • Up-and-down focusing possible	• A large number of slides can be scanned without supervision • Image can be viewed from any computer with a web interface • Relatively low bandwidth required • Entire specimen can be stored, retrieved and shared indefinitely • Access to entire case • Possibility of producing unlimited copies of images with high resolution. • Software for teleconferencing, image management, and image analysis available.
Disadvantages	• Interpretation limited to captured field of views • Some expertise needed to capture images • Image acquisition labor intensive with possibility of sampling error • Frequent lack of clarity and poor focus with low power magnification	• No compatibility with current LIS • Higher bandwidth required • Technician required on site during the viewing session • Host navigating and focusing requires some expertise	• Significant time required for slide scanning • Cost of equipments • Lack of multi-planar focusing for cytology • Need for increased resources to scan glass slides • Speed of image acquisition and image resolution often limited • Limited vendor interoperability

Streaming/Dynamic/Robotic

Streaming telepathology represents the live transmission of images from a microscope or a macroscopic platform using a digital streaming camera (such as a static digital camera with streaming software or a digital video camera). A voice connection such as via telephone or teleconferencing may allow a live communication between the referring and the consulting individuals. The streaming image can be either controlled by the referring personnel with a standard microscope equipped with a digital camera or by the receiving observer with the use of a robotic microscope. Streaming telepathology may be more labor intensive than WSI, especially with the use of a robotic microscope, but recent experience shows that in certain situations, it may be somewhat faster because it skips the intermediary scanning step.

In a setting of reasonable bandwidth and transmission speeds, the ready availability of screen-sharing tools may make this also the most economical option. The possibility of performing up-and-down focusing is also viewed as a major advantage in certain subspecialties such as microbiology, cytology and haematology. Dynamic telepathology appears as the mode of choice for providing immediate adequacy assessment of cytology specimens by telecytology [7]. Advantages and disadvantages of this technology are presented in Table 3.3.

Whole-Slide Images

WSI involves the use of an automated microscopic glass slide scanner that captures serial images from the entire specimen on a microscope glass slide which are 'stitched' together to create a virtual image. This image is then stored and can be viewed remotely via an image management software. Whole slide imaging is a complex telepathology solution but presents numerous advantages listed in Table 3.3. At this point in time, WSI appears to be the most promising modality for most applications in the anatomic pathology laboratory [21]. Extensive literature is available on the reliability of WSI for major clinical activities such as intraoperative consultations (frozen sections) [10, 26–28], secondary consultations [10, 29–31] and primary routine pathology work [8, 9, 20, 32].

Hybrid Multi-modality Telepathology Systems

Recently, despite the increasing use of WSI for clinical applications, there has been a re-emergence of interest at using dynamic-robotic telepathology systems, in part, to circumvent the lack of real-time up-and-down focusing using the WSI technology and possibly also concern over delayed FDA approval of WSI for primary diagnosis. In most if not all hybrid systems, a low magnification image is captured and forwarded to the telepathologist who, after examination of the image, uses a live telecommunications link to view areas of interest at higher magnification [33]. It is worth noting that early telepathology systems used in the 1990s were in fact examples of 'hybrid' multi-modality telepathology systems [2]. WSI uses the Z-stacks technology, which provides multiple images at different levels, to compensate for the lack of real-time focusing capabilities. The major disadvantages of this technology are the significantly increased scanning time required, the huge size of images and the frequent need to rescan the slide to obtain the needed level of interest. Hybrid telepathology systems combine static and dynamic technologies and, therefore, real-time focus adjustments are provided by the dynamic-robotic telepathology module. The major advantages over WSI are the shorter turnaround time needed to render an urgent diagnosis, for example in the case of a frozen section, and the possibility of live up-and-down focusing on specific areas where cell aggregates are present, such as in many cytopathology specimens.

Mobile Devices

Smartphones and other mobile devices offer a great potential to perform telepathology because they are relatively cheap compared to commercial slide scanners, they are portable, provide internet connectivity, possess excellent digital cameras and can be easily attached to a microscope. The University of Pittsburgh Medical Center recently launched an application to be used with the iPhone which provides a solution to submit DP images for expert opinion and to incorporate a diagnostic report into this web-based application [34].

Recently, the Food and Drug Administration has approved such an application for use with radiologic images [35]. Image fidelity and resolution makes the iPad potentially suitable for WSI evaluation of frozen sections or consultations. Current literature shows that the accuracy of frozen section interpretation is acceptable but difficulties with slide navigation at high magnification causes frustration leading to an increased risk of diagnostic errors and is viewed as one of the major obstacles to a more widespread use [35].

Target Population for use of Digital Pathology

Academic Centers

DP clearly resonates with the mission of the academic center on all three fronts, education, research and clinical care. As noted above, DP enhances the educational capability of the center for undergraduate, graduate and post-graduate audiences. DP expands the toolbox for researchers in academia, whether they are working on a basic science issue studying expression of characteristics on the cellular or subcellular level, or seeking translational data using tissue materials, or studying the outcomes of a category of patients enrolled in a clinical trial. On the clinical care realm, DP clearly offers a solution for getting diagnostic samples to the right subspecialist consultant quickly and efficiently, whether for initial evaluation or in consultation after first viewing [19]. Clinical care conferences, which at academic centers abound, as noted above are also enhanced by use of DP, and simplify the movements of people and information.

Remote Hospitals

Access to care is the major challenge for residents in rural or remote areas, and usually this is due to the difficulty in retaining specialists, or even enough primary care-givers in the community. In Canada, for example, lack of access to pathologist frozen section support has been often cited as a reason a surgeon does not wish to

practice in a small hospital [36]. The uneven quality of diagnostic services in these areas so highly dependent on the quality of a single practitioner is also problematic. Engagement in a DP-network and other networks can be part of an excellent solution for rural hospitals on the tissue and microscopic diagnosis front, as it can be in the general lab realm. In these settings the utility of DP is not limited to surgical pathology but also often needs to include other aspects of microscopy [37]. Application of DP and telehealth tools generally has been a long-term priority of the US military system in recognition of the value of this approach [38, 39].

Large Cities

Access to optimal care is often not a problem limited to rural or remote settings. As hospital or healthcare systems expand their reach and offer services in more decentralized ways, one not uncommonly encounters the demand for specialized services (frozen sections, especially) in low volume settings which would be wasteful of a full-time pathologist, or settings where sub-specialist support of a general pathologist would offer better quality care [40]. This movement towards "point of care" pathology cannot be accomplished without the benefits of DP. Such settings also underscore the need for low cost scanners or other imaging tools of varying capacity or throughput that can be deployed across the system to facilitate image exchange and consultation.

Developing Countries

Access to care is THE problem in developing countries, stemming not just from economic disparities, but also to lack of specialists, technical and professional training opportunities, and to healthcare and social or governmental infrastructure. In any comprehensive evaluation of the solutions to this issue, the particulars may vary somewhat between locations, but engagement in a DP network is at least a part of the solution [41–45]. The accompanying figure demonstrates the dramatic difference in distribution of pathologist subspecialists in various countries of the world, and highlights a great disparity that DP can begin to bridge. Charitable, humanitarian and for-profit ventures are in progress to address or exploit these disparities (Fig. 3.1).

Barriers and Facilitators to Implementation

Despite overwhelming advantages to the use of DP for clinical use, several barriers to a more widespread adoption of the technology have been repeatedly reported [1, 5]. Evaluation studies identified technological, organizational and human factors to

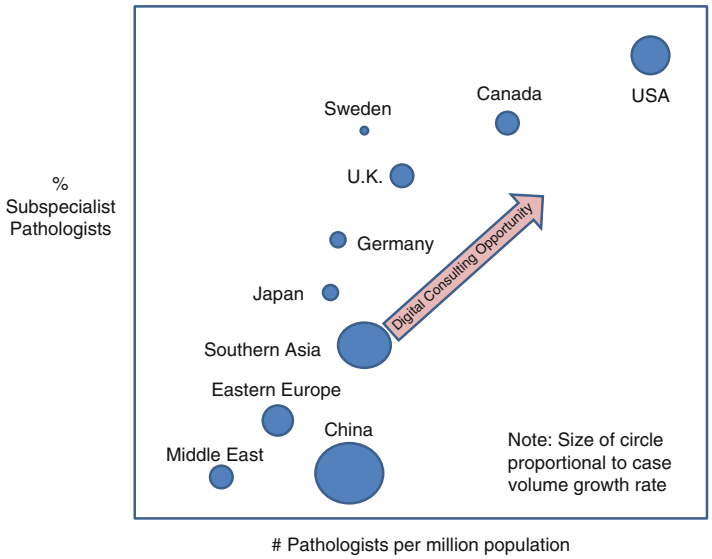

Fig. 3.1 Distribution of pathologists and proportion of subspecialist pathologists

explain the relative resistance of pathologists, surgeons and technicians to use telepathology. Human factors remain however among the most important challenges [46]. For one thing, since glass slides are still available, many pathologists are reluctant to abandon their comfort zone and prefer to keep using the microscope. Furthermore, surgeons hesitate to trust pathologists whom they know little and, conversely, pathologists can have reservations to work with technicians they do not know. Success relies on efficient change management strategies including close tutorship and a highly coordinated effort between medical, laboratory staff, biomedical, administrative and IT support teams working on different sites. Despite all those supportive efforts, it is clear that telepathology also requires pathologists and surgeons to change their work practices, and to develop mutual confidence between distant technologists, pathologists and surgeons. The recently released guidelines on whole slide imaging validation for diagnostic purposes by the College of American Pathologists [23] and of national guidelines such as those of the Canadian Association of Pathologists [21], the Royal College of Pathologists [47] and The American Telemedicine Association [22] are among the strategies aimed at encouraging wider adoption of the technology by the world pathology community.

However, additional technological improvements are also needed to reach this goal. It is clear that the technology has not reached the same level of maturity as teleradiology, mainly with regard to software application ergonomics, more specifically to the speed and the ease of user interfaces that are often seen are inadequate [2, 12]. Furthermore, most commercially available DP solutions cannot be easily integrated with local laboratory information systems making their use laborious. Archiving and image retrieval is also an important challenge because of the size of

digital images. Finally, difficulties at clearly visualizing micro-organisms and the need to rescan a fair number of slides for varying technical reasons [48] represent other barriers to a more widespread use of the technology in the routine practice. Technological advances in DP have however been significant in recent years and recent experiences confirm that pathologists are increasingly comfortable with the use of the technology [9].

Legal and Licensure Issues

Regulatory issues have been a major psychological and financial barrier to DP, drawing so much attention that scientific and organizational advances have seemed to pause [49–51]. No scanners or systems to produce WSI have been FDA approved for use as a tool for primary (initial) diagnosis. But this FDA stance, designating these devices as Class III (high risk, no comparable device) [52] has been challenged by many DP advocates as too restrictive for a tool used by licensed physicians to make a medical diagnosis. Canadian regulators classified the devices as Class II [24], and regulatory approval was obtained by three manufacturers in 2014. Indeed the FDA stance does not preclude pathologists from validating their planned use and proceeding to use WSI "off-label." The College of American Pathologists has issued guidelines for this purpose [23]. The FDA only governs what claims the manufacturer can make in marketing their device, though in the past, the FDA has attempted to leverage vendors ability to sell to sites they had reason to believe were going to use a product for clinical off-label purposes. Scanning systems and imaging algorithms have been FDA approved for ER, PR, and Her2 scoring [53].

Centers for Medicare and Medicaid Services (CMS) and other payers in the US have not taken a position on WSI relative to reimbursement, aside from their stance on other technologies or tools that require a laboratory to validate their use prior to patient reporting and billing for services. In certain Canadian provinces, reimbursement issues have been successfully negotiated with the pathologists community [46].

Telepathology also raises unique liability issues because of its capability to transcend jurisdictions. Physician multi-jurisdictional licensure is a major issue in the United States where pathologists may be involved in several states requiring a different license. It is also an issue in other federal countries such as Canada and in unions of independent countries such as the European Union [54]. The ability of DP to allow the distant separation of the patient, the patient sample and the diagnostic images raises physician licensure issues similar to those encountered when digital radiology services began to offer round-the-clock interpretation from physicians located oceans away from the patient [55]. The general standard has been that the physician must be licensed in the location (state) where the patient is being treated. But a similar requirement is not mandated for a consultant rendering a subsequent opinion on a sample. As DP service systems begin to grow and offer much wider (initial) access to sub-specialist diagnosticians, no doubt the role of state licensure boards in assuring quality of care will come under pressure to streamline the scrutiny.

The current existence of national practitioner databanks for adverse events may be the precursor of nation-wide licensure in the US. A much broader query about this issue arises in the matter of international consultation, reimbursement and licensure, a matter which is likely to undergo transition as the practices become more wide-spread.

Organizational Issues

Many aspects of DP require high levels of organization and infrastructure, particularly in informatics. The generation of a high volume, data-dense information stream from pathology imaging poses a storage and integration challenge in order to optimize the value of DP to clinical medicine, or other endeavors. Critical decisions about system and storage/viewing organization have long term implications and should be made with these considerations in mind. Device and data integration however are not the only issues as workflow, and conventional histology production must also be optimized to enable a successful transition to DP adoption, even on a limited scale [38, 56]. Workspace design and user interface issues must be addressed as well.

One difficulty at establishing a telepathologynetwork in jurisdictions with a public health care system such as in Canada and the European Union is to bridge the gap between the need to offer consistent pathology coverage in a region and the necessity for each institution to prioritize its own in-house cases and to meet predefined turnaround times. Several factors such as tradition of practice, institutional regulations, shortage of pathologists and the lack of financial incentives to read distant cases, are among the major barriers to the development of such integration but the affordances of telepathology will force healthcare networks around the world to redefine the routing of surgical pathology cases and adopt a more integrated and comprehensive pathology coverage. These kinds of issues mandate the casting of a broad net of stakeholders when contemplating a project so that benefits and costs that accrue and are incurred asymmetrically can be managed successfully. Aligning competing interests in this way can predict success where otherwise a stalemate would be the result.

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Chapter 4
Business Models in Digital Pathology

Connecting Patients, Pathologists, and Others

Lewis A. Hassell

Introduction

The advent of many different tools for applying digital imaging tools to pathology images is reflective of the myriad uses of these materials in the healthcare realm, ranging from the research laboratory seeking to establish the safety of a new drug, to the teacher seeking a more accessible way to enable students to learn fundamental pathologic processes. When speaking of the kinds of places where whole slide scanners reside today, and where they will be tomorrow, one needs to understand the use cases discussed elsewhere, along with the technical and regulatory landscape that has been erected around them. But more importantly than even these perhaps it is vital to recognize the value that digital pathology (DP) has, does, and potentially can add to the activities which previously have relied on "hard copy" glass slides and fixed location microscopy. Because DP doesn't eliminate steps or many other fixed overhead costs in the same way that digitization did for radiology [1], the returns on investment have a strikingly different combination of costs and benefits geared more to the context of use.

Successful and Sustainable, and Other Goals

The triple mandate in healthcare, and perhaps in other businesses as well, has been faster, better and cheaper. While the relative gains on these three axes may vary between products, the assumption that one could succeed by simply advancing on one or two of the three has proven to not always have been true as more settings demand

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movement on all three. (Disruptive innovations that change the size of the market by providing a dramatically cheaper product or service that is of inferior quality but still "good enough" to "get the job done" for a segment previously not consuming a product or service might be cited as an exception to this; however, it can also be argued that to those previously non-consumers, the advance still represents an advance on all three axes (Clayton Christensen Institute, Jobs to be Done, http://www.christenseninstitute.org/key-concepts/jobs-to-be-done/ accessed 11 Nov 2014).

In order for DP to be successful in a setting, it must be sustainable economically, i.e. the value or benefit brought must at least equal the costs expended. To a single pathologist viewing the cost of delaying receipt of his glass slides so that they can be scanned digitally, and requiring him to examine them in that manner using an interface that often takes more time to navigate, and at best is equal to his facility with a glass slide and conventional microscope, the costs seem obviously skewed against the innovation. Critically however, those costs and benefits often must be viewed in a much larger context than the simple economies of a single stakeholder. This need to assess and gain buy-in from multiple stakeholders with economic interests involved presents one of the key barriers to sustainability. It also may go without saying that the "economic" interests of one or more parties may be difficult to value in the market, and hence to some observers seem to be irrational choices. (Such might for example be the reputation gain that comes from being early in adoption.)

The change in value that DP brings to a given situation may also be viewed as either disruptive of existing models or as an adaptive improvement. Consultations that required physical movement of slides over vast distances at great cost (both in terms of funds and time) are suddenly fairly simply and cheaply moved and the answer returned digitally, changing the dependence on delivery services, airline schedules, and even clerical personnel to package and ship. While this change would be disruptive to the intermediaries' business models built up around this process, it does not fundamentally change the paradigm of diagnostic expertise and the patient, pathologist and consultant relationship. In contrast, the availability of digital pathology resources to allow a teenager in Lahore to study and master the same materials as the graduate trainee in Los Angeles and thus ultimately add the same value to the care of a patient alters the dynamic for patients in either location. Similarly, the availability of advanced DP tools for image search, comparison (and potentially also diagnosis) may make the entire care paradigm much more fluid [2]. For the sake of this chapter however, we will focus on existing models or proposed models.

Assumptions

There are several key assumptions on which these business models rest both in the present and projecting ahead. But these assumptions should not be considered eternal truths when many minds and strong incentives exist to shift them.

1. Tissue is the issue. By this we mean that for a very vast array of diseases, study of the tissue and cellular architecture microscopically yields crucial information for treatment decisions.

2. The various preservation and staining processes applied to tissue, with all their artifacts and shortcomings, will continue to provide reliable information, and potentially newly correlated information, predictive of behavior of diseases.
3. Given the enormous wealth of information available from sectioned tissue, expert interpretation is critical to the discernment of noise from information in tissue and the assignment of diagnoses based thereon, i.e. a pathologist, and potentially a very specifically trained sub-specialist pathologist, has value to add.
4. The distribution of this critical expertise is highly uneven around the world, or even within a single practice.
5. Patients and society benefit when the truth (i.e. the right diagnosis) is known.

If you can comfortably accept these long-standing, but still tenuous assumptions, we can move on to a discussion of the value and how organizations might be structured to allow value to flow through them to the stakeholders involved.

Identifying Value and the Beneficiary of the Value

The existing paradigm for clinical care is predominantly one where tissue samples are used to create glass slides which are then interpreted by a pathologist within a reasonable geographic proximity to the patient, their clinical caregiver and the laboratory processing the sample. Stakeholders in the process include each of these parties, patient, clinician, lab and its owners/workers, and pathologist. To this list might be added other clinicians who could/will care for the patient, insurers or society who will pay for the care, device and drug manufacturers whose products are or will be used in that care, and society at large who will also be influenced by the outcome of the care; be that loss of a talented citizen, new discoveries unfolded through the care, or other benefits (Fig. 4.1).

From the perception of these various stakeholders, DP adds value to the process when the incremental improvement in quality and accuracy, and any operational efficiencies exceed the marginal costs of the additional time, effort or capital required to implement the system. Since the costs of time or effort may be asymmetric relative to the distribution of the value returned in terms of quality or accuracy, it is generally needful to expand the circle of stakeholders in any investment consideration.

From a stakeholder perspective Table 4.1 summarizes the value that DP potentially brings to each constituency and what costs they incur to implement DP.

If there are readily identified stakeholders whose work model is disrupted with implementation of DP, they might be anticipated to be the most vehement opposition to its introduction, but in reality, any of those in the table above who carry high incurred costs, without a commensurate added direct value in their value proposition could be easily anticipated to be resistant. Business models thus dependent on a limited scope of stakeholders which include highly resistant elements will predictably face the most difficulty.

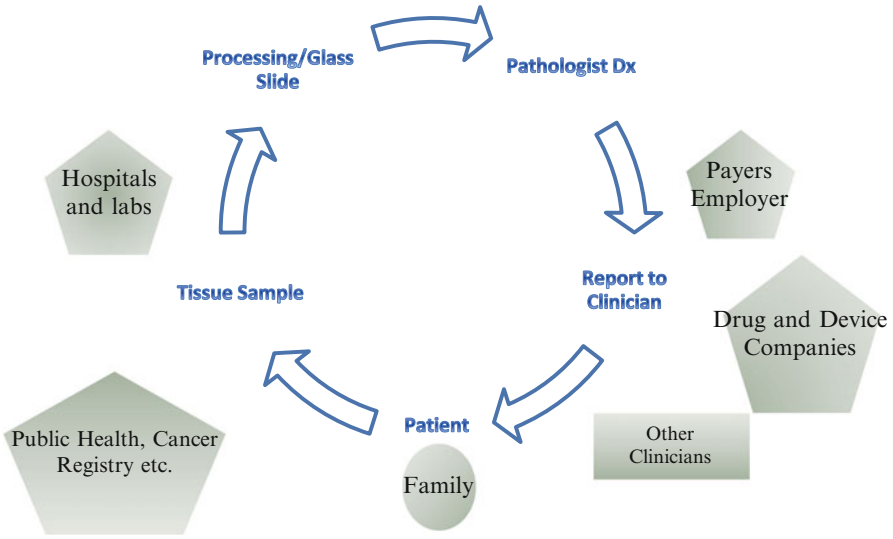

Fig. 4.1 Stakeholders in the diagnostic process

Business Models to Capture Value

To date, the majority of DP systems have been placed on a capital acquisition basis either by direct purchase or via a lease agency intermediary, perhaps with a service agreement and pertinent software licensing fees. Obviously this model needs to appeal to a single stakeholder's value proposition and interests, although some instruments, such as ours at the University of Oklahoma Health Sciences Center were a shared purchase between two departments with a combination of teaching and research interests. Other purely commercial entities have acquired scanners to support scanning on a contract basis per slide, for whatever purposes. Some commercial laboratories have employed them as a competitive advantage allowing them to make special stains available digitally faster than they or a competitor, could physically ship the stains back to the requesting lab or physicians. In some instances, image analysis algorithms via automated FDA-cleared methods, with their associated higher reimbursement model have been the impetus, perhaps on a "per click" basis to reduce capital outlay, for acquisition. Often these contracts do not address uses or costs/charges beyond the image analysis.

Another novel business model employed to extract value from DP (but not primarily to encourage initial adoption) is used by a company offering blinded peer-review of digitized cases for quality assurance purposes. Their marketing approach employs several pricing models (per click, per case, per subscriber) according to the situation of the practice, and attempts to balance these costs against potential CMS

Table 4.1 Costs and benefits of digital pathology to various stakeholders

Stakeholder	Value added by DP	Costs incurred with DP
Patient	Accurate diagnosis including consultant sooner QA enhanced Ease of transport and personal viewing	Personal storage
Clinician	Accurate diagnosis QA enhanced confidence Ease of viewing	Time to explain findings to patient
Pathologist	Ease of comparison with prior material Ease of image manipulation Productivity gain in specialty-specific and level-loading scenarios Digital libraries Image analysis tools such as computer-assisted dx Mobile access Saved movement to remote sites	Time to examine increased Learning curve for new tool
Other clinician	Easier access to primary pathology images	
Hospital/Lab	Slide filing streamlined Rigor of DP increases histology quality Risk profile reduced Easier, better QA Reduced microscope costs	Capital costs for scanner and storage media Operating costs of scanning
Consultant pathologist	Easier material management Ability to retain images for teaching/ research	Learning curve for evaluating digital slides Time of evaluation increased
Drug/Device company	Advanced image analysis may inform treatment choices and connect patients to treatments faster Sales of scanners and storage software	Liability for misuse High development and validation costs
Public health-Cancer Registry-Research	Potential access to primary data	IT Systems upgrades
Payer/Employer	Accurate diagnosis w/ Reduced wasted care	Increased consult costs

reimbursement adjustments based on participation in a quality Maintenance of Certification program, and liability reduction. Collaboration or co-marketing with other scanning network services has also been employed to advance acceptance of their service model. (See http://www.leicabiosystems.com/events-education/news/news-details/article/leica-biosystems-partners-with-qualitystar-to-provide-epathology-based-quality-assurance-expertise/ accessed 11 Nov 2014.)

Creative means to capture the full value of DP by any of a host of mechanisms on the part of proponents and vendors without imposing steep new costs on single stakeholders have yet to fully resolve this issue of adoption generally. Niche solutions appear to be the norm. But not all these options have been examined and more

attention could be given to changes in the price-setting mechanism, payer, price carrier, timing, or segment. (See Stefan Michel, Capture More Value, Harvard Business Review, Oct 2014.) Some vendors have moved from a capital equipment sale or lease model to a per case or per slide model (price carrier change) and others have introduced a change to capture value at the time of a networked consultation (segment and payer change). Efforts to change the pricing (as via CPT codes for a methodology) have not yet been attempted, though these were successful in influencing the adoption of liquid-based cytology methods in the past, and no doubt will be employed once WSI attains wider approval for initial diagnosis.

Educational Organizations

What about the educational models? There are changes afoot in the educational delivery models associated with DPs entry into pathology education. These have the potential to dramatically change the paradigm and offer new markets for quality education just as DP has done for consultation. To date, these have not been monetized on any sort of transactional basis, though educational sessions mediated through WSI have been included as a "value-add" in DP-enabled consultation services (S. Binder, personal communication). The value proposition for educational institutions with space and capital equipment investments in standing microscopy labs have largely been or are transforming to lower cost virtual microscopy labs, just as the same value gains have been employed in continuing education sessions and educational assessments, thus requiring participants to only transport a laptop computer or even a tablet instead of a bulky microscope to such sessions. Any financial savings associated with these value-based shifts have not to my knowledge been associated with any reduction in tuition or exam fees, though the pace of increase might have slackened an imperceptible tad.

Return on Investment

The discussion of return on investment (ROI) is an important element of the purchase decision and how the technology will be deployed, and a challenge to the vendors striving to maximize their ability to collect value for the product. But the challenge is that no two scenarios carry the same relative values. In some, such as an educational use case, the liabilities are nil, and the potential reduction in diagnostic liability a non-issue, so only direct space and equipment costs can be compared along with personnel time savings directly. Even in a diagnostic setting, the differences between one environment or geography in how that quality or liability issue is valued can be tremendous. Further, for many of these indirect or only intermittent financial elements, no agreed-upon method exists to measure or value them for full

inclusion in the ROI. Ho et al. for example, extrapolated savings based on over- or under-treatment projections from just two tumor types to numerous others, and allocated no savings to reduced liability costs associated with those changes in treatments [3]. Importantly however, their analysis reflected a clear economic advantage to DP when rolled out over an entire multihospital system, with multiple stakeholders, reflecting again the need to view the gains on a macro level rather than at the level of an individual site or individual.

When the World Changed: Inventing the Future

So when did, or will the world of pathology become digital? [4] (Soenksen D, Digital Pathology adoption? Expect it in niches, CAP Today, 2007 (Feb). http://www.cap.org/apps//cap.portal?_nfpb=true&cntvwrPtlt_actionOverride=%2Fportlets%2FcontentViewer%2Fshow&_windowLabel=cntvwrPtlt&cntvwrPtlt%7BactionForm.contentReference%7D=cap_today%2Ffeature_stories%2F0207Digital.html&_state=maximized&_pageLabel=cntvwr, accessed 11 Nov 2014) Many years from now, it is likely that historians will look back on these decades around the turn of the millennium and remark that the transition from analogue, raw-data evaluation, such as hard-film radiographs and tissue-section glass slides were the last bastions holding out against the revolution that began when men learned to represent complex data in binary, digital fashion that could be easily manipulated, stored, transmitted, and brought to serve the needs of people so much more easily in silico. (DARK Daily Oct 12, 2012, Digital pathology should leapfrog digital radiology's adoption timeline, http://www.darkdaily.com/digital-pathology-should-leapfrog-digital-radiologys-adoption-timeline-1015#axzz3Jd643omE, accessed 11 Nov 2014.) The economic values of that shift will be so overwhelmingly evident at that point drawn as they will be among the massive societal advantages of same, that students of history may have difficulty grasping that there was even reluctance to embrace the change. Pathologists today however, are far more than old curmudgeons of a by-gone era guarding the paraffin and glass treasures of the past. Rather, we are the sages that prophetically predict the behaviors and outcomes of disease or disturbances in the life-force of our fellow men from subtle clues hidden in the visual array of artifacts and seemingly trivial variances we see every day, who wisely demand that any challenge to this sacred priestly trust be tested and proven to offer more than just a view of the underside of the cheese. We are the ones shepherding this new tool into life hoping and eager for better abilities to serve our fellows, whilst still doing our best to serve their needs with the tools we have inherited from our forefathers dating back to Virchow and Leewenhoek. When the air clears and all the stakeholders can see clearly the values to outweigh the costs, DP will be part of the new order, and pathologists will be there proud to have been part of the birthing of this new paradigm in diagnosis, still pleased to serve and predict the future.

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Chapter 5
Telepathology and Digital Pathology Research

Elizabeth A. Krupinski, Achyut K. Bhattacharyya, and Ronald S. Weinstein

Introduction

Telepathology is the pathology service component of digital pathology. Digital pathology is a technology; telepathology is a service performed by pathologists at a distance. Early studies, preceding the establishment of telepathology services were done in the analog video imaging mode. They cannot be accurately referred to a "digital pathology".

Research on the forerunner of telepathology is found in the "television microscopy" and "video microscopy" literature that dates back to 1951. A television camera was mounted on a light microscope to televise black-and-white microscopic images in real-time at the RCA-David Sarnoff Research Laboratories in Princeton, New Jersey. By 1960, video microscopy set-ups were widely deployed in research laboratories around the world. They were being used in biological

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research laboratories for observing enhanced images of biological specimens; mobility studies of a wide spectrum of biological organisms and biological processes; and for quantitative light microscopy [1].

The first use of "telemedicine" light microscopy in clinical medicine was in 1968 17 years after television light microscopy was introduced in New Jersey. The clinical application was that of remotely examining black-and-white images of blood smears and urine samples using remote analogue video microscopy [2]. This was a component of a pioneering, multi-specialty telemedicine program, the Massachusetts General Hospital (MGH)-Logan International Airport Telemedicine Program, that went live in 1968. A co-author of this chapter (RSW) participated in some of the first telemedicine microscopy cases as a third year MGH pathology resident. Prior to the initiation of the MGH television microscopy service, Dr. Robert E. Scully, a Harvard Medical School faculty member and a staff pathologist at the MGH, carried out a feasibility study in which he examined black-and-white video images of blood smears, urine samples, and a small number of surgical pathology cases. This is regarded as one of the first examples of telepathology clinical transformational research. Scully was able to diagnose all 100 test cases, although he asked for color information from the remote laboratory technician in a few cases [2].

In 1988, Dr. Scully was asked how many actual clinical cases he had personally examined, and he replied, "Ron, two or three max." (R. S. Weinstein, personal communication, Chicago, Ill. 1988). Ironically, the MGH-Logan International Airport Telemedicine Program never actually used the word "telepathology". That is related to the fact that the Anatomic Pathology Laboratories and the Clinical Pathology Laboratories at the MGH were in separate departments. For patients at the walk-in telemedicine clinic at the Logan International Airport, "clinical microscopy specimens", such as blood smears and microscopic urine sediments, were read out by Department of Medicine staff members. The MGH Clinical Pathology Laboratories were not merged with the Anatomic Pathology Laboratories and incorporated into the MGH Department of Pathology until around 1991. As a historical footnote, the personnel in the MGH-Logan International Airport Telemedicine Program avoided using the term telepathology, respecting the Department of Pathology's prerogatives and the de facto prohibition of crossing into another disciplines' turf. Hospital credentialing and the mechanisms for granting of clinical privileges in hospitals reinforce the boundaries of medical specialty silos.

The origin of "modern telepathology" is defined operationally as the point in time when the term "telepathology" was introduced into the literature. This coincides with the initiation of the continuous stream of transformational clinical research in telepathology, as well as the submission of the first patent application.

The innovation cycle, including commercialization and clinical implementation for telepathology began in earnest in 1984, nearly 30 years ago [3–6]. The drivers of the innovation at that time included the level of inter observer variability for surgical pathology diagnoses which was compromising the quality of certain cancer clinical trials in the United States; the emergence and proliferation of surgical pathology subspecialties along with its own set of access to quality care issues; and the spread of advanced medical technologies into new markets, especially in the

Table 5.1 Innovations in telepathology system designs

Histopathology and cytopathology glass slide imaging systems	Year[a]
Television microscopy	
System assembly and testing[b]	1952
Research applications	1955
Clinical applications	1968
Static image telepathology	1985
Dynamic robotic telepathology (with static image gross tissue mapping for slide navigation system)	1986
Hybrid dynamic robotic telepathology/Static image telepathology[c]	1989
Automated WSI (WSI) Telepathology	1991
Integrated automated and operator-directed virtual slide processor	1994
Ultra-Rapid WSI processor[d]	2003
Dynamic robotic/Static imaging + WSI telepathology[e]	2011

[a]Dates are approximations based on publications, lectures, announcements, corporate annual reports, oral histories, or other sources of information
[b]RCA/David Sarnoff Research Laboratories, Princeton, NJ
[c]Designation "hybrid" indicates that the system houses two independent microscopy imaging modes, dynamic robotic telepathology and static image telepathology
[d]Under 1 min scanning time (×20 objective lens) for digital imaging a 1.5 cm^2 histopathology tissue section
[e]The term "dual" indicates the simultaneous use of multiple imaging modes, for example, using WSI telepathology and dynamic robotic telepathology, in different layers, even toggling back-and-forth, in a single diagnostic session

developing countries [7, 8]. Major disparities in access to the highest level healthcare in US rural communities and small cities is an issue of concern to US policy makers.

The start also can be traced back to specific concerns over the high levels of inter-observer variability among experts staging and grading urothelial carcinomas of the urinary bladder for accession into National Cancer Institute-funded clinical trials in the 1970s and 1980s [3, 9, 10]. Robotic telepathology was invented, patented and commercialized with this application in mind, although the then-stated concern was over the need to provide coverage of remote hospital frozen section services, especially for providing read outs of breast frozen section specimens [4, 9–11]. Although early versions of robotic telepathology systems failed to achieve the diagnostic accuracy required for urinary bladder second opinions for clinical trials, they were adequate to support remote routine surgical pathology services and intra-operative frozen section services requirements, continuously from 1989 to the present time [12–17]. There had been forays into the uses of earlier light microscope video imaging technologies that predated the start of modern telepathology, but had some overlapping objectives and success stories (Table 5.1).

The literature on research in telepathology is extensive and complex [13, 18]. It encompasses the majority of the papers labeled telepathology and/or "digital pathology", the enabling imaging technology for telepathology. There are over 1000 published papers from 400 laboratories in dozens of countries listed in PubMed under

the key words “telepathology”, “digital pathology” “virtual slides” and “Whole Slide Imaging” (WSI) [19, 20]. The large majority of these papers address various aspects of telepathology research topics. To date, three monographs on various aspects of telepathology-related research have been published [18, 21, 22].

Survey of Telepathology Research

Currently, there is a body of fundamental and translational research that is described and explained in approximately 1000 published scholarly papers and 100 US patents that represent the bulk of the intellectual property for the field to telepathology [19, 20]. These correlate with eight steps in the telepathology process plus a larger category, human factors, which come into play across the entire spectrum of items. The list provides a framework for discussing the components of the telepathology research enterprise. Of course, part of the challenge is to interconnect the research in these overlapping areas of innovation. What is interesting about interoperability is not exclusively about the technical issues but includes interoperability issues that affect policy, business models, and market issues. Resolution of these issues is key to gaining acceptance of telepathology for routine clinical practice.

Research in pathology covers a wide gamut of topics from basic science to translational to clinical, but there is another area that is just beginning to be investigated in depth—the impact of the work environment on slide and/or WSI interpretation. In large part the impetus for these studies stems from similar studies in radiology that arose as radiology transitioned from film to digital reading and concerns about how to design the optimal digital reading room from both a human factors and diagnostic perspective emerged [23–26]. These areas are covered in some depth in the chapter. Many research papers have been published on telepathology image acquisitions and diagnostic accuracy studies. Definitive diagnostic accuracy papers remain to be written [27, 28]. With respect to image acquisition systems, multiple papers have been written on most of the types of digital pathology imaging systems listed in Table 5.1. The exception would be the “Integrated Automated and Operator-Director Virtual Slide Processor”. Such a device was demonstrated at European telepathology meetings in the mid-1990s, but appear to have been short lived as commercial products, as the glass slide throughput speeds for whole slide image manufacturing rapidly accelerated.

Digital Image Acquisition Systems

At the heart of every digital microscopy setup is a compound light microscope. Static imaging, enabled by image grabber boards, has played some role in each telepathology system (Table 5.1). Between 1984 and 2014, the sizes of static image files increased 10,000-fold, enabling high resolution Whole Slide Images to replace

Fig. 5.1 Aperio ScanScope AT digital slide scanner. Aperio Slide Scanner (Leica Biosystems, Inc. Buffalo Grove, Illinois, USA)

the single static images used, as galleries of single images, for diagnoses at the earliest implementations of static image telepathology (Fig. 5.1). Along the way, low resolution (i.e., 60 K) static images were used to create low resolution maps for use in guidance systems for dynamic robotic telepathology systems [29].

Dynamic robotic telepathology, as originally demonstrated in 1986, used real-time analog video image transmission. The diagnostic telepathologist had remote control of a robotic motorized microscope and could control all stage movements, including focus and magnifications by rotating a remotely controlled motorized microscope turret. Today, dynamic robotic telepathology systems include a still image (i.e., store-and-forward or static image) option. In actual practice, these systems combine the synchronous imaging mode with an asynchronous imaging mode. As real-time imaging takes place, the distant telepathologist can capture higher resolution static images at higher resolution, and archive them as part of the permanent patient's laboratory record.

An obvious advantage of dynamic robotic telepathology has been the capability of the distant system operator to adjust the focal plane "on the fly". The system can be up-and-down focused upon demand. Since the glass slide is attached to the motorized microscope's stage during dynamic robotic telepathology diagnostic session, it is as simple to focus the microscope stage up and down as it is to change the stages X- and Y-coordinates, when moving the slide laterally. As typically used until now, WSI has always been done asynchronously. At many institutions, viewing of the whole slide images in a viewer had been done often long after the glass slide was removed from the motorized microscope stage built into the WSI device. Glass slides may be returned to the glass slide storage area far away from the WSI system. This strategy may now be complicated by the new concept of combining dynamic robotic telepathology with WSI telepathology as elaborated upon in this paper. WSI devices are currently being introduced by vendors that incorporate a real-time feature or pseudo-real-time feature into their WSI telepathology systems. Of the current major vendors of systems, Aperio, Olympus, Leica, and Hamamatsu are leading the way.

There are currently two technical approaches to achieving up-and-down focusing of WSI files: one is with synchronous real-time imaging; and the other uses an innovative hybrid form of synchronous and asynchronous imaging ("Z-stack" imaging). Both of these approaches are now being tested and mark by the leading WSI-telepathology system vendors. A Z-stack feature is marketed by Aperio under the trade name "TelePath Live". Olympus and Hamamatsu both have a Z-stack module as well. An option rich Z-stack system is offered by Hamamatsu; a system currently marketed by Olympus as well. The product is marketed under the name, "ScanScope". This can digitize 30 areas of 30 levels in a histopathology slide, at Z-axis intervals of 0.1 μm in height. The digitization process is remarkably fast. They have achieved a pixel size of 0.17 μm of tissue area/square per pixel, which is a noteworthy technical achievement and sets the bar for other WSI device companies. Through-focal image viewing on the Hamamatsu viewer is reasonably smooth, although there is still perceptible "jumping" from one Z-stack level to the next. However, what they are capturing in Z-stacks is approaching being seamless in quality that will be necessary for true three-dimensional viewing of tissue features.

The Aperio and Olympus systems have multiple cameras on-board, one of which is a real-time video camera that allows the remote system operator to take over control of microscope functions and perform dynamic robotic telepathology imaging tasks using a robotically-controllable microscope that is, in fact, embedded in many WSI systems. The remote system operator can view the glass slide while it is mounted on the motorized light microscope stage that is an integral part of every WSI system. The remote system operator then selects areas of the slide in which Z-stack imaging is to be carried. The area is outlined (typically with a graphic of a rectangular box). Variables are selected from a presentation screen on their system control monitor. These include: number of Z-axis slices; and height intervals between the Z-axis slices. The imaging system may either use autofocus to determine the null point of reference or have an initial focus level selected manually. Area for which Z-stack slices are captured can be identified on the initial whole slide image which now serves as a "section map". Thus, the system operator can toggle back-and-forth between the whole slide image file and the Z-stack digital files. The area that can be viewed in the Z-stack mode corresponds of the area initially selected for the processing of each Z-stack. Actual use of the Z-stack feature has now shown that this Z-stack module adds to the virtual microscopy viewing experience and is likely to add to the diagnostic accuracy of WSI in a small but important number of WSI telepathology cases. It remains to be seen if this also increases user satisfaction with WSI, in any meaningful way.

There is another approach to fusing dynamic robotic microscopy and WSI, which may provide additional benefits. Current Z-stack technology aims at enabling a system operator to intervene during the manufacture of whole slide digital image files and to append selected Z-stacks of images to basic whole slide image file. A benefactor will be the telepathologist who will have final responsibility for signing out the case and, of course, ultimately the patient. The triage pathologist overseeing the processing of the composite whole slide image file plus its Z-stacks may be different from the pathologist who signs out the case.

In the future, the process could be reversed. Synchronous case management could follow asynchronous whole slide image processing in the batch mode. Instead of having Z-stacks incorporated into the initial whole-slide image product, and then reverting to asynchronous imaging at a more convenient time, the process could be reversed. This might be far more efficient since synchronous imagine might be justified for a small subset of surgical pathology cases or cytopathology cases. There are at least three other advantages. First, using an asynchronous-to-synchronous strategy, glass slides would only be remounted in the cases where process is justified; and the sign out pathologist would do it. It could have a continuous focus feature, rather than electronic step sections.

In the past, many system owners have not even realized that dynamic robotic microscope are actually integral parts of many WSI systems because many of the microscope features are either not activated or, in some systems, deactivated. Vendors of WSI systems have wanted customers to think that they are selling something that is entirely novel, but that is not always the case.

There are workable solutions to the up-and-down focus issue. It turns out that replicating the type of repetitive up-and-down focusing that goes on during conventional light microscopy, when pathologists or students view glass slides using a conventional light microscope, is technically very challenging for designers of digital microscopy imaging systems. In fact, designers of what would become today's WSI systems largely ignored the desirability of emulating this feature of the traditional light microscopy slide viewing process. While up and down focusing would have been very low on the list of priorities of system designers of the early WSI systems, this moves higher on the list of system designers challenged to explain the apparent reluctance of practicing pathologists to embrace WSI. There are many practical overriding factors that come into play for the current strong preference of pathologists to stay with glass slides rather than migrate to WSI. These include such primary considerations as high equipment costs, electronic slide storage costs, access to broad band telecommunication, and longer case viewing times especially for inexperienced telepathologists. Currently, a convincing value proposition for doing WSI may not be achievable. However, even if the value proposition were compelling, pathologists' acceptance could still be a barrier.

By adjusting the height of the focal plane within a tissue section, WSI could be produced at different depths in a histopathology tissue section. Using specialized viewing software, it became possible to display whole slide images in an up-and-down focus mode, with the digital image on the screen jumping from one whole slide image to the next, at identical and matched X–Y-coordinate locations. However, processing of a set of 3–30 whole slide images is very time-intensive, and the storage of the huge amounts of data generated by the processing of multiple whole slide images per case is generally impractical.

On the evolutionary tree, some digital imaging modalities, such as array microscopy, evolved into innovation cul-de-sacs where they were either adopted for other unrelated applications, such as a component of next-generation genomic scanners in the case of array microscopy, or simply disappeared, such as the operator-director WSI-introduced in the mid-1990s but never caught on [30].

Image Viewing Displays

The physical display, its properties, and the images are clearly important. However, as pathologists are spending more hours every day using displays to interpret images workstation-user interface becomes an important issue [31]. Graphical user interfaces (GUIs) need to be fast, user friendly, intuitive, able to integrate and expand, and reliable with simple menus and file managers. Image processing and analysis tools need to be easy to use and customizable. Menu options need to be accessed via single mouse click navigation; the display needs to have visually comfortable colors or gray scales and an uncluttered desktop. Ergonomically positioned input devices such as mouse, keyboard, and pad, ergonomically positioned monitors should be used. From a perceptual perspective the default image presentation quality is extremely important, so it is crucial to provide optimized image information in the initial default presentation so the pathologist can make decisions with as little unnecessary image manipulation as possible so as not to prolong viewing times.

One critical aspect is the display since, historically and even predominantly today; pathology glass slides have been viewed directly with the light microscope. The transition to viewing digital images on computer displays brings to bear a number of important perceptual and ergonomic questions regarding the impact of the display on interpretation efficiency and efficacy/accuracy [24, 32]. The image viewing and interpretation process can be considered from two major perspectives. First is the display and how various factors affect image quality. Second is the pathologist who relies on their perceptual and cognitive systems to process the information displayed. Today there are a variety of displays available and used for viewing WSI, ranging from high-end medical-grade to commercial off-the-shelf (COTS) low-end displays. However, there are few if any regulations for display performance specifications such as a minimum resolution, bit-depth, minimum/maximum luminance, white point, color temperature or calibration [33].

There are two aspects of color that need to be considered. The first is color accuracy or the ability of a system to produce exact color matches between input and output. The second is color consistency or the ability of a system to yield data that is identical or at similar to the color perceptual response of the human visual system (like the DICOM Gray Scale Display Function used in radiology). This is a more difficult to achieve, however since color perception itself is a rather complicated issue. One option is the use of the ICC (International Color Consortium) device profiles that provide a standardized architecture, profile format and data structure for color management and data interchange between different imaging devices. The profiles incorporate characterization data for color-imaging devices along with data tags and metadata that detail a set of transforms between the native color spaces of a device and a device-independent color space. Computer operating systems can use these color management modules or software applications that utilize the ICC profiles to provide consistent and perceptually meaningful color reproduction for input devices, output devices, and color image files.

There are some proposed methods for image acquisition and display for WSI, but in general they have not been validated or evaluated with respect to their impact on diagnostic interpretation performance [34]. For example, Yagi has been developing techniques for color validation and optimization, one of which takes two standard slides that are scanned and displayed by a given imaging system [10, 35–37]. One of the slides is embedded with nine filters having colors purposely selected for H&E (hematoxylin and eosin) stained WSIs, and the other slide is an H&E stained mouse embryo. The displayed images are compared to a standard to identify inaccurate display of color and its causes. The question of whether inaccurate display affects observer performance has not been addressed. Another group has concentrated more on display characterization and the tools used for calibration [38, 39]. In one study, they characterized three probes for measuring display color: a modification of a small-spot luminance probe and two conic probes based on black frusta. They found significant differences between the probes that affect the measurements used to quantify display color. They proposed a method to evaluate the performance of color calibration kits for LCD monitors using the idea of a Virtual Display—a universal platform to emulate tone reproduction curves. The model processes video signals based on a preprogrammed LUT containing the tone reproduction curves of the display being evaluated and determines whether the calibration kits are sufficient. Sufficiency however is not judged with respect to observer performance, but rather with respect to physical display property characterization and measurement.

One critical aspect is the display, since historically and even predominantly today, pathology slides have been viewed directly with the light microscope. The transition to viewing digital images on computer displays brings to bear a number of important perceptual and ergonomic questions regarding the impact of the display on interpretation efficiency and efficacy/accuracy [8, 24, 32]. The image viewing and interpretation process can be considered from two major perspectives. First is the display and how various factors affect image quality. Second is the pathologist who relies on her perceptual and cognitive systems to process the information displayed. Today there are a variety of displays available and used for viewing WSI, ranging from high-end medical-grade to commercial off-the-shelf (COTS) low-end displays. However, there are few if any regulations for display performance specifications such as the minimum resolution, bit-depth, minimum/maximum luminance, white point, color temperature or calibration [33].

Workstations; Cockpits; General Surgical Pathology Practice Environment

The room in which the workstation is located is often overlooked but very important. Ambient lighting should be set at 20–40 lx to avoid reflections and glare on the display while still providing adequate light for the human visual system to adapt to

the surrounding environment and the displays. Light colored clothing and lab coats can increase reflections and glare even with today's LCDs so they should be avoided. External noise should be kept at a minimum, and proper airflow and temperature should be set to maintain a comfortable environment.

Workflow Analysis

As digital workstations, computer-based image analyses, and other related capabilities have developed with the advent of WSI, some studies have focused on characterizing workflow since these digital modalities have impacted significantly the actual image preparation and interpretation process [40–43]. These studies are very useful for understanding and optimizing the overall process, and optimizing total workflow but do not focus on in-depth analyses of particular critical aspects.

Human Factors

An interesting research tool for studying WSI workflow and how pathologists view WSI in general is the use of eye-position recording. One of the first studies in this area was conducted to assess eye movements of medical students, pathology residents, and practicing pathologists examining virtual slides on a digital display monitor. Twenty WSI breast core biopsy cases were shown to three pathologists, three pathology residents, and three medical students while their eye-movements were tracked. The study demonstrated for the first time that when a virtual slide reader initially looks at a virtual slide his or her eyes are very quickly attracted to specific regions of interest likely to contain diagnostic information. In a matter of seconds, critical decisions are made regarding the selection of areas for further examination at higher magnification [44]. Since this study first appeared, there have been a number of other research investigations using eye-position recording to study the ways pathologist interpret WSI and various factors in the reading environment that impact search strategies [45–48].

There is concern that the digital reading environment may be contributing to levels of fatigue and visual strain that may negatively impact diagnostic performance [49–53]. This can result from the long hours that many clinicians including pathologists are spending viewing softcopy images. Common physical symptoms include visual strain, headaches, blurry vision, and dry eyes. There is increasing evidence, at least in radiology, that long work days in a digital reading environment increases fatigue and negatively impacts diagnostic accuracy (by about 4 %) as well as the time it takes to review a case [49, 54].

"Low Reward" vs. "High Reward" Innovations

The 1986 editorial which introduced the term "telepathology" into the English language also acknowledged that the invention, testing, commercialization, and clinical diffusion of the technology into routine pathology practice would be a long and arduous process [3].

It should be pointed out that the stakes for "inventing" robotic telepathology were generally perceived to be relatively low compared with other innovative medical imaging technologies since telepathology didn't represent the creation of a new imaging technology, such as CT and MRI in radiology. Rather, telepathology represented an adaptation of a proven technology, conventional light microscopy so that surgical pathology could simply be performed at a distance. This proved to be a significant barrier to the adoption of telepathology down the road. Because surgical pathology diagnoses, rendered using conventional light microscopy have been the "gold standard for medical diagnosis for a century, the challenge was to equal the current levels of diagnostic accuracy achievable with conventional light microscopy".

A brand new technology will be heralded as a breakthrough once new bodily structures or pathological lesions are visualized. Innovators starting with the "gold standard" in an area of medical imaging, surgical pathology light microscopy, and then attempting to simply duplicate it, was always somewhat of a fools' errand, no matter how meritorious the rationale for doing it might have been. The road to success in telepathology system development is littered with brilliant solutions and remarkable innovations, but there have never been any home runs. Yet at the end of the road, FDA approval of a telepathology system for use for rendering primary surgical diagnosis could be close at hand. Then, broad acceptance of telepathology and all of its contingencies, and its successful insertion into routine laboratory usage may be seen. Of course, this may benefit from a new driver, the formation and expansion very large integrated healthcare systems in the United States. Many barriers disappear when telepathology is practiced within integrated health care systems.

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Chapter 6
Teleconsultation

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Introduction

Digital pathology has been successfully implemented around the world mainly for education, clinical pathological conferences, and research and its integration into clinical diagnostic activities is rapidly increasing. Although its use for primary diagnoses on routine clinical material remains rather limited, certain niches such as consultations between pathologists and frozen sections are clearly expanding. In this century of increasing diagnostic complexity, personalized medicine and molecular pathology, obtaining the opinion of an expert may be critical for patient management. Sharing whole slide images (WSI) instead of glass slides to get an opinion from a remote expert concurs to efficiency gains but digital pathology also offers additional advantages such as the possibility to request opinions from more than one expert and, for experts, to share challenging cases with others abroad. Globally, the patient is the first to benefit from this technology since the improved

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efficiency resulting from teleconsultations leads to faster patient management. This chapter presents the spectrum of current and potential clinical applications of teleconsultations.

Historical Background of Telepathology and Digital Pathology

The term "telepathology" was introduced into the English language in 1986 by Weinstein [1]. The first recorded event of "telepathology" occurred in the late 1960s, when a real-time "television microscopy" service was established between Massachusetts General Hospital (MGH) and Logan Airport Medical Station in Boston, Massachusetts and black and white real time television images of blood smears and urine specimens were sent from Logan Airport to MGH for interpretation [1]. The first robotic telepathology system was invented and patented by Dr. R. S. Weinstein. The first patent application was submitted in 1987 and granted in 1993.

Since the 1960s, telepathology systems, technology and services have continued to be developed and continue to evolve [2]. Historically, development has been in three broad types of telepathology systems including dynamic, static and hybrid systems. Dynamic systems are essentially remote-controlled microscopes that give the pathologist a live view of the distant microscopic image while allowing him or her to move the stage, focus, and change the magnification, remotely. The clear advantage to dynamic systems is that they give the consultant tremendous flexibility in perusing the entire slide to examine in detail any specific field at any power. Disadvantages to dynamic telepathology systems include the expensive and proprietary nature of the host and client stations and the tremendous bandwidth needed to carry live, full-motion video.

Static ("store-and-forward") telepathology requires that the referring pathologist capture a collection of still digital images for transmission to the consultant. The major disadvantage is the loss of control experienced by the consulting telepathologist, who must rely on the referring pathologist to capture all of the necessary diagnostic fields to support an adequate examination. On the other hand, static systems can be extremely versatile. Any system that captures images in standard file formats, when coupled with any file transfer protocol program or almost any reasonable E-mail system can be used to perform static telepathology.

The third historical approach used hybrid systems that attempt to combine some of the better features of both static and dynamic systems. Hybrid telepathology systems couple remote-controlled microscopy with high-resolution still image capture and retrieval. This approach requires a significantly lower bandwidth than purely dynamic systems do while providing high-quality static images for diagnostic, reporting, and medical record-keeping purposes.

Virtual slide telepathology also known as whole slide imaging (WSI) is the most recently developed mode of telepathology. WSI has resulted from technical advances during the recent decade which have led to the creation of high-quality,

high-resolution images of entire glass slides known as whole slide imaging (WSI), using innovative, automated, high-speed, high-resolution WSI scanners [3]. WSI scanners incorporate robotic motion, digital camera technology, and high-quality microscope optical components controlled by software to scan and traverse the entire glass slide to acquire a digital image "replica" of the slide. In addition to movements along the X and Y axis of the slide during scanning, as the histology specimen has a variable depth dimension (i.e., Z axis).

Technologies used in telepathology have historically evolved over time. In the 1990s, a large scale study done by Veterans Affairs (VA) hospital demonstrated the wide-scale clinical application of telepathology [4]. These telepathology applications included both anatomical pathology such as for use in frozen sections and for clinical pathology services. The VA group involved in this study used an Apollo dynamic telepathology system. The telepathology study showed a high diagnostic concordance of robotic telepathology with light microscopy. In addition, a decreased turnaround time for surgical pathology cases was reported at the remote sites [4]. By 2009, the VA study had expanded and had reported on their experience with over 11,000 telepathology cases. Pathologist-specific discordance rates using dynamic/robotic telepathology were reported to be in the range of 0.12–0.77 %) [5].

In 1993, the Armed Forces Institute of Pathology (AFIP) launched a static imaging consult. This was an attempt to provide expert consult service for difficult anatomical pathology cases and was available for global teleconsultation [6]. By 2001, dynamic telepathology was adopted by the United States Department of Defense (DOD) within the Army Telemedicine Program. In 2005, these systems were converted to a WSI platform. Today, the type and complexity of telepathology platforms continue to evolve and the clinical applications continue to grow. In order to increase their use of telepathology and intent to capitalize on the rapid advances being made in digital pathology, the United States Airforce Medical Services (US AFMS) introduced whole slide imaging-based telepathology to its pathology practice in 2007. As a first step in these efforts, under a congressional appropriations award, a model digital pathology network comprised of WSI systems was built by the AFMS pathology centers with the potential to expand to additional and smaller AFMS pathology centers in the future [7].

Due to globalization of healthcare and the worldwide shortage of pathologist, the last few years has seen an emergence of digital pathology networks. Several vendors have developed products for digital imaging, image transmission, display and image storage. The goal is to provide end users with an increasing range of products to enable telepathology and include products for low cost, rapid scanning platforms and image viewers. Several vendors have started to create international digital pathology networks, providing users and consulting groups with collaborative telepathology portals. These digital pathology networks provide virtual consultant platforms with web-enabled access and some feature a cloud-based solution. The last 5 years has seen rapid development of mobile technologies and the use of smart phone and tablets for telepathology. As mobile health (mHealth) continues to grow, we are likely to witness greater use of telepathology using mobile devices (e.g. tablets, cell phones, wearable glasses such as Google Glass).

Telepathology systems continue to evolve but it is interesting to note that some of the recent applications such as smartphone based telepathology continue to use static images as a method of teleconsultation. A notable advance in the field was the publication of the updated guideline document for telepathology by the American Telemedicine Association in 2014 [8].

Teleconsultation Activities

Intraoperative Consultations Using Digital Pathology Methods

One of the great utilities for digital pathology methods is in the performance of rapid interpretations to guide intraoperative or intraprocedural patient management. The main benefits of digital pathology in this application are increased expertise at any site and improved productivity. The ability to bring subspecialty expertise to any facility, whether local or remote, means that operators at remote sites, where intraoperative consultations were either not available, or only done through generalist pathologists, will now be able to receive expert consultations in any subspecialty in real time. This system would allow a concentration of subspecialty services in a central location that can consult to multiple remote sites, thereby improving expertise and efficiency. Productivity gains can also be achieved within single centralized facilities by allowing pathologists to optimize time commitment via the performance of consultations in multiple sites within their facilities from a single workstation. Networking between digital pathology workstations adds the additional capability of obtaining interpathologist consultation in particularly challenging cases, all in real time, and all with minimal disruption in the usual workflow of the participating individuals. In addition, the use of digital pathology can increase the "temporal" range of pathology services with night call no longer requiring the long drive in to the hospital for a brief look at a frozen section or cytology specimen. A single pathologist can now provide immediate night call services to many sites from home or from an "on call" facility.

In addition to the consultations themselves, digital intraoperative consultations have the advantage of providing the means for improved quality assurance and continuing education maneuvers. For instance, if WSI are used for the rapid interpretations, archived material can allow after the fact rereview to determine reproducibility parameters, and will allow for the collection of libraries of interesting, important, and challenging cases. Snapshots of important fields of view from dynamic streaming methods can provide similar information, particularly if pathologists document fields which they consider the most important in support of their final interpretations.

The two most common intraoperative/intraprocedural interpretations are for frozen section and rapid cytologic assessments. Both procedures guide the operator in making vital decisions about how to proceed in fluid situations. Frozen section interpretationscan provide for a variety of maneuvers including decisions on the proper surgical procedure to perform, the taking of additional tissue or margins,

guiding the acquisition of proper tissue for banking or molecular testing purposes, and informing the surgeon about the etiology of the disease when it was not known prior to the procedure. Rapid cytology interpretations can provide similar information, but its more commonly applied application is in the assessment of an adequate specimen.

Although static images have been used in the past for intraoperative assessments, current procedures are most commonly performed via either dynamic video streaming technology or by the use of WSI. Dynamic video streaming has a number of important features that make it useful in rapid assessments. First, it is relatively inexpensive and hence can be widely available. It requires only a microscope with a high resolution digital camera attached to a computer where the real-time image can be displayed. That computer must have a high speed Internet/network connection which will allow "screen sharing" with other computers. There are a variety of screen sharing software packages available which provide the remote site with an identical digital output as is present at the primary site. The consultant generally connects to the remote site by telephone and then instructs the operator on the movement of the slide, focusing, and magnification. In cytologic specimens, the real-time nature of the procedure with focusing capability can be useful in order to better visualize the three-dimensional groups inherent in these types of specimens. The most prominent disadvantage of this method is that the remote observer may not see the entire specimen and may focus on areas that the on-site operator has preferentially shown; a process which introduces an inherent bias into the procedure. A variety of studies have shown the utility of using real time telepathology for rapid cytology interpretations [9–16]. Some studies have shown no, or only minimal differences between rapid and final interpretations. These studies have brought to light issues of work flow important to telecytology and the rapid interpretation process [14]. With the rise in the use of fine needle aspiration biopsy, more biopsies are being performed in more places, and overall optimization will require more attention from the cytologist. The use of telecytology is a less disruptive method of delivering that service, because small numbers of trained cytologists will be able to cover many sites of biopsy performance from a single "connected" office. As experience has been gained there have been cases noted where distinctions between subtle morphologic changes may be necessary for reliable interpretations, and as such in person on-site evaluation may sometimes be a more appropriate solution. Therefore in many laboratories a rule has been introduced that if the consultant has any difficulty arriving at a rapid interpretation within the first several minutes of viewing the case remotely, they should revert to on-site evaluation. In most operators' experience the number requiring on-site assessments has been only a small minority of cases. To date there has been only limited use of whole slide imaging for cytologic interpretation [17]. Expense of the scanning devices, the time necessary to scan a smeared slide containing a large area of cellular material, and the inability to focus through three-dimensional groups have all been detriments to adoption.

The use of digital methods for frozen section histopathologic interpretations has been more widely accepted than for cytology rapid interpretations. Methods used for frozen section studies have included static imagery, dynamic video streaming,

robotic telepathology, and whole slide imaging. Static image telepathology has been utilized for many years at the University of Pittsburgh primarily for transplant pathology interpretations [18] and has been in use for a number of years in Japan for general frozen section coverage to remote sites [19]. It is simple, image format neutral and rapid, but it is limited by the bias of appropriate field of view selection. Dynamic robotic interpretation allows for the advantage of real time telepathology with the addition of remote control, minimizing the inherent bias of sender bias as noted above. This methodology has been used for many years and has been shown to be robust in terms of accuracy and efficiency in applications ranging from dermatopathology margin analysis, and with thoracic and neuropathology specimens [4, 18, 20]. The need for expensive equipment at the site and the time-consuming nature of the robotic interaction has limited the use of this technology going forward and has largely been replaced by dynamic video streaming applications and whole slide imaging. Video streaming applications (similar to those noted above for cytology) have been shown to be effective in Mohs surgery application [21] and are a commonly used method for institutions performing frozen section night call from home. Whole slide imaging is seeing an expanding role in frozen section evaluation. Neuropathology applications have been most widely cited primarily because of the need for centralization of neuropathologic subspecialty expertise [22–25]. In Toronto at University Health Network, neuropathology frozen sections transitioned from robotic dynamic systems to WSI in 2006 and the authors reported a decrease in turnaround time, a low (5 %) deferral rate, and similar diagnostic accuracy when compared to light microscopic examination [26]. Another study indicated good success with frozen section interpretation in ovarian frozen sections, noting that the overall correlation between benign and malignant/borderline entities was 96 %. Similar to reports of secondary permanent section consultations by WSI, interpretations requiring high magnification detail examination presented the most risk of error [27]. In another review of a broad group of frozen sections by WSI from multiple anatomic sites, diagnostic discrepancies were reported in only 1.4 % of cases [28].

Other issues reported to effect WSI in frozen section analysis have been technical, and have included the need for excellent histologic preparations, scanning process image quality control which includes making sure that all tissue has been scanned and is in optimal focus, and insuring optimal coverslipping technique which includes coverslip placement and limiting mounting media to avoid contamination of the delicate transport mechanism of the scanning device [26].

Guidelines for the implementation of systems for intraoperative digital pathology have been put forth by the Canadian Association of Pathologists [29]. In their document, the Association stresses the need for adequate training of support personnel, particularly when no pathologist is present on site—specifically in procedures related to the grossing of the specimen, including orientation, adequate identification of the margins, and appropriate tissue sampling. In addition, information technology support staff must be available for maintenance and intraprocedural troubleshooting of the scanner and telepathology infrastructure. Similar guidelines recently established by the American Telemedicine Association stressed, in addition, the availability of gross images of the specimen at the time of frozen section

examination to complement the overall evaluation [8]. These guidelines also note that pathologists performing frozen section interpretations must adhere to licensure and regulatory restrictions which are known to vary across individual countries and states.

In summary, intraoperative consultations for both histologic frozen sections and rapid cytology are one of the first widely utilized applications for digital telepathology. Results to date indicate excellent correlation to the current standard of routine light microscopy, and offer significant advantages in terms of productivity enhancement and "projection" of subspecialty expertise to remote sites. Use of relatively low cost dynamic video streaming has advantages for cytology where specimens may be three-dimensional or cellular areas may be poorly defined and widespread on slides; while WSI may be the best technology for "flat" histologic specimens. As costs decline and expertise and acceptance increases, the use of digital telepathology will undoubtedly grow and will be paralleled by improved patient outcomes in the future.

Telecytopathology

Telecytology involves the transmission of cytology images for remote evaluation. Telecytology can be utilized for diagnostic purposes (e.g., rapid on-site evaluation, consultation, reviewing intraoperative smears), education (teleconferences), and quality assurance (e.g., proficiency testing) [30, 31]. With advances in digital imaging there has been increased interest in telecytology. Early telecytology efforts focused mainly on gynecological cytology [32]. More recently, as shown above, telecytology has been employed for rapid on-site evaluations of fine needle aspirations (FNA) [33, 34]. For immediate FNA assessments, pathologists are usually required to travel to a distant site where the aspiration biopsy is being performed. Telecytology allows the pathologist to view these slides remotely, which is less disruptive and more cost effective. For consultation purposes, telecytology avoids the potential for unique and irreplaceable glass slides to get lost or broken.

Telecytology can be accomplished using static (store and forward), dynamic (real time), and/or hybrid systems. Most early publications about telecytology used static photos [35, 36]. Static images can be readily acquired using microscope-mounted cameras, and today even with mobile phone cameras. The advantage of using static images is that these systems are generally cheap, easy to use, and readily available. These digital files also tend to be small and easy to transmit (e.g. via email). However, this manual method is labor intensive and relies on an individual that is knowledgeable about cytology to photograph representative material. Moreover, the images only capture a small field of view without the ability to focus. As a result, many cytology laboratories currently rely more on live telemicroscopy using a microscope-mounted camera [18]. In this instance, the host driving the glass slide continuously streams an image in real-time to the pathologist's remote workstation. If necessary, a pathologist can also remotely access the computer attached to the

microscope with the camera via desktop sharing software. While this streaming method overcomes focus problems, the interpretation is still dependent on the expertise of the host navigating the slide [37].

With advances in technology, telecytology has shifted to using more sophisticated technology such as whole slide imaging (WSI) devices that incorporate robotic microscopes [38]. Stand-alone robotic microscopes have been used most successfully with intraoperative consultations (e.g., frozen sections), and less so for telecytology [39]. By remotely controlling the robotic microscope, pathologists are able to perform live navigation and focusing of an entire glass slide. WSI also allows an entire glass slide to be rapidly digitized that can then be remotely viewed. Both of these methods minimize the need for an experienced on-site operator for appropriate field selection, but are more expensive solutions. For telecytology, the main limitations of WSI are the inability of some scanners to accept slides without coverslips (which is important when rapidly preparing slides for on-site evaluation) and problems with resolution or fine focusing of thick cytology smears and three dimensional cell groups. Some WSI scanners offer Z-stacking to produce multiplane images, but this generally takes long to scan slides. As a result, for telecytology WSI tends to be more useful for seeking second opinion consultation than for use during on-site evaluations. Given that multiple different stains (e.g. Diff Quik, Papanicoloau, H&E and other special stains) are often used in cytology, it is important to note that there may be a larger number of slides to digitize compared to surgical pathology. Telecytology validation studies should accordingly utilize cytology cases [40].

Macroscopy Supervision

Telepathology for macroscopy (gross pathology) is infrequently used compared to telemicroscopy. This may explain why there is a paucity of literature on macroscopic telepathology [41–43]. Gross telepathology may be employed to remotely supervise trainees or pathology assistants who have specific questions regarding a pathology specimen, to share specimen resections with surgeons during intraoperative consultation (e.g. for orientation and/or areas to be sampled for frozen section), and less often for education purposes. Gross telepathology can be performed using a sophisticated system including a grossing station, videoconferencing device and a drawing tablet [43] but it can also be performed using an inexpensive commercial webcam or with a dedicated, high-resolution digital camera (Fig. 6.1) that is part of a gross imaging workstation/platform [44]. The software provided with stand-alone gross imaging stations may not always include functionality to share images. In such cases, laboratories may need to rely on a separate teleconferencing or desktop sharing application (e.g. TeamViewer). When sharing gross images it is important to incorporate a mechanism for the host and consultant to discuss relevant information about the case (e.g. clinical history). Such bidirectional communication can be accomplished using a telephone or the Internet (e.g. chat function, annotation tools).

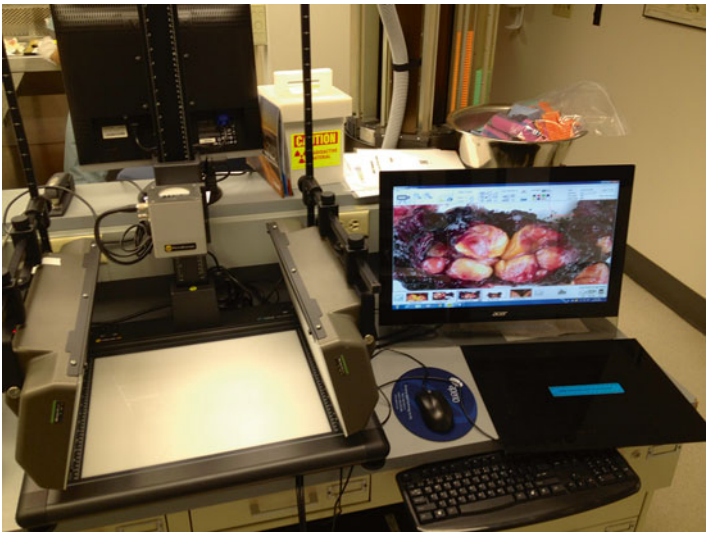

Fig. 6.1 Stand-alone contemporary macro imaging station (SPOT pathStation2) that can facilitate telepathology of large gross pathology specimens

The digital camera used should ideally be able to accommodate samples of varying size and there needs to be adequate lighting. It may not always be necessary to capture and save shared images. Gross imaging systems typically do not permit remote control of the camera (e.g., focus, zoom); this function is usually handled by the individual handling and showing the specimen. The utility of mobile devices including Google glass (GLASS™) for sharing gross images is promising, but remains to be validated for routine clinical use [45].

Tele-Autopsy

Teleautopsy represents a potentially new and attractive digital pathology application. Teleautopsy allows the pathologist to perform the external and organ macroscopic examination without having to either move to the remote site or to transfer the body to the pathology laboratory. This is particularly attractive for autopsies requiring specific expertise and in a context of increased workload and shortage of pathologists reported in different parts of the world and for which any time spent at moving from one place to the other results in reduced efficiency. Furthermore, recent literature confirms that autopsy rates are declining everywhere around the world. This decline is attributed in part to the increased precision of modern radiological tools and the poor reputation and decreased interest at performing autopsies [46]. One of the rare examples of teleautopsy network reported in the literature

is the Veterans Integrated Service Network (VISN) connecting 8 hospital-based laboratories. The VISN extends across portions of three states and uses digitized images generated using hand-held digital cameras or gross tissue imaging workstations [47]. In Switzerland, the VIRTOPSY virtual autopsy project uses radiologic imaging facilities and was initiated in 2000 and has been using high-technology imaging techniques applied to forensic autopsies [48, 49]. More recently, the same clinical team launched the VIRTOBOT, a multifunctional robotic system that allows the pathologist to obtain distant automated surface scanning of the body and to remotely take selective biopsies [49, 50]. In Canada, the Eastern Québec Telepathology Network which shares diagnostic pathology services among 21 hospitals [51], is currently experimenting teleautopsies using a videoconferencing device with remote control of the focus and orientation of a high-definition camera. To be efficient and to insure a high level of confidence, a teleautopsy setting requires the support of well-trained and reliable technologists or pathologist's assistants.

International Teleconsultation Networks

It is often easier to move images across borders than it is to send biological material (slides and/or blocks) or transport patients. Telepathology has thereby facilitated access to pathology experts around the world. This is of great benefit to underserved and rural areas where there is a shortage of pathologists. In these areas not only is there a high demand for diagnostic consultation, but education and guidance on patient management as well. Telemedicine in Africa, for example, has proven to be a very useful conduit of healthcare [52]. A review of telepathology consultation between the University of Pittsburgh Medicine (UPMC) in the USA and KingMed laboratories in China for a 2 year period revealed that in many (approximately 75 %) of cases patient management was impacted as a result of expert diagnoses [53]. In recent years, teleconsultation has become a highway to competition of services and a novel source of international trade. Digital consults offer a new means to insource pathology services.

Over the years there has been a plethora of international telepathology ventures (Table 6.1) [54]. iPATH, developed by the University of Basel, was one of the most successful telepathology platforms [55, 56]. iPATH served over 150 user groups around the world and allowed over 15,000 telepathology cases to be examined. Because the iPATH system used open source software, local server installations were located all over the world. The contemporary telepathology forum called Medical Electronic Consultation Expert System (MECES) exploited Web 2.0 and whole slide imaging technologies [57]. More recently, international telepathology networks have increasingly been established by large academic centers (e.g. UPMC, MD Anderson) and commercial vendors offering collaborative portables, cloud services and business partnerships (e.g. PathCentral, AccelPath, ePathAccess, Corista, Xifin).

Table 6.1 List of some international telepathology projects

– Réseau International de Télémédecine (RESINTEL) and TRANSPATH network
– Fundamentals of Modern Telemedicine in Africa (FOMTA) project
– Réseau Afrique Francophone de Télémédecine (RAFT) project
– Telepathology Services of the Armed Forces Institute of Pathology (AFIP)
– Pathologie, Cytologie, Développement (PCD) telepathology service
– Telepathology consultation centre of the Union International against Cancer (UICC-TPCC)
– Arizona International Telemedicine Network
– iPath telepathology platform
– Medical Electronic Consultation Expert System (MECES)

Technologies employed to support international telepathology have advanced over the years [18]. Early efforts relied on store-and-forward systems where static images were the mainstay of image exchange. The transplant pathology service at UPMC reviewed over 3000 static digital consultation cases with acceptable diagnostic concordance between digital and glass diagnoses [58]. More recently, whole slide imaging has been used. WSI can be remotely viewed in two ways: WSI files can either be accessed on a remotely shared server owned by the host facility (or third party), or transmitted and uploaded (e.g. via a web portal) to a server owned by the consultant group [59]. The former arrangement requires strong cooperation between IT groups of all parties, and permission to access foreign servers. Although the latter system may result in time delays due to image transmission, viewing images is less likely to suffer from network delays. Newer platforms to support telepathology have begun using agnostic viewers, cloud services, more open access platforms and plug-in technology.

Evaluation of general international telemedicine collaborations has revealed several factors that are key to success [60]. These include low cost, use of simple technologies and bi-directional communication. Also important are incentive-based programs, locally responsive services, strong team leadership, training, and user acceptance. Of course, there are also several barriers to cross-border telemedicine. These obstacles include cultural factors (e.g. language, trust), limited resources (e.g. finances, trained staff, availability of ancillary tests), IT infrastructure (e.g. network limitations, firewalls), time zones, regulatory issues, sustainability factors (e.g. cost, inconsistent use, poor scalability), and top-down (e.g. contracts, formal agreements) versus a bottom-up approach (e.g. empowered by end-users). When dealing with international business collaborations it is imperative to ensure that all parties involved adhere to applicable laws. This includes international safe harbor regulations which refer to a process for companies (and institutions) in the USA to comply with the European Union (EU) directive related to personal data protection.

The Foreign Corrupt Practices Act (FCPA) is another federal law in the USA, concerned with the bribery of foreign officials, which is important to be aware of when dealing with international trade.

Future Direction

It is expected that the virtual slide technology with its overwhelming advantages will be called to progressively supplant the conventional microscope, more particularly for teleconsultations which are usually requested in cases requiring rapid management and treatment decisions. In addition to clearly improving efficiency, virtual slides offer many more advantages. To name only a few of them, contrary to conventional glass slides, the color quality of virtual slides persists, regardless of the duration of storage and the number of copies performed is unlimited. Furthermore, contrary to the microscope, virtual slides do not require constant resetting of the focus plane and brightness. Virtual slides also offer the possibility of viewing several stains of the same case simultaneously. Finally, virtual slides allow annotation, for teaching or discussion, and quantitative evaluation of objects and structures [61]. Computer-assisted diagnostic systems with imaging and learning algorithms have already been developed. For example, algorithms aimed at grading astrocytomas [62] and predicting prognosis [63] have been tested using digital images. In the future, systems that will recognize certain tumor types and analyze markers in specific tumor compartments are called to expand. For health care organizations and managers, telepathology has been implemented to prevent interruption of frozen section activities in case of the absence of an on-site pathologist [43].

However, despite all those overwhelming advantages, the implementation of virtual microscopy in the daily practice of pathologists is generally slower than expected in most jurisdictions around the world. Part of the barriers to a wider adoption is technological, more specifically with regard to software application ergonomics, of which the speed of user interfaces is felt by many users as inadequate today to support high-volume practice [26, 64]. However, human factors remain among the most important barriers [65]. Despite many advances and clear evidence of the accuracy of clinical diagnoses by telepathology for routine pathology cases [66–68], many pathologists are reluctant to abandon their comfort zone as glass slides are still available with current technologies. The maintenance of both glass slides and virtual images also implies the duplication of storage facilities. This parallel storage system is one of the major differences with teleradiology. However, ongoing research efforts let us believe that the replacement of glass slides by some form of direct microscopy on unprocessed and unstained sections using imaging technologies such as multiphoton microscopy (MPM) [69, 70], optical coherence tomography (OCT) [71], full-field optical coherence tomography (FFOCT) [72] or Raman spectroscopy [73] is expectable in a foreseeable future. Finally, besides these technological and human factors, a number of legal and regulatory issues are being addressed in different parts of the world. For instance, the

liability risk is clearly increased for international experts receiving worldwide consultation requests. Multi-jurisdictional licensure is already a major issue in federal countries such as the United States and Canada and in unions of independent countries such as the European Union where pathologists may be required to obtain different licenses. In that respect, when both the health care professional and the patient are in two different jurisdictions, it is critical to determine the type of licensure required to insure liability coverage [74]. Digital solution licensure, which is the case in Canada and the European Union where several companies were granted Licensure for using digital whole-slide images for routine pathology use, is also critical for a wider adoption of the technology for diagnostic work because it is directly bound with liability [75]. Finally, the fast expansion of telepathology around the world is fostering international collaborations to standardize information parameters for digital pathology, health terminology and standardization of automatic image analysis [76].

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Chapter 7
Education

Liron Pantanowitz and Anil V. Parwani

Introduction

Digital images used in pathology education include static images (snapshots), live images (e.g., streaming), and more recently whole slide images (WSI). This chapter focuses primarily on the utility of WSI in Pathology education. WSI scanners are capable of digitizing entire glass slides to generate digital slides. In general, WSI scanners used to generate high resolution virtual images are more expensive than other digital imaging systems (e.g. microscope-mounted digital camera). Also, WSI files tend to be much larger than other digital image types. Using viewer software, WSI can be viewed over the Internet or an internal network on a computer monitor or mobile device. Interactive user interfaces such as trackballs, joystick controls, and touchscreen displays enhance WSI viewing and navigation, which make WSI particularly beneficial for education. Image viewing software also allows users to edit, annotate, analyze, and easily share WSI. As a result, WSI have begun to replace the use of glass slides and traditional light microscopes. WSI offers a myriad of opportunities for education, training, competency evaluation, and proficiency testing [1–3]. Table 7.1 lists some of the educational activities possible with WSI.

WSI are more interactive than static images. Compared to glass slides, digital slides are easier to share, with multiple users anywhere and at any time. They permit training material to be standardized, because the same digitized slide sets can be offered to all trainees, unlike glass slides which may be different from one level (section) to the next. Their portability, ease of maintenance, ability to annotate images (which can be selectively hidden from trainees), and ease of being used to construct tests make WSI desirable for educational purposes. WSI are particularly

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Table 7.1 WSI uses in education

Medical, dental and veterinary school
Pathology training
Allied pathology schools (cytotechnology)
Examinations
Proficiency testing
Continuing medical education
Virtual tracking and tutoring
Teleconferences
E-learning (web-based teaching)
Virtual workshops
Interactive publications

valuable when associated with relevant metadata (e.g., clinical information, text emphasizing teaching points, case discussion). Disadvantages of using glass slides for teaching include the expense of microscopes (especially multi-headed microscopes for large groups), restricted access to trainees, loss of stain quality over time, and limitations of the type of glass slides that can be shared. Compared to glass slides WSI do not fade, break, or disappear over time. Moreover, not all representative glass slides may get included into teaching sets because they may be either too hard to prepare (e.g., decalcified sections of bone and teeth), are rare cases, unsuitable for recut slides to be prepared (e.g., small biopsies with limited tissue), consult slides that need to be returned, and unique cytology cases (e.g., irreplaceable Pap tests, or other cases with only one glass slide). With WSI, such slides can now be digitized and incorporated into teaching sets.

Graduate Education

WSI has been successfully used in graduate)education for medical [4–6], dental [7, 8], and veterinary schools [9, 10]. The overall feedback obtained from students about using WSI has been positive. Both students and faculty support the use of WSI to teach histology, pathology, and cytology. Thumbnail images are helpful when navigating WSI, as they allow students to maintain their orientation regardless of location or magnification. WSI promotes more interaction with faculty and between students (Fig. 7.1). Tutors find it easier to explain issues and findings to students when using monitors, as opposed to showing them findings under a microscope. Students have also been found to work faster with WSI, more likely to use study slides in preparation for practical examinations when virtual slides are available, and enjoy the novelty factor of this new modality of teaching. It is anticipated that, in time, more graduate schools will begin to abandon their light microscopes for computers and WSI (Fig. 7.2).

Fig. 7.1 The use of WSI to teach medical students enhances faculty and student interaction (image courtesy of Sara E. Monaco, MD from UPMC, USA)

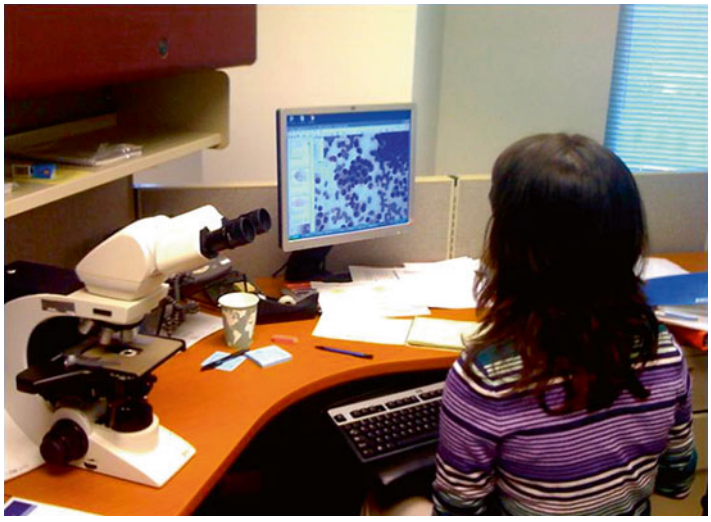

Fig. 7.2 This pathology resident opted to study cytology using a digital slide teaching set instead of glass slides on a conventional microscope

Pathology Training

WSI has proven to be beneficial in training pathology residents [11–13]. Digital slide teaching sets are a great tool for pathology residency programs for many of the aforementioned reasons. Not only are WSI teaching sets often more comprehensive and easier to access for trainees, they also help standardize training (e.g., grading of tumors), offer self-paced virtual rotations, make it logistically easier to manage and archive conference materials, and can even be used to assess competency [14–17]. For similar reasons, WSI have been successfully employed to educate cytotechnology students [18]. Annotated digital pathology slides have been shown to be superior to non-annotated slides for the purpose of resident education [19]. Training users on the system is important, because not only is diagnostic accuracy with virtual microscopy dependent on year of residency training, but also prior experience with WSI [20]. Tracking tools incorporated into WSI can be used to tutor trainees and provide quantitative metrics to help evaluate their competency at examining slides [21]. Exposing pathology trainees to WSI is important so that they are able to use this technology when they graduate. Moreover, WSI are increasingly being used on formal tests, such as board examinations [22]. Examinations that apply WSI technology typically require more sophisticated test management software [3, 23]. While digital slide sets in most programs are being used to supplement traditional microscopy training, in the near future they will likely completely replace conventional microscopy.

Tracking and Tutoring

WSI technology makes it possible to track and audit how individuals view and navigate digital slides [21, 24–26]. For example, one can track how users view a slide in four dimensions (x and y axes, zoom, and time), the areas of the digital slide they examine for given periods of time, as well as record any comments the user makes about the areas they have viewed. Researchers have been able to study the process by which pathologists arrive at a given diagnosis. To accomplish this, they have used a combination of slide exploration strategy (i.e., digitally recorded slide navigation with mapped search patterns), perceptual information gathering, and cognitive decision making [27]. Examining eye movements with eye-tracking cameras while viewing WSI also provides information about the decision-making process. By using such tools, investigators have found that trainees spend significantly more time than expert pathologists reviewing virtual slides. Moreover, pathologists often select areas for viewing at higher magnification outside their central vision. Therefore, not only are WSI tracking tools helpful to tutor and assess trainees, but by providing them with feedback collected data can help them improve their diagnostic skills [28].

e-Learning and Virtual Workshops

Today, e-learning (i.e., electronically supported learning) such as teleconferences and webinars is common in pathology. Web 2.0 technologies have enhanced out-of-classroom and in-classroom educational experiences. The virtual learning environment is popular because it supports distant, flexible, and cost-effective learning. Available e-learning applications in pathology often include WSI. Use of interactive WSI augments problem-oriented teaching [29]. Similarly, virtual workshops have become an accepted method of providing continuing medical education [30]. Such workshops are often cheaper for participants who no longer need to travel to meetings. Prior to attending a meeting, participants used to receive glass slides or Kodachrome plastic projector slides of the cases to be shown beforehand. Making digital slides of such cases available online has reduced the cost for organizers and improved the quality of material being shared. Several online educational slide sharing services (e.g., PathXchange) and public websites (e.g., vMic Pathorama, Slide2Go) offer online virtual teaching sets. Virtual atlases or digital slide boxes that support web-based learning are now offered by many pathology societies, such as the virtual slide library of the International Academy of Cytopathology [31]. At present, there are at least three pathology journals that provide their readers with access to WSI accompanying certain published articles: the International Journal of Surgical Pathology, Diagnostic Pathology, and Archives of Pathology and Laboratory Medicine [32–34]. Several textbooks have also started incorporating WSI for readers to access, which are extremely easy to use with mobile devices (e.g., iPad).

Proficiency Testing

WSI has been utilized for internal and external performance improvement and continuing medical education programs. For example, the College of American Pathologists (CAP) offers a virtual Performance Improvement Program in Surgical Pathology to members. At the University of Pittsburgh Medical Center web-based WSI of previously discrepant intraoperative (frozen section) consultations were made available to pathologists as part of their quality assurance program (Fig. 7.3) [35]. Web-based case review allows many users to simultaneously access digitized slides and promote timely evaluation. It is reassuring that the diagnostic scores of pathologists for such continuing medical education exercises do not appear to be compromised by converting to WSI [36]. With recertification in pathology becoming more important, it is likely that WSI will be increasingly used for Maintenance of Certification programs. In cytopathology, WSI has been recommended for proficiency testing [37, 38]. One could argue that WSI, by not reflecting real-world experience where cytologists still use glass slides, is not a true test of proficiency. Nevertheless, employing WSI for proficiency testing is certainly more cost effective and offers better standardization of test materials.

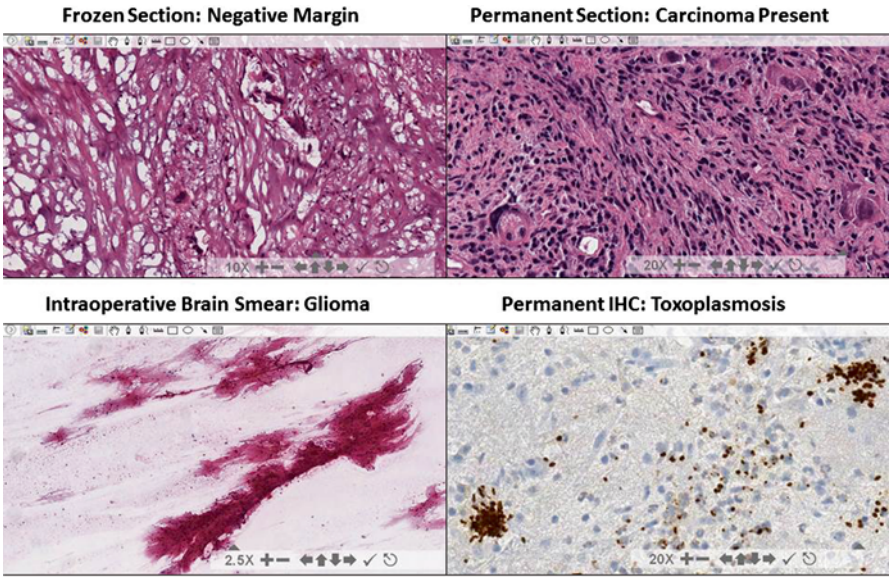

Fig. 7.3 A set of WSI hosted on a website allows pathologists to review prior difficult intraoperative (frozen section) consultation cases for continuing education purposes. The *top case* shows a tumor margin (*top left*) called negative at frozen section that (*top right*) revealed carcinoma on the permanent section. The *bottom case* shows a brain smear (*lower left*) thought to represent a glioma at the time of intraoperative consultation that (*lower right*) subsequently turned out to be toxoplasmosis confirmed using immunohistochemistry

Conclusion

In many settings, classrooms, and pathology laboratories around the world WSI has started to replace glass slides and conventional microscopes [3, 39]. WSI is being successfully employed for undergraduate and graduate education, training of pathology residents, as an educational tool in allied pathology schools, for virtual tracking and tutoring, teleconferencing, e-learning, virtual workshops, embedded in publications, and on examinations. WSI supports flexible and cost-effective distant learning and augments problem-oriented teaching, competency evaluation, and proficiency testing. New human-computer interfaces such as touchscreen displays and tracking tools have encouraged the use of WSI for education. As WSI technology improves and these imaging systems become cheaper and more user friendly we can expect to see more extensive use of digital slides for education in pathology.

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Chapter 8
Legal/Regulatory

Stanley Leung and Timothy C. Allen

Digital Pathology and Medical Licensure

It is clear that the current system of state medical licensure creates a difficult environment for the adaptation of telemedicine and more specifically digital pathology. The confusing array of different state requirements, or in some cases, vague or silent regulations concerning telemedicine, have resulted in a number of alternative models that may alleviate some of the procedural burden in practicing in multiple jurisdictions remotely.

Consultation Exception

A number of states have a consultation exception to their state licensure regulations such that a physician who is not licensed in the state can practice, at the request of a licensed physician, in consultation with the in-state physician. The scope of these laws vary from state to state, but generally proscribe the extent of contacts within the state, such as restricting the number of patient consultations or prohibiting a physical presence (such as an office) of the out of state physician [1]. While these laws seem to be a good start for digital pathology, many of these laws did not anticipate the advent of telemedicine, much less the more specific practice of pathology, and are difficult to apply to an active, continuous digital pathology service, rather than the sporadic consultation for which these laws were intended.

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Special Purpose License

For many years, the Federation of State Medical Boards has promoted a model of limited licensure for physicians practicing in another state through electronic means [2]. By applying for a special purpose license, this allows physicians who are not physically present in the jurisdiction of the patient to practice electronically, but does not allow them to do so physically within the state. This model is predicated on the physician holding an unrestricted license in another state and subjecting the physician to the oversight of the state's medical practice board. In fact several states have already established a special purpose license for out of state telemedicine physicians [3]. Some of these are restricted to just physician to physician contacts, such as pathology and radiology, while others include physician to patient interactions as well.

Endorsement/Reciprocity

State boards may grant licenses to health professionals licensed in other states that have equivalent standards through a process known as endorsement. In this case, the state may entirely accept the licensure requirements of the other state, or at least forego primary source verification, and still may require additional qualifications or documentation before endorsing a license issued by another state. Licensure by endorsement is used by state boards to grant licenses to professionals licensed in other states that have equivalent or more stringent standards. Professionals seeking licensure by endorsement may need to submit an application, original transcripts, letters of recommendation and fees to the state board for review and approval [4]. Each state retains separate disciplinary authority over its licensees. This process however has the potential for significant delays and results in needless duplication.

The concept of reciprocity is quickly becoming a remnant of the past. If a physician held a license to practice medicine in one state, most or all of the other states would grant a medical license based on the existing state license. Reciprocity denotes a relationship between two states where one state gives the subjects of another state certain privileges, on the condition that subjects from the later will be treated similarly in the former state. A licensure system based on reciprocity requires the authorities of each state to negotiate and enter agreements to recognize licenses issued by the other state without further review of individual credentials. This is the easiest form of multistate physician practice. Unfortunately, it also made it easy for unqualified or unlawful physicians to do the same. Under reciprocity, if a physician is practicing in a state with an illegally obtained or invalid license, it would not be difficult for that individual to get a medical license in a reciprocal state. Few, if any, states have true reciprocity in medical licensing in an effort to better protect patients and ensure quality of care.

Compact/Mutual Recognition

Similar to obtaining a driver's license, the compact/mutual recognition model allows medical practice in all member jurisdictions, but should the physician relocate to a new home state, then an unrestricted license to practice medicine in that new state would be required. The Federation of State Medical Boards (FSMB) has created model legislation that could be used to create a multistate agreement, or "compact" system. The model legislation calls for at least seven states to participate in the compact and with participating states to have representatives on a governing commission. Once enough states have joined the effort, participating states would share credential and disciplinary information on physicians licensed by their states with other states so they could quickly issue their own licenses without collecting the usual load of paper work normally required [5, 6].

This model can be seen at work in the Nurse Licensure Compact (NLC), an agreement that allows mutual recognition of a nursing license between member states. Enacted into law by the participating states, member states allow a nurse that resides in and possesses a current nursing license in a state that is a member of the NLC to practice in any of the other member states without obtaining additional licensure in that state. It applies to both registered and practical nurses and is also referred to as a multi-state license. While a nurse's license may be multi-state, permanent relocation to another Compact state requires obtaining licensure in the new state, as their residency has changed. Likewise, a license obtained in a Compact state that is not the primary state of residence is not mutually recognized by the other NLC members. While either home state or the remote state may take disciplinary action, only the home state can take action on the license [6].

Uniform Application

A uniform application and expedited license model is currently promoted by the FSMB. The application contains two sections. The core section contains data fields required by all boards such as education and training. A state-specific addendum allows boards to exercise some autonomy by receiving state-specific information required for licensure. The uniform application retains the physician-provided data in a secure repository which is available to the physician electronically should the physician elect to apply for licensure in another jurisdiction that has adopted the uniform application process. The FSMB encourages applicants to use in conjunction,)the Federation Credentials Verification Service (FCVS), as data entered into FCVS populates the uniform application and vice-versa [7]. The uniform application has been adopted by any state boards while several others are in discussions with FSMB regarding its utilization [8]. While a uniform application was not designed to promote telemedicine, it does streamline the application process for unrestricted licenses in multiple jurisdictions.

National Licensure

Perhaps the most sweeping model is that of a national licensure for medical practice. This is oftentimes described in two forms—a complete federalization of the licensure process and a hybrid structure that mixes a combination of federal licensure and state regulation. The first approach would entail complete federalization of licensure for telemedicine, which would not only establish federal administration of telemedicine licensing, but would also preempt all state regulatory functions in the practice of medicine. The second is a hybrid approach where granting telemedicine licenses would occur at the federal level, but the states would retain authority over the practice of medicine and the ability to enforce local standards of practice [9].

The resistance against a national licensure usually reduces to a protecting local perogatives of the state, whether that is quality of care, trade protection, or just protecting what has been traditionally a local function and the growth of its associated bureaucracy. While a federal licensing solution would be appealing in terms of uniformity of standards and easy of licensing for the telemedicine physician, it is unlikely such a large intrusion by the federal government into a traditionally state function would be universally welcomed. Therefore, other models may be necessary to promote the utilization of telemedicine and more specifically digital pathology.

Some commentators have described a hybrid federal-state system where states would retain oversight in professional standards and conduct, while a federal agency would grant licenses and maintain a database on disciplinary action. With uniform national standards, the federal government would have authority to issue telemedicine licensure to qualified physicians under these standards. However, this requires establishment of a large federal agency and may result in variances in sanctio ns due to the reliance on individual jurisdictions to enforce professional standards and conduct [9].

Private Accreditation

A more politically acceptable approach might be to develop a self-regulatory mechanism for telemedicine similar to private health care accreditation. For a health care organization to participate in and receive payment from the Medicare or Medicaid program, it must be certified as complying with the Conditions of Participation, or standards, set forth in federal regulations. This certification is based on a survey conducted by a state agency on behalf of the Centers for Medicare & Medicaid Services (CMS). However, if a national accrediting organization, such as The Joint Commission, has and enforces standards that meet the federal Conditions of Participation, CMS may grant the accrediting organization “deeming” authority and “deem” each accredited health care organization as meeting the Medicare and Medicaid certification requirements. The health care organization would have “deemed status” and would not be subject to the Medicare survey and certification process [10].

In pathology practice, the closest example private health care accreditation is CMS regulation of all laboratory testing performed on humans in the United States through the Clinical Laboratory Improvement Amendments (CLIA). Wide in scope, CLIA covers approximately 244,000 laboratory entities [11]. Organizations such as the College of American Pathologists have deeming authority for laboratory accreditation [12]. In a similar manner, through federal pre-emption of telemedicine, private national deeming organizations can help set and enforce standards in telemedicine practice by certifying physicians for interstate practice of medicine through telehealth technology. Physicians seeking deemed status recognition for their telemedicine license must document that they are licensed under the deeming authority CMS-recognized deemed status program, and the organization must recommend to CMS that licensure be granted through deemed status in a process similar to current deeming status for accreditation [13]. This would be a nationalized form of special purpose licensing with oversight from authorized private organizations. This is in contrast to what some have suggested in establishing a national specialty board for telemedicine, developed and administered through a group like the American Telemedicine Association [9]; such a concept would be in addition to a state based license and not alleviate the barriers and burdens to multi-jurisdictional licensure and remote practice. However, such a national association with recognized expertise in telemedicine could function as a possible deeming authority for telemedicine licensure.

If a deeming organization could, through federal preemption, license physicians for the limited purpose of telemedicine, it may be even more beneficial to allow specialty specific organizations apply for deeming authority. Specialty organizations would have the ability to set the standards of practice and police its practitioners more effectively than through state boards not always familiar with particular specialty circumstances. Certainly, the utilization and requirements of telemedicine technology would be different for a pathologist reading a remote frozen section or consulting on a difficult tumor than for a psychiatrist remotely counseling a patient. By allowing specialty organizations the ability to license its subjects for the narrow purpose of telemedicine, there would be significant expertise in the application and limitations of telemedicine in those specialty situations. Moreover, specialty organization are best suited to respond to specific practice standards as telemedicine technology changes. This is unique in involving specialty boards in the licensing process, and would require an alternative national organization for physicians not certified by an American Board of Medical Specialties member organization. Conversely, requiring telemedicine physicians to have primary certification in a medical specialty board as a prerequisite to a telemedicine license may be a desirable result—subjecting telemedicine physicians to additional practice standards and oversight while limiting the scope of practice. Regardless, by looking to private national organizations to license physicians for the practice of telemedicine in a particular specialty, would still allow a local jurisdiction to subject a physician to local professional standards, just adding a well-defined supplement to quality of care oversight for the community.

Additional Legal and Regulatory Issues

While digital pathology has local applications, it is from digital pathology's potential for distance-irrelevancy that exponential value is anticipated. As such, regulatory and legal issues surrounding the use of digital pathology track closely with those of telemedicine generally.

Medical Malpractice

Medical malpractice insurance coverage issues for the use of digital pathology for interstate diagnoses mimic those of medical licensure. Medical malpractice insurance typically covers claims made in the state one practices, and therefore may limit coverage to the state for which the insurer originally agreed. Pathologists risk exposure to uninsured claims for interstate, or intrastate, digital pathology-based diagnoses that extend outside their typical coverage arena. As such, it behooves pathologists considering engaging in primary diagnosis via digital pathology to ascertain the limitations of their medical malpractice insurance, and if necessary to obtain additional coverage for digital pathology activities that extend beyond their prior physical area of diagnosis. Written assurance from the insurer that extended digital pathology practice is covered is highly recommended.

In a lawsuit involving an intrastate pathologic diagnosis, issues of where the lawsuit can or should be filed, which state's law prevails, and other such issues should be addressed either contractually or under well-settled choice of law doctrine. No new choice of law issues should be anticipated by the use of digital pathology for interstate pathology diagnosis.

The Health Insurance Portability and Accountability Act

The Health Insurance Portability and Accountability Act (HIPAA), made law in 1996, was meant to protect patient information in electronic health record systems, reduce fraud and abuse, and increase efficiency of health care delivery. Issues regarding privacy under HIPAA are well-settled in the hospital and clinic setting, and digital pathology and its extension to telepathology should not in and of themselves require additional or different legal interpretation or logistical changes. The duties to maintain patient confidentiality and safeguard patient information remain; and issues surrounding transfer and storage of electronic data are the same as with hard-copied, written documents.

The major HIPAA concern with digital pathology and its telepathoology extension involve maintaining the)HIPAA-derived duties of confidentiality and patient privacy with the increased access to the electronic information afforded by technology. That said, as electronic medical records become commonplace and telemedicine expands, institutional safeguards are being developed to ensure

confidentiality, privacy, and safety from access of hackers or other unauthorized individuals or groups that can be used in the digital pathology and telepathology setting as well as other areas of the telemedicine arena.

The Food and Drug Association's Role

The United States Federal Food and Drug Administration (FDA) regulates medical devices and associated software in order to meet its duty of ensuring that they are both safe and effective. The FDA considers its authority to extend to include both digital pathology medical devices and telemedicine medical devices. Currently, the FDA has not approved a digital pathology medical device for use in rendering a primary pathologic diagnosis; however, many other countries have done so. Once the FDA does provide that approval, many of the issues addressed in this book with immediately become cogen.

Antitrust Law

Antitrust laws prohibit unreasonable restraints of trade, monopolization, and anti-competitive mergers and acquisitions. Digital pathology's telepathology presence raises the concern about information sharing, including price information sharing, that might lead to claims of "price fixing" arising from the increased opportunities for price collusion that can be anticipated to stem from extended diagnostic relationships. Without appropriate barriers, digital pathology-based telepathology's development might be inhibited.

Further, digital pathology-based telepathology, established to laudably serve rural, underserved areas, may also carry risk for claims of antitrust and Stark law violations due to assertions of monopoly formation. And while possession of a significant market share alone is not anticompetitive, predatory conduct or other behavior deemed as taking unfair advantage of a large market share in order to extend monopoly power or injure competitors risks claims of Sherman Antitrust Act violations. In areas with little competition or easy market entry, this risk should be very low.

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Chapter 9
Standards for Digital Pathology and Whole Slide Imaging

Bruce A. Beckwith

Abbreviations

AP LIS	Anatomic Pathology Laboratory Information System
DICOM	Digital Imaging and Communications in Medicine
HL7	Health Level 7
IHE	Integrating the Healthcare Enterprise
IOD	Image Object Definition
ISO	International Organization for Standardization
JPEG	Joint Photographic Experts Group
JPIP	JPEG 2000 Interactive Protocol
LDIP	Laboratory Digital Imaging Project
OME	Open Microscopy Environment
PACS	Picture Archiving and Communication System
TIFF	Tagged Image File Format
USB	Universal Serial Bus
XML	Extensible Markup Language
WSI	Whole Slide Image/Imaging

According to the International Organization for Standardization (ISO), a standard is "a document, established by consensus and approved by a recognized body, that provides, for common and repeated use, rules, guidelines or characteristics for activities or their results, aimed at the achievement of the optimum degree of order in a given context" [1]. This is a formal definition of a generic standard, but it applies to

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informatics standards as well. When considering medical informatics standards, it is useful to think about the "activities or their results" as being processes which generate medical information. This information may be in the form of electronic documents or images, such as pathology specimen images, which are annotated with demographic and medical information regarding the source patient.

First, we should consider the fundamental roles that standards play. Informatics standards provide a common way to represent data so that it can be readily understood by a variety of systems and users who share access to this information. In some sense standards are a mechanism to provide a shared world view or common understanding between systems which may be very different in terms of functions or capabilities (e.g. a radiology image viewer that can display images from both ultrasound and PET/CT machines). It is also important to realize that there are a wide variety of levels at which standards may be aimed. For instance, there are standards concerned with physical interconnection (e.g. Universal Serial Bus or USB), general digital image storage (e.g. Joint Photographic Experts Group File Interchange Format or JPEG/JFIF) or medical metadata which might be associated with an image (e.g. Digital Imaging and Communications in Medicine or DICOM). The standards that we will be concerned with in this chapter are generally at a fairly high level of abstraction, mostly concerned about the metadata that gives context and real world relevance to the imaging data. We will now spend some time discussing image file formats, metadata and workflow considerations.

Image File Formats

A number of companies have been involved in digital pathology imaging over the years and there are a wide variety of useful imaging techniques ranging from photography of gross specimens, to digital photography via a microscope mounted camera to whole slide imaging. Not surprisingly, there are many ways to store and view these images. Digital photographs taken by a microscope or handheld camera are of relatively modest size, with current consumer grade cameras capable of capturing images in the 20–40 megapixel range. Typical image file formats like JPEG (which most commonly uses lossy compression) and TIFF (which may use lossless compression) are fine for these sorts of images. See Table 9.1 for a brief comparison of some important file formats.

Table 9.1 Selected digital image file formats

File Format	Compression	Useful for
JPEG	Usually lossy	Single images
TIFF	Lossy or lossless	Single images or tiled images
JPEG 2000	Lossy or lossless; higher compression with fewer artifacts than JPEG	Tiled images, supports streaming using JPIP

While digital camera images may be relatively large, perhaps containing 6000 by 4000 pixels, common image viewers and editors can easily handle these files. However, a whole slide image may be hundreds of thousands of pixels in each dimension, which takes storage, retrieval and manipulation needs to a whole different level. The file may be so large that there may not be enough memory on a given computer to read the entire file into random access memory for viewing or editing. A related issue to consider is viewing speed. For a relatively small image (say a 16 megapixel photograph which is stored compressed using JPEG and has a file size of 5 MB), it may be perfectly adequate to store this image in a network location and transfer a copy of the entire file to a different computer on the network and then decompress and load the entire image into a viewer program. There may be a short wait while the file is transferred but once it is loaded in the viewer, the viewing experience will likely be very good. However, for a WSI file which may be many gigabytes in size, the transfer time is likely to be unacceptable, and the entire file may not be able to be loaded into a viewer anyway. One solution to this issue is to use streaming, where the image viewer requests certain portions of an image and the image server sends this much smaller subset of the image to the viewer. When additional areas are requested the amount of data that needs to be transferred and read into memory is manageable. JPEG 2000 is an example of a commonly used file format that supports streaming using the JPEG 2000 Interactive Protocol (JPIP) and it is supported by DICOM. Use of JPEG 2000 and JPIP has been demonstrated with whole slide images [2], but it has not been widely adopted in digital pathology so far, perhaps because JPEG 2000 is considered to be computational intensive as compared to other formats. Whole slide imaging vendors generally use proprietary file formats which may contain a variety of image formats and metadata structures in order to optimize performance with their viewing applications (see Table 9.2).

Another issue that comes up when considering these very large images where image compression is clearly advantageous is whether lossless or lossy compression will be used. Since uncompressed WSI images may easily be tens of gigabytes when stored, this is a crucial decision. Even though prices for storage systems continually drop, we are still not at the place where users can ignore the cost of storage or the additional time needed to transfer very large files. Various factors play into the decision to store images using lossy compression. Lossy compression can achieve higher compression ratios, but in the US there is uncertainty about whether

Table 9.2 Examples of WSI vendor file formats

Vendor	Filename extension	Characteristics
Aperio	SVS	Single file; TIFF based format
Hammamatsu	VMS	Multiple file; JPEG based
Leica	SCN	Single file; BigTIFF with XML metadata
3DHistech	MRXS	Multiple file; can use various image formats

lossy compressed images will be able to be used for diagnostic purposes without exposing the pathologist to legal risk. Studies have supported the utility of using lossy compression for WSI files in some circumstances [3]. From a standards point of view, it is important to be able to support lossy or lossless compression to allow the user to make decisions regarding the various tradeoffs between size, image quality and viewer responsiveness.

DICOM: Addressing Metadata and Workflow

One of the first questions that may occur is why use of a particular image file format, such as Tagged Image File Format (TIFF) or JPEG is not sufficient standardization for using digital pathology images, especially WSI images. There are two major considerations, metadata and clinical workflow. Regular digital image formats can handle much of the image data just fine, and as mentioned, JPEG 2000/JPIP supports streaming, but they have limited metadata fields available. These formats were designed with the needs of typical photographers in mind, not medical personnel and certainly not pathologists. In order to be able to make best use of medical images, it is desirable to be able to associate relevant patient and technical information with the image. Vendor formats may allow for associating some metadata, but since there is not a common vendor format and no common underlying data model, the files will not be able to be shared between all devices, viewers and software programs that a department might have. See Table 9.3 for a list of some types of devices or systems which might interact with digital pathology files.

The need to address similar issues with radiology images lead to the creation of the DICOM standard. DICOM is the most widely used medical imaging standard in the world. It is a high level communications standard which facilitates interchange of images and metadata and has been widely adopted in radiology. It allows for image acquisition devices from one manufacturer to work smoothly with a PACS system from a different vendor and an image viewer from yet another company.

Table 9.3 Devices or systems which may interact with pathology images

Device/System	Role
Slide scanner	Creates WSI image data
PACS/Image archive	Stores image object
AP LIS	Contains workflow and report information, history of specimen and slide preparation and results of pathologic examination
Pathologist slide viewer	Viewing of WSI objects; may be customized for pathologist's needs
Image analysis software	Generates quantitative or qualitative data from images
Electronic medical record or general image viewer	Allows other clinicians to view whole slide images; current general purpose DICOM viewers will need to be modified to properly display WSI

The standard addresses workflow, as well as image transfer, which is a key point. DICOM started out focused on radiology imaging, but has steadily added other types of medical imaging, including cardiology, endoscopy, and ophthalmology. About 20 years ago, it was recognized that it would be valuable to incorporate support for pathology images into DICOM. The so called "visible light" supplement 15 [4] which addressed photography, endoscopy and microscopy was approved in 1999. Not surprisingly, this supplement did not address whole slide imaging. It did create Image Object Definitions (IODs) for four new visible light object types. IODs are the core structure for images in DICOM. The image pixel data is stored using a variety of image formats recognized by the standard, and there is a wrapper of metadata regarding various image acquisition, context and patient attributes. Unfortunately, the availability of photography and microscopy image objects did not lead to any significant use of DICOM within the pathology community. As whole slide imaging became more widespread, the desire to extend DICOM to handle WSI files became manifest and a new working group for pathology was created in 2005.

When the working group started examining the current structure of DICOM, it became apparent that there would be a number of challenges. Some of these were technical relating to hard coded limits in DICOM on overall size and pixel dimensions of images as well as the fact that the traditional DICOM model had been a "store and forward" model where an entire image was sent whenever it was requested. The working group recognized that there was an additional fundamental issue though. Namely, the information model of DICOM assumed that patients were the subject of imaging, whereas in pathology, specimens are the typical subject of images.

In DICOM, there are three basic levels of image objects: study, series and image. A study corresponds to a radiologic procedure done for a patient, such as a Computed Tomography or CT scan. A study contains one or more series, each of which is a collection of image objects. A series may have one or more image objects. In the case of a CT, a series may contain a number of different images, each of which represents a different cross sectional level or "slice" in the patient. This structure however, had no place for specimen imaging, which is of primary importance for pathology imaging. In addition, information about various aspects of the specimen including preparation steps, such as fixation, stain type, antibodies used for immunohistochemistry is important and needs to be specified; just as information about patient preparation, such as oral or intravenous contrast is relevant to a CT study.

One of the less obvious concepts that were added was that of a container. This was added to allow for harmonization with the major medical communications standard, HL7, which has a data model which includes the concept of a container. The need for containers is perhaps more obvious when considering liquid specimens which are the most common specimens in clinical laboratories. Anatomic pathology specimens are typically transported in some sort of container, such as a jar and then they are dissected and chemically processed and embedded in paraffin. In the case of paraffin embedded tissue, the container is the block; while once a section is made using a microtome, the slide and the coverslip comprise the container—being in some sense equivalent to a jar and a lid.

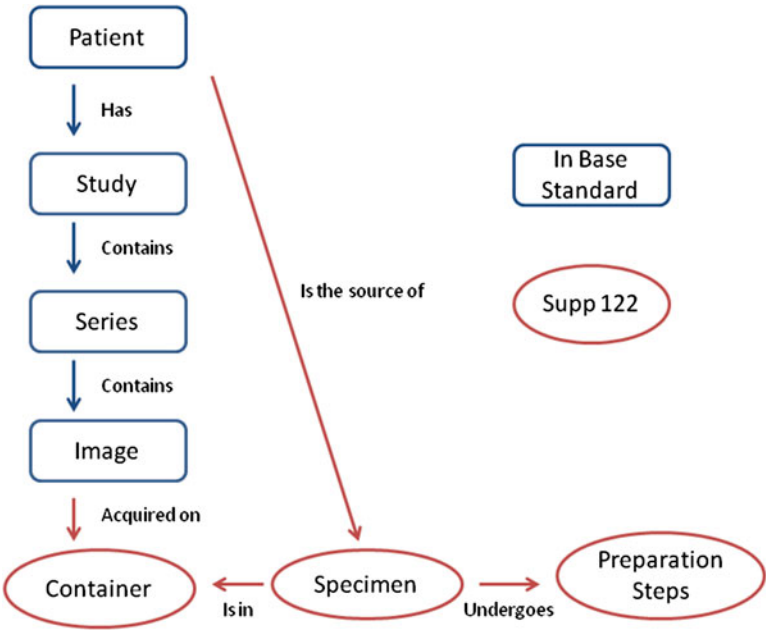

Fig. 9.1 An illustration of some of the key concepts in DICOM, including those introduced in Supplement 122. For images in most other medical specialties, the usual relationship is that the patient is the subject of imaging procedures. However, in pathology the specimen, which is derived from a patient, is the subject of imaging. Note that a study is the highest level of the image object hierarchy

DICOM Supplement 122 [5] was the first output of the pathology working group and it extending and harmonizing the concept of a specimen. Figure 9.1 gives a graphic representation of some of the key relationships in the DICOM model. Supplement 122 also introduced data elements that allow a more complete description of the sampling, processing and slides used for microscopic imaging. These elements can be used with both the older microscopy image objects defined in Supplement 15 as well as the whole slide imaging objects which introduced later. The concepts in Supplement 122 include support for multiple specimens on a single slide, such as might occur with a tissue microarray or when separately identified tissue fragments are embedded together, being distinguished by shape or ink color. See Table 9.4 for a summary of the types of information added to DICOM by the various pathology related supplements.

After adding these important pathology concepts to DICOM, the working group moved on to the more complicated task of defining an image object for whole slide images. DICOM typically relies upon existing file formats for pixel data whenever possible, so that JPEG and TIFF formats were already available for use within the standard. However, there were two main constraints—the need to accommodate larger pixel dimensions (as mentioned, the base standard has fixed size limits for

pixel dimensions and file size) and the need to transfer only the relevant part of an image. One of the major decisions was whether to pursue an entirely new image object that was not backwards compatible with the existing standard (e.g. increase or remove pixel dimension and file size limits). In some respects this would have been more straightforward, but it would have meant that existing DICOM compatible archives would not have been able to easily accommodate these new objects. The group decided that making the WSI image object fit within existing limitations and method of access would be preferable.

One of the ways that WSI scanner manufacturers can deal with the challenges of image size and need for streaming is to create a so called image pyramid. This is a conceptual construct which uses various precomputed "magnification levels" of the same slide image to allow faster access to particular regions and magnifications of the image data. For instance, let's say that a slide is scanned by a WSI instrument at a resolution equivalent to the magnification provided by a 20× objective using a typical light microscope. This image is the base image and it is often divided into subregions called tiles. A WSI viewer can ask for a certain region by specifying which tiles it wishes to have delivered. However, if a user wants to look at a certain area at the equivalent of only 4× magnification, then a large number of 20× tiles will need to be sent and the viewer will need to down sample this large amount of image data to construct a lower resolution 4× view of the region. However, by precomputing lower magnification views of the image data, perhaps at 10× and 4× as well as a thumbnail view of the entire slide, the viewer can retrieve data from the lowest magnification layer that will meets the user's request, reducing the amount of data transferred and the amount of real time computation needed to render a given at the cost of additional storage space.

Table 9.4 Examples of metadata in DICOM relevant to pathology images

Type of Information	Supplement 15	Supplement 122	Supplement 145
Specimen	Basic specimen information including collection procedure	New specimen module with detailed information including specimen types and sampling procedures and container information	–
Preparation	Specimen processing and staining	More extensive information about fixation, processing and staining	–
Image type	Single field of view	–	Whole slide images; introduced multi-frame tiled images
Optical path	Microscope illumination and magnification	–	More extensive optical information including filters and wavelengths
Image localization	Slide coordinates (positioning on stage)	–	Additional image positioning data; backwards compatible with slide coordinates

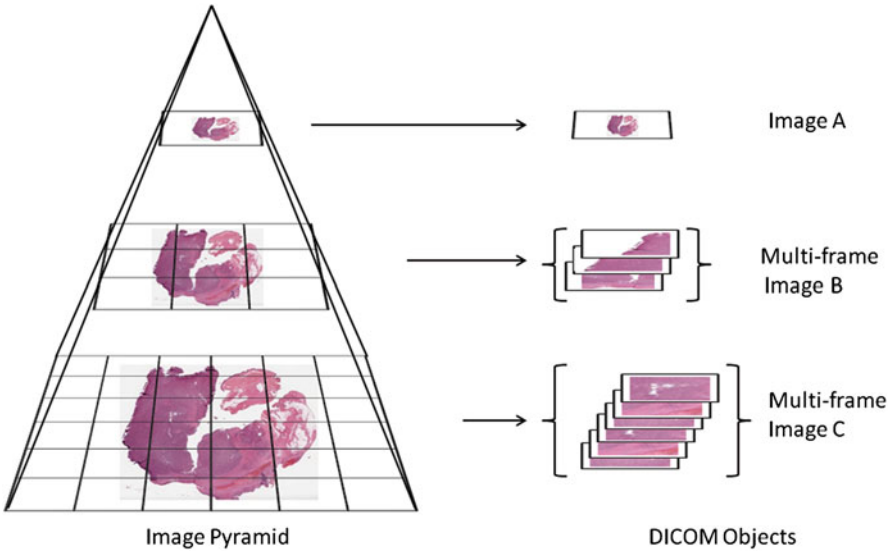

Fig. 9.2 This figure illustrates how a whole slide image, composed of multiple tiles at three different resolutions (magnifications) might be represented as an image pyramid as well as one way that the various layers might be stored as individual or multi-frame image objects within DICOM. In this example each different resolution layer in the pyramid is stored as a separate object, but all of the individual tiles from the lowest level are stored together as individual frames in a single multi-frame object

The second output of the Pathology Working Group was Supplement 145 [6] which was approved in 2010. This supplement introduced a Whole Slide Microscopy IOD which supports tiled images and the concept of an image pyramid by using multi-frame image objects. Each multi-frame object can contain multiple related images, such as tiles from a particular level of the pyramid. Figure 9.2 illustrates a hypothetical image pyramid and one way that it could be represented in DICOM objects. One very useful feature of the IOD is that it allows multiple image layers at the same resolution to be defined. This capability could be used to store so called Z-plane information or image data from slightly different focal planes at the same magnification. This is particularly valuable when examining sub-cellular structures, such as nuclei at high power. Importantly, each layer allows for sparse tiling, which means that the image creator can populate only a subset of image tiles in each layer in the pyramid. This allows for more efficiency, since areas which are not of interest do not need to be included in the image file. The image creator can also add additional layers which may be the result of using different filters or wavelengths of light. There is also flexibility in terms of the tile size for each layer. The tile size is determined by the object creator and can be as large as the largest single image size which DICOM allows (64 K × 64 K pixels) if desired.

When moving from the conceptual to the concrete, the image object creator also has flexibility in how to organize image tiles into image objects. For instance, a thumbnail image at the top of the pyramid may be stored as a traditional DICOM single frame image. A layer of similar resolution image tiles can be stored as one multi-frame image object, allowing each Z-plane to be stored separately. Alternatively, a spatial region which is represented in multiple Z-plane layers could be stored together in the same multi-frame image object. A special image flavor was created for slide label images. The reason for this is that many scanners capture a separate image of the slide label for positive identification of the slide being imaged and this may be accomplished using a separate camera. This type of image has metadata that can contain the decoded contents of a bar code or text present on the label (from optical character recognition or manual entry). It is useful to separate the label image from the specimen image since WSI can be used for many purposes including research and education, not all of which need to retain patient specific information.

In parallel with the work going on within DICOM, another standards organization, Integrating the Healthcare Enterprise (IHE) has been working toward a vision of a fully integrated Anatomic Pathology digital workflow. IHE does not develop standards, but rather creates technical frameworks and integration profiles which define common integration needs and specify how to accomplish these interactions using healthcare standards such as HL7 and DICOM. In the Anatomic Pathology space, IHE has published a technical framework [7] which includes two sections of integration profiles for common activities, such as accessioning, processing, and reporting a biopsy specimen submitted for pathologic examination. The framework includes imaging considerations as well. The Anatomic Pathology workgroups of HL7, DICOM and IHE are continuing to work together to move toward the goal of a seamless interoperability for anatomic pathology [8]. One method that IHE uses to help adoption of standards is Connectathons. These are live events where vendors gather together and set up model systems and then send electronic transactions to each other using the relevant standards and integration profiles. Results of the testing are evaluated and published. These Connectathons are well established in the area of radiology and help to continue moving the domain forward in terms of interconnectivity.

Given that DICOM has all that is necessary to support clinical use of pathology images, and IHE is working to help define the interactions between various systems involved with clinical pathology imaging, what else needs to happen now? Clearly, adoption of the standard by both scanner and AP LIS vendors is one of necessary steps needed to move to a standards based pathology imaging workflow. In addition, if pathology images are going to be handled along with other medical images and stored in an enterprise PACS or Image Archive, then these systems will need to become compliant with Supplements 122 and 145, as will as image viewers. There will be challenges, since these systems were not originally designed with WSI images in mind and there will be many modifications needed. For instance, not all AP LIS systems store information at the same level of granularity that the DICOM

metadata now supports. Another, less obvious issue that may hinder rapid adoption is that there are multiple patents that are applicable to whole slide imaging and companies may need to decide how to approach these intellectual property issues.

Other Related Efforts

While this chapter has mainly been concerned with recent developments in DICOM, there are other projects which are relevant and should be mentioned. First, between 2004 and 2006 the Association of Pathology Informatics sponsored a project called the Laboratory Digital Imaging Project which had a goal of creating an Extensible Markup Language (XML) based specification for pathology image objects which would provide a common format for file interchange and be compatible with DICOM. This was an ambitious effort but unfortunately it was not able gain sufficient traction and it foundered [9].

Another effort to mention is the Open Microscopy Environment (www.openmicroscopy.org). This project is aimed at research biological microscopy, not at medical applications, but it has created a data model in XML which is expandable and self describing [10]. They also provide open source software through a collaborative development model. It may be of interest to those using digital microscope imaging for research purposes.

A third project which is aimed at addressing the lack of a universal data format for whole slide images is OpenSlide (openslide.org), which has created a vendor neutral C library for viewing and manipulating whole slide images in a variety of different vendor formats [11]. While not a standard, this project provides a useful tool to help bridge the gap until digital pathology standards are widely adopted in practice. Given the long time frame that is typical of standards adoption, this project may be relevant and useful for a long time into the future.

Conclusion

As we move toward an era where digital pathology becomes more commonplace in clinical practice it has become clear that simply being able to exchange an image file is insufficient to fulfill the needs of a practicing pathologist. The scanning of a slide and the viewing of the resulting image are key steps, but in addition, the associated metadata needs to be combined with the image file so that the images can be considered in combination with the clinical information. In addition, there are multiple systems which are involved with creating, storing, viewing and annotating pathology images and the entire workflow must be considered if digital pathology images are going to be seamlessly integrated into the work of practicing pathologists. We now have the relevant standards in place to permit this, but they need to

be adopted, which typically is a slow and challenging process. Pathologists can help move this forward by advocating with vendors to adopt relevant standards and support broad interoperability that will enable the highest level of patient care.

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Chapter 10
In Vivo Microscopy

Anne Marie Amacher, Christopher A. Garcia, and Andrew Quinn

Introduction In vivo microscopy (IVM) is the general term for the many non-microscopic technologies that allow clinicians, pathologists and researchers to visualize or gather molecular-level information from tissues at or near the resolution of a microscope. Although IVM has been a routine component of ophthalmology practices, primarily for visualization of the retina, for roughly two decades, it has only recently begun to gain traction in other specialties, including dermatology, gastroenterology, interventional cardiology and pathology. The term IVM implies that imaging may be exclusive to tissues within (or on the surface of) a living organism; however, numerous ex vivo applications also exist, including many investigational undertakings exclusive to pathology. This chapter will focus on those IVM applications most relevant to the practicing anatomic pathologist and will explain the basics behind the predominant imaging technologies, including optical coherence tomography (OCT) and confocal laser microscopy, both of which are optical techniques that rely on computer algorithms to reconstruct light into images or image series. As IVM is an emerging and rapidly evolving discipline in medicine, both OCT and confocal microscopy are in a constant state of re-invention, and countless other technologies are under development. Likewise, physicians are actively exploring potential uses for all these technologies with emphases on (1) their feasibility, practicality and safety in clinical workflows and (2) the establishment and validation of

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actionable diagnostic criteria. As with all emerging health care technologies, pathologists must carefully consider their involvement in this space by exploring the technologies and existing literature, engaging in research endeavors and considering all aspects and impacts of clinical implementation—from image viewing and storing to report generation and reimbursement. This chapter will thus conclude with a delineation of IVM resources available to pathologists.

Technologies There are a number of IVM technologies, including OCT and confocal microscopy, both of which are approved by the Food and Drug Administration (FDA) for clinical use, as well as multiphoton microscopy (MPM) and optical spectroscopy, which have emerged more recently. The basic technological principles, applications, and limitations of these better-established in vivo optical technologies will be described here. As with all imaging technologies, IVM applications carry with them significant informatics challenges, including data storage and workflow considerations, as well as significant costs. Discussions of these issues are beyond the scope of this chapter.

OCT is an important IVM tool utilized routinely in several clinical settings. OCT, an interferometry technique, performs non-invasive, real-time, high-resolution optical sectioning by probing a specimen with a beam of light and measuring the reflected light as a function of depth to produce a one-dimensional scan known as an A-scan. Sequential A-scans create two- or three-dimensional cross-sectional images in a manner analogous to ultrasound [1]. The imaging depth of OCT is greater than that of CLE by a few millimeters [1]. OCT provides both structural images and functional information, such as the dynamic chemical composition, and optical and mechanical properties of tissues. It is able to image body surfaces as well as hollow organs and soft tissues when used in conjunction with endoscopic probes and subcutaneous needles, respectively [1]. An additional advantage of OCT is that it does not require an exogenous contrast agent unlike CLE and MPM (see below). Although OCT has greater resolution compared with ultrasound, it is not able to resolve single cells [1]. OCT is the standard of care in the diagnosis, monitoring and treatment of vitreoretinal traction, macular holes, glaucoma, diabetic retinopathy and age-related macular degeneration [1]. OCT-based research into cardiovascular, dermatologic and gastrointestinal (GI) diseases is extensive, well established and discussed in separate sections. An FDA-approved adaptation of intravascular OCT—optical frequency domain imaging (OFDI), which allows for faster acquisition of tomographic images—is currently available in the United States [1–3].

Confocal microscopy was developed by in 1955 [4]. Its key features, which are maintained in modern confocal laser microscopes, are point-by-point illumination of the specimen and use of pinhole apertures to exclude out-of-focus light from tissue planes above and below the plane of interest [5]. Thus, confocal laser microscopes can perform real-time, "optical sectioning" of specimens that are thicker than the plane of focus, allowing for 3D tomographic reconstruction of tissues in an en face presentation. Confocal laser microscopy utilizes either reflected light or fluorescent contrast agents to produce high-resolution histologic images.

A commonly used exogenous contrast agent is intravenously administered fluorescein, which demonstrates vasculature and highlights cytoplasm and extracellular matrix, but fails to stain nuclei, a la eosin [6]. Other agents, which have no FDA-approved clinical uses, include acriflavine hydrochloride and cresyl violet. Topically applied acriflavine hydrochloride stains nuclei. Drawbacks of this agent include potential mutagenicity and limited tissue penetration [7, 8]. Cresyl violet stains cytoplasm, but does not highlight vascular structures.

There are two FDA-approved confocal laser endomicroscopy (CLE) platforms: endoscope-based CLE (eCLE) and probe-based CLE (pCLE). The eCLE device (Pentax Endomicroscopy System, Fort Wayne, NJ) consists of a miniature confocal microscope at the tip of a dedicated endoscope and uses blue laser light conveyed by a fiber-optic cable. In the pCLE platform (Cellvizio Endomicroscopy System, Mauna Kea Technologies, Paris, France), laser light is delivered via a probe within the working channel of a standard endoscope from a confocal microscope external to the patient [9]. Though eCLE has a greater lateral and axial resolution, a wider field of view, and an increased mucosal imaging depth (up to 250 μm) compared to pCLE, it is also considerably larger, presenting an obstacle to its use in a clinical setting. The small size of pCLE allows for its use in conjunction with biopsy and fine needle aspiration procedures and has thus resulted in an increased adoption rate relative to eCLE [6]. The FDA has approved pCLE for use in the respiratory tract as well, and research examining the use of CLE at other anatomic sites (e.g., gynecologic tissues, liver, pancreas and urinary tract) is underway.

CLE is expected to improve the diagnostic yield of biopsies and decrease the number of unnecessary biopsies. The advantages and limitations of CLE in the diagnosis of lesions associated with Barrett esophagus and colon polyps have been described [10]. For example, the use of pCLE in addition to white light endoscopy increases accuracy in detection of high-grade dysplasia and early cancer in Barrett esophagus patients compared with white light endoscopy alone and reduces the number of biopsies performed [11]. Similarly, chromoendoscopy-guided CLE assesses adenomatous and non-adenomatous features of colorectal polyps with high accuracy [12].

There are several inherent technical limitations associated with CLE. CLE also increases procedure time relative to conventional endoscopy. However, this increase can obviously be offset if biopsies are not performed [13]. Likewise, though increasing light source intensity improves imaging accuracy, photobleaching and photodamage to subsequent specimens may occur. Additionally, CLE images provide en face images rather than the customary, perpendicular mucosal representations of anatomic pathology. Finally, although classification criteria have been described for CLE interpretation of non-neoplastic and neoplastic GI tissues (e.g., Mainz criteria for eCLE [14] and Miami Classification for pCLE [10]), there is no currently accepted standard for CLE images of the GI tract or other organs [15].

MPM, also known as two-photon, three-photon, or nonlinear microscopy is another optical sectioning, high-resolution technology that is related to CLE and gaining traction in clinical IVM applications. Rather than using one laser as a light source and pinholes as in CLE, MPM employs at least two ultra-short pulsed lasers

that coincide at the focus point, producing a multiphoton effect resulting in fluorophore excitation. The incident laser light is limited to the focal plane of interest, distinguishing it from CLE. Restricting fluorophore excitation to a smaller portion of the tissue at a single point in time decreases photobleaching and photodamage to the specimen [16]. It also increases sensitivity because all emitted light is captured [5]. Other advantages of MPM include increased imaging depth (up to 1000 μm), higher-contrast images, and subcellular resolution capability [17, 18]. The major disadvantage of MPM is the high cost of the lasers [5]. Applications of MPM include real-time intra-vital visualization of the interaction of bacterial pathogens with their hosts [19], and cancer cells with their stromal surrounds and in response to therapy [20]. MPM of astrocytes, dynamic calcium communication in neurons, and blood vessel staining in live brain has greatly increased knowledge of neurologic functions [21]. Experimental work examining MPM in skin, kidney, lung, prostate, heart and other tissues has also been performed [22–26]. MPM data has largely been obtained from in vivo animal models and ex vivo human tissue biopsies.

"Optical spectroscopy," a term used to describe a variety of optical imaging technologies, such as reflectance spectroscopy, fluorescence spectroscopy and Raman spectroscopy, adds biochemical information to real-time, in vivo morphologic assessments. Optical spectroscopy techniques can be used alone or in conjunction with one another or other in vivo imaging modalities (e.g., OCT) to simultaneously assess multiple biomarkers, such as beta-carotene, collagen, elastin, lipid, oxygenated hemoglobin and water via a fiber optic probe at the bedside [27]. Clinical applications of optical spectroscopy are at an early stage. Studies investigating the utility of optical spectroscopy in the evaluation of vulnerable atherosclerotic plaques and breast, colorectal, esophageal and urinary bladder lesions are in progress [27–30].

Gastrointestinal Tract OCT and CLE (both e- and pCLE) technologies are being widely applied in investigating and characterizing tissues in the hollow organs of the GI tract. OCT is primarily used to visualize a hollow organ in cross section, allowing for the pathologist to inspect (at a resolution of 10 μm) the epithelium, basement membrane, lamina propria and blood vessels for proper identification of tissues and architectural abnormalities, and to guide endoscopic sampling [31]. The resolution is currently too low to directly visualize nuclear dysplasia, but irregular glands can be visualized and areas corresponding to dysplastic tissues can be identified by their darker appearance (larger, crowded nuclei scatter more light than their more normal counterparts; [31]). With this understanding, OCT has been employed in the endoscopic surveillance of the esophagus to detect patterns suspicious for Barrett esophagus, dysplasia and esophageal adenocarcinoma. Studies have also shown OCT to aid in detecting sub-squamous areas of Barrett esophagus [32].

CLE technologies provide much higher resolution imaging than OCT, but—to reiterate—do so in an en face plane as opposed to a cross section. CLE technologies have been well evaluated concerning the diagnosis of Barrett esophagus and colorectal polyp characterization [10]. The Miami Classification for pCLE [10] provides recent consensus criteria for these diagnoses (and more) by pCLE. As the fluorescein used in pCLE studies does not permeate the nucleus, a key criterion for evaluating

for dysplasia is the identification of cells that are much darker than what is normally seen in the same organ. Dynamic examination of the vessels also contributes greatly to the published criteria [10]. Studies have shown pCLE images to have a high agreement with true histopathology diagnoses concerning the differentiation of adenomatous and non-adenomatous colorectal polyps [12].

There are many ongoing investigations concerning the application of OCT and CLE technologies in further evaluation of the GI tract. Relatively little has been studied concerning applications in the stomach, but a small study has shown CLE to be accurate in determining malignancies in gastric cancers [33]. In the small intestine, early studies have shown CLE to be accurate in detecting celiac changes of the small intestine [34]. In the colon, eCLE evaluations of dysplasia arising from inflammatory bowel disease are ongoing [35]. A newer form of OCT, called volumetric laser endomicroscopy (VLE), images large, continuous regions of the GI tract at a higher resolution than current, commercial OCT technologies, and has demonstrated great potential to change the way physicians sample, investigate and diagnose the above entities.

Cardiovascular System OCT, specifically OFDI because it does not necessitate vascular occlusion for visualization [38], has become a staple of clinical research for coronary artery imaging in the settings of (1) acute coronary syndrome where a percutaneous coronary intervention (PCI) may be needed and (2) post-intervention stent monitoring [36]. Though clinicians and researchers have used OCT to identify the many various types of atherosclerotic plaques, plaque rupture and thrombi [37, 38], and even demonstrated its superiority to existing standards (e.g., angioscopy and intravascular ultrasound (IVUS); [39]), its ability to visualize thin cap fibroatheromas (TCFAs), which are believed to be the most vulnerable of plaques, has allowed for appropriate risk stratification pre-PCI. Namely, the presence of a TCFA begets an increased risk of post-PCI reperfusion failure and subsequent myocardial infarctions [36]. With respect to intracoronary stents, OCT has also proven itself superior to IVUS at identifying neointimal strut coverage (and atherosclerosis), strut malapposition and edge dissection [36, 39–41]. OCT has furthermore been instrumental in identifying mechanisms of late stent re-stenosis and thrombosis. For these reasons, and on account of its excellent safety profile [42], OCT has actually achieved regulatory approval for clinical use worldwide [43] and become an increasing presence in novel intravascular device trials [41] and a standard for pathologic endpoints in some instances [3].

Due to shallow tissue penetration (up to 2.5–3.0 mm, approximately 7.0 mm less than IVUS; [37, 39]), a small scan diameter (up to 7–10 mm, approximately 5 mm less than IVUS; [3]), incomplete neointimal resolution [40], and variations in fibrous cap thickness [38], OCT generally cannot characterize the full extent of lesions in larger caliber coronary arteries [41] and histologic correlation studies have been suboptimal in this regard. Additionally, given its relative novelty, rigorously validated imaging criteria do not yet exist (Gutierrez-[39, 41]). However, consensus groups have published comprehensive guidelines covering device calibration, image acquisition and storage protocols and standards, reporting recommendations,

and feature identification (both real and artifactual), including the establishment of diagnostic criteria and supporting levels of evidence [42, 44]. Autopsies notwithstanding, though anatomic pathologists diagnose very few intravascular and vascular conditions in routine practice, it is this area of criteria validation, as well as characterization of non-atherosclerotic vascular conditions, where they can have the greatest impact moving forward. Indeed, the majority of the OCT criteria for lesion and artifact identification have been derived from correlation studies performed by pathologists on post mortem tissues [45].

Skin Dermatologic IVM techniques, namely reflectance confocal microscopy (RCM) on account of its resemblance to histopathology, have focused most heavily on the identification of benign and malignant melanocytic lesions due to both their paramount importance in dermatology and the natural reflectance of melanin. As RCM is an en face, confocal technique, the acquisition of images from each of the epidermal layers and the superficial dermis is necessary to render an interpretation [46]. Indeed, RCM has been shown to facilitate a reduction in unnecessary biopsies of benign melanocytic lesions [47]. Likewise, various RCM scores, which focus on both architectural and cytologic features, yield sensitivities and specificities ranging from 83.8 to 97.3 % and 69.3 to 96.9 %, respectively, for melanoma [47, 48]. These values compare favorably to the existing standard: dermoscopy [48]. Basal cell carcinoma scores result in sensitivities as high as 100 % with specificities ranging from 88.5 to 95.7 %. Hyperkeratotic lesions have thus far proven too thick to reliably diagnose via RCM techniques [47]. They also tend to lack the melanin necessary to produce an adequate reflectance signal [49].

RCM's en face nature often precludes definitive invasion assessment [47], as do areas where the epidermis is naturally thicker [49]. Though RCM)can visualize structures as deep as the papillary dermis with a field of view up to 8 mm wide, larger devices suffer from an inability to be properly positioned on smaller, less flat surfaces, such as the ear [49–51]. Nevertheless, even with smaller devices, tissue penetration remains a major limitation in both OCT and RCM techniques [43, 46]. And the usual diagnostic pitfalls (e.g., distinguishing some melanomas from some Spitz nevi) are no less of a challenge with IVM technologies [46]. Investigations involving RCM and numerous other IVM technologies are also ongoing to identify features of aging, inflammatory disorders, photodamage and other pigmented lesions, as well as to continue to refine diagnostic criteria for skin cancers and assess margins during Mohs procedures [51–53]. Although an FDA-approved OCT platform is available for use in the skin, clinical trials have not yet demonstrated improved diagnostic accuracy with this technology [1]. However, recent work with OCT has suggested some utility in assessing photodamage, scar formation and the triumvirate of common skin cancers [46].

The dynamic nature of)RCM visualization and image acquisition has allowed for new diagnostic considerations, particularly with respect to the vasculature. For example, coiled glomerular vessels can be a feature of squamous cell carcinoma [46]. As with histopathology, early approaches to inflammatory conditions (and neoplasia) are based on pattern recognition [50]. However, current RCM technologies suffer from an inability to identify types of inflammatory cells [50].

Nevertheless, one study on allergic contact dermatitis demonstrated the ability of RCM to identify preclinical disease [47]. As with other organ systems, though some image interpretation criteria exist, including automated ones for melanocytic lesions, these criteria are in need of validation [48].

Pancreaticobiliary Tree Clinical IVM applications in the biliary tree mainly focus on better identification of indeterminate strictures [54]. The primary technology employed is pCLE with intravenous fluorescein administration during cholangioscopy or endoscopic retrograde cholangiopancreatography (ERCP), which, along with endoscopic ultrasound (EUS), traditionally suffer from low cyto- and histopathologic sensitivities due to the diminutive samples they yield. Though few prospective studies exist, recent data suggests that pCLE, when compared to or combined with anatomic pathology, improves the sensitivity and diagnostic accuracy of these endoscopic techniques for elucidating indeterminate strictures [10, 54, 55]. However, head-to-head, pCLE is less specific than anatomic pathology [54, 55]. For these reasons, validation of benign and neoplastic criteria are under investigation [55]. Other, more novel applications involve nCLE examination of cystic and solid pancreatic lesions. However, these investigations are primarily limited to feasibility assessments at this time [54].

Bronchial Tree IVM as an adjunct to bronchoscopy has the potential to increase the diagnostic yield of pulmonary biopsies because OCT is capable of imaging both entire bronchial segments and distal peripheral lung nodules with the use of needle-based catheters [56]. OCT can distinguish non-neoplastic lesions, such as hamartomas and usual interstitial pneumonitis, from malignant neoplasms [57], and identify. OCT can even identify pre-invasive cancers in the bronchial mucosa [58]. However, additional studies are needed to correlate OCT image characteristics with histopathologic findings in inflammatory lesions.

pCLE has shown potential in identifying pulmonary pathology with elastin as an endogenous contrast agent (exogenous fluorescein does not contribute useful information; [59]). Because the changes in elastin within bronchial and alveolar walls in many lung diseases are non-specific, it is still difficult to correlate pCLE findings with specific diseases [59]. MPM is a more promising technology in pulmonary imaging. MPM generates images with cellular-level detail, allowing for recognition of lymphocytes and macrophages. MPM can also distinguish neoplastic from non-neoplastic tissues and specify tumor subtypes [60].

Central Nervous System IVM of intracranial tumors and other central nervous system abnormalities has demonstrated the potential to replace frozen section analysis and other imaging modalities as a primary means of intraoperative diagnosis and margin evaluation. A number of IVM techniques have been studied for this purpose. In patients with high-grade gliomas, intraoperative use of confocal endomicroscopy with intravenous 5-aminolevulinic acid (5-ALA) contrast provides greater diagnostic accuracy and resection adequacy compared to standard neuro-navigation-guided surgery [61]. Low-grade gliomas also show microscopic cellular fluorescence with this technique [62, 63]. Other contrast agents that demonstrate histologic features that can distinguish tumor from normal brain in animal models include acridine

orange with acriflavine hydrochloride, indocyanine green (ICG), sodium fluorescein and sulforhodamine [64, 65]. Confocal endomicroscopy with sodium fluorescein has also been shown to distinguish tumor from normal brain in intraoperative human studies [62, 63, 66] because the agent does not penetrate the blood brain barrier, which results in staining of background tissue associated with the tumor.

Other IVM modalities with potential applications in neurosurgical patients include neuro-endovascular OCT evaluation of cerebrovascular disease [67], MPM assessment of calcium dynamics within the brain [18], and spectrally-resolved fluorescence imaging for distinguishing tumor from normal brain [68].

Ex Vivo Applications IVM technologies can similarly assist pathologists in dealing with commonly encountered issues in biopsied or resected tissues. Spectroscopic techniques, such as spatial frequency domain imaging and spatially offset Raman spectroscopy, can provide intraoperative margin assessment of breast excisions [69–73]. Confocal laser microscopy has also been used to determine margin status in breast, gastric and skin resections [74–79]. And elastic scattering spectroscopy can detect metastatic breast cancer deposits in a bivalved sentinel lymph node immediately following excision with a sensitivity of 76 % for the diagnosis of foci larger than 2 mm [80].

Evolution The current crop of IVM devices is gaining clinical approval and adoption worldwide, and numerous other technologies are under development. The last decade has witnessed a relative explosion of IVM literature. Though by no means standards of care yet, IVM-specific Current Procedural Terminology (CPT) codes exist (for clinicians and pathologists; see details below), and applications are certainly taking hold in the research world. As IVM offers a real-time, point-of-care near-histopathology equivalent, it stands to be a major disruptive force to the practice of anatomic pathology. To date, most IVM applications have evolved with minimal contribution from the pathologist beyond rendering interpretations in correlation studies. However, pathologists must consider increasing their participation in technology exploration with scientists and vendors, research endeavors, ongoing clinical implementations and regulatory developments by emphasizing their collective expertise in providing cyto- and histologic differential diagnoses, understanding disease fundamentals and managing large volumes of data. Pathologists must likewise embrace these technologies as potential tools for improving the care they provide during intra-procedural consultations and in the laboratory. By facilitating proper validation of clinical IVM applications, pathologists can help ensure their continued adoption and the sustainability of the field [43].

Pathology-Specific IVM CPT Codes [81][1]

Category I—88375: optical endomicroscopic image(s), interpretation and report, real-time or referred, each endoscopic session

Category III—0351T: optical coherence tomography of breast or axillary lymph node, excised tissue, each specimen, real-time intraoperative; 0352T: interpretation

[1] The aforementioned codes are accurate as of the publication of this work.

and report (of 0351T), real-time or referred; 0353T: optical coherence tomography of breast, surgical cavity, real-time intraoperative; 0354T: interpretation and report (of 0353T), real-time or referred

Resources The following meetings have regularly featured IVM applications and technologies: the Annual International Molecular Medicine Tri-Conference, CAP—THE Pathologists' Meeting™, Pathology Visions, SPIE Photonics West and the United States and Canadian Academy of Pathology Annual Meeting.

The following web sites contain useful information about IVM technologies and clinical and investigational endeavors therewith (vendor sites omitted): Beckman Laser Institute & Medical Clinic (http://www.bli.uci.edu/), College of American Pathologists' In Vivo Microscopy Topic Center (http://www.cap.org/apps/cap.portal?_nfpb=true&cntvwrPtlt_actionOverride=%2Fportlets%2FcontentViewer%2Fshow&_windowLabel=cntvwrPtlt&cntvwrPtlt%7BactionForm.contentReference%7D=committees%2Fivm_topic_center.html&_state=maximized&_pageLabel=cntvwr), International Society for Optics and Photonics (http://spie.org/), Laser Biomedical Research Center (http://web.mit.edu/spectroscopy/lbrc.html), Network for Translational Research (NTR): Optical Imaging in Multimodality Platforms (http://imaging.cancer.gov/programsandresources/specializedinitiatives/ntroi), Oregon Medical Laser Center (http://omlc.org) and Wellman Center for Photomedicine (http://www2.massgeneral.org/wellman/about.htm).

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