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

E.A. Krupinski, Ph.D. (✉)
Department of Medical Imaging, University of Arizona College of Medicine,
1501 N. Campbell, Tucson, AZ 85724, USA

Arizona Telemedicine Program, University of Arizona College of Medicine,
1501 N. Campbell #1156, Tucson, AZ 85724, USA
e-mail: krupinski@radiology.arizona.edu

A.K. Bhattacharyya, M.D.
Department of Pathology, University of Arizona College of Medicine,
1501 N. Campbell #5205, Tucson, AZ 85724, USA
e-mail: abhattac@email.ariozna.edu

R.S. Weinstein, M.D.
Department of Pathology, University of Arizona College of Medicine,
1501 N. Campbell #5205, Tucson, AZ 85724, USA

Arizona Telemedicine Program, University of Arizona College of Medicine,
1501 N. Campbell #1156, Tucson, AZ 85724, USA
e-mail: Rweinstein@telemedicine.arizona.edu

K.J. Kaplan, L.K.F. Rao (eds.), *Digital Pathology*,
DOI 10.1007/978-3-319-20379-9_5

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.

References

1. Inoue S, Spring KR. Video microscopy. The fundamentals. 2nd ed. New York, NY: Plenum Press; 1986. p. 50–599.
2. Vivian W. Status of video communication technology for medical care. In: Bashshur RL, Armstrong PA, Youssef ZI, editors. Telemedicine. Explorations in the use of telecommunications in health care. Springfield, IL: Charles C. Thomas; 1975. p. 59.
3. Weinstein RS. Prospects for telepathology. Hum Pathol. 1986;17:433–4.
4. Weinstein RS, Bloom KJ, Rozek LS. Telepathology: system design and specifications. SPIE Proc Vis Commun Image Process. 1987;845:404–7.
5. Krupinski E, Weinstein RS, Bloom KJ, Rozek LS. Progress in telepathology: system implementation and testing. Adv Pathol Lab Med. 1993;6:63–87.
6. Weinstein RS. Risks and rewards of pathology innovation: the academic pathology department as a business incubator. Arch Pathol Lab Med. 2009;133:67–73.

7. Prout GR, Wesley MN, Greenberg RS, Chen VW, Brown CC, Miller AW, Weinstein RS, Robboy SJ, Haynes MA, Blacklow RS, Edwards BK. Bladder cancer: race differences in extent of disease at diagnosis. Cancer. 2000;89:1349–58.
8. Weinstein RS, Graham AR, Lian F, Braunhut BL, Barker GP, Krupinski EA, Bhattacharyya AK. Reconciliation of diverse telepathology system designs. Historic issues and implications for emerging markets and new applications. Acta Pathologica, Microbiologica et Immunologica Scandinavica (APMIS). 2012;120:256–75.
9. Weinstein RS, Bloom KJ, Rozek LS. Telepathology and the networking of pathology diagnostic services. Arch Pathol Lab Med. 1987;111:646–52.
10. Weinstein RS, Graham AR, Richter LC, Barker GP, Krupinski EA, Lopez AM, Erps KA, Yagi Y, Gilbertson JR, Bhattacharyya AK. Overview of telepathology, virtual microscopy and whole slide imaging: prospects for the future. Hum Pathol. 2009;40:1057–69.
11. Kaplan KJ, Weinstein RS, Pantanowitz L. Telepathology. In: Pantanowitz L, Balis U, Tuthill M, editors. Pathology informatics: modern practice & theory for clinical laboratory computing. Chicago, IL: American Society for Clinical Pathology Press; 2012. p. 257–72.
12. Nordrum I, Engum B, Rinde E, et al. Remote frozen section service: a telepathology project to northern Norway. Hum Pathol. 1991;22:514–8.
13. Weinstein RS, Bhattacharyya AK, Graham AR, et al. Telepathology: a ten-year progress report. Hum Pathol. 1997;28:1–7.
14. Dunn BE, Almagro UA, Choi H, et al. Dynamic robotic telepathology: department of veterans affairs feasibility study. Hum Pathol. 1997;28(1):8–12.
15. Dunn BE, Choi H, Recla DL, et al. Robotic surgical telepathology between the Iron Mountain and Milwaukee department of veterans affairs medical centers: a 12-year experience. Hum Pathol. 2009;40(1):1092–9.
16. Dunn BE, Choi H, Almagro UA, Recla DL, et al. Routine surgical telepathology in the department of veterans affairs: experience-related improvements in pathologist performance in 2200 cases. Telemed J. 1999;5(4):323–37.
17. Weisz-Carrington P, Blount M, Kipreos B, et al. Telepathology between Richmond and Beckley Veterans Affairs Hospitals: report on the first 1000 cases. Telemed J. 1999;5(4): 367–73.
18. Kayser K, Szymas J, Weinstein RS. Telepathology: telecommunications, electronic education and publication in pathology. New York, NY: Springer; 1999. p. 1–186.
19. Della Mea V. 25 years of telepathology research: a bibliometric analysis. Diagn Pathol. 2011;6 Suppl 1:526–31.
20. Cucoranu LC, Vepa S, Parwani A, Weinstein RS, Pantanowitz L. Digital pathology: a systematic evaluation of the patent landscape. J Pathol Inform. 2014;5:16.
21. Kayser K, Szymas J, Weinstein RS. Telepathology and telemedicine: communication, electronic education and publication in e-health. Berlin: VSV Interdisciplinary Medical Publishing; 2005. p. 1–257.
22. Kayser K, Molnar B, Weinstein RS. Digital pathology virtual slide technology in tissue-based diagnosis, research and education. Berlin: VSV Interdisciplinary Medical Publishing; 2006. p. 1–193.
23. Krupinski EA. Medical image perception issues for PACS deployment. Semin Roentgenol. 2003;38:231–43.
24. Krupinski EA. Optimizing the pathology workstation “cockpit”: challenges and solutions. J Pathol Inform. 2010;1:19.
25. Siegel EL, Reiner B. Work flow redesign: the key to success when using PACS. J Digit Imaging. 2003;16:164–8.
26. Wang J, Langer S. A brief review of human perception factors in digital displays for picture archiving and communication systems. J Digit Imaging. 1997;10:158–68.
27. Kayser K. Introduction of virtual microscopy in routine surgical pathology—a hypothesis and personal view from Europe. Diagn Pathol. 2012;7:48.
28. Weinstein RS, Descour MR, Liang C, Bhattacharyya AK, Graham AR, Davis JR, Scott KM, Richter L, Krupinski EA, Szymus J, Kayser K, Dunn BE. Telepathology overview. From concept to implementation. Hum Pathol. 2001;32:1283–99.

29. Weinstein RS. Static image telepathology in perspective. Hum Pathol. 1996;27:99–101.
30. Weinstein RS, Descour MR, Liang C, Barker G, Scott KM, Richter L, Krupinski EA, Bhattacharyya AK, Davis JR, Graham AR, Rennels M, Russum WC, Goodall JF, Zhou P, Olszak AG, Williams BH, Wyant JC, Bartels PH. An array microscope for ultrarapid virtual slide processing and telepathology. Design, fabrication, and validation study. Hum Pathol. 2004;35:1303–14.
31. Krupinski EA, Berbaum KS, Caldwell RT, Schartz KM, Kim J. Long radiology workdays reduce detection and accommodation accuracy. J Am Coll Radiol. 2010;7:698–704.
32. Pantanowitz L, Valenstein PN, Evans AJ, Kaplan KJ, Pfeifer JD, Wilber DC, Collins LC, Colgan TJ. Review of the current state of whole slide imaging in pathology. J Pathol Inform. 2011;2:26.
33. Badano A, Revie C, Casertano A, Cheng WC, Green P, Kimpe T, Krupinski E, Sisson C, Skrovseth S, Treanor D, Boynton P, Clunie D, Flynn MJ, Heki T, Hewitt S, Homma H, Masia A, Matsui T, Nagy B, Nishibori M, Penczek J, Schopf T, Yagi Y, Yokoi H. Consistency and standardization of color in medical imaging: a consensus report. J Digit Imaging. 2014. doi:10.1007/s10278-014-9721-0.
34. Silverstein LD, Hashmi SF, Lang K, Krupinski EA. Paradigm for achieving color reproduction accuracy in LCDs for medical imaging. J Soc Inf Disp. 2012;20:53–62.
35. Yagi Y. Color standardization and optimization in whole slide imaging. Diagn Pathol. 2011;6:1–15.
36. Murakami Y, Gunji H, Kimura F, Yamaguchi M, Yamashita Y, Saito A, Abe T, Sakamoto M, Bautista PA, Yagi Y. Color correction in whole slide digital pathology. 20th Color and Imaging Conference Final Program and Proceedings, Society for Imaging Science and Technology; 2012. p. 253–8.
37. Sharma A, Bautista P, Yagi Y. Balancing image quality and compression factor for special stains whole slide images. Anal Cell Pathol. 2012;35:101–6.
38. Cheng WC, Caceres H, Badano A. Evaluating color calibration kits with virtual display. Proc SPIE Med Imaging. 2012;8292:82920A.
39. Saha A, Kelley EF, Badano A. Accurate color measurement methods for medical displays. Med Phys. 2010;37:74–81.
40. Seung P, Pantanowitz L, Parawni AV, Wells A, Oltvai ZN. Workflow optimization in pathology. Clin Lab Med. 2012;32:601–22.
41. Braunhut BL, Graham AR, Richter LC, Webster PD, Krupinski EA, Bhattacharyya AK, Weinstein RS. Fifth generation telepathology systems. Workflow analysis of the robotic dynamic telepathology component. Diagn Pathol. 2013;8:S3.
42. Ho J, Aridor O, Parwani AV. Use of contextual inquiry to understand anatomic pathology workflow: implications for digital pathology adoption. J Pathol Inform. 2012;3:35.
43. Schmid J. Pathology workflow and the integration of image analysis. Diagn Pathol. 2010;5:S17.
44. Krupinski EA, Tillack AA, Richter L, Henderson JT, Bhattacharyya AK, Scxott KM, Graham AR, Descour MR, Davis JR, Weinstein RS. Eye-movement study and human performance using telepathology virtual slides. Implications for medical education and differences with experience. Hum Path. 2006;37:1543–56.
45. Krupinski EA, Graham AR, Weinstein RS. Characterizing the development of visual search expertise in pathology residents viewing whole slide images. Hum Path. 2013;44:357–64.
46. Krupinski EA, Silverstein LD, Hashmi SF, Graham AR, Weinstein RS, Roehrig H. Observer performance using virtual pathology slides: impact of LCD color reproduction accuracy. J Digit Imaging. 2013;25:738–43.
47. Mello-Thoms C, Mello CAB, Medvedeva O, Castine M, Legowski E, Gasrdner G, Tseytlin E, Crowley R. Perceptual analysis of the reading of dermatopathology virtual slides by pathology residents. Arch Pathol Lab Med. 2012;136:551–62.
48. Walkowski S, Lundin M, Szymas J, Lundin J. Students' performance during practical examination on whole slide images using view path tracking. Diagn Path. 2014;9:208.
49. Elze MC, Taylor-Phillips S, Mello-Thoms C, Krupinski EA, Gale AG, Clarke A. The variation of radiologists' performance over the course of a reading session. Proc SPIE Med Imaging. 2013;8673:867310.

50. Ikushima Y, Yabuuchi H, Morishita J, Honda H. Analysis of dominant factors affecting fatigue caused by soft-copy reading. Acad Radiol. 2013;20:1448–56.
51. Fritzsche FR, Ramach C, Soldini D, Caduff R, Tinguely M, Cassoly E, Moch H, Stewart A. Occupational health risks of pathologists—results from a nationwide online questionnaire in Switzerland. BMC Pub Health. 2012;12:1054.
52. Reiner BI, Krupinski E. The insidious problem of fatigue in medical imaging practice. J Dig Imaging. 2012;25:3–6.
53. Ruutainen AT, Durand DJ, Scanlon MH, Itri JN. Increased error in preliminary reports issued by radiology residents working more than 10 consecutive hours overnight. Acad Radiol. 2013;20:306–11.
54. Krupinski EA, Berbaum KS, Caldwell RT, Schartz KM, Madsen MT, Kramer DJ. Do long radiology workdays affect nodule detection in dynamic CT interpretation? J Am Coll Radiol. 2012;9:191–8.