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Research Article

Digital pathology: A systematic evaluation of the patent landscape

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Abstract

Introduction: Digital pathology is a relatively new field. Inventors of technology in this field typically file for patents to protect their intellectual property. An understanding of the patent landscape is crucial for companies wishing to secure patent protection and market dominance for their products. To our knowledge, there has been no prior systematic review of patents related to digital pathology. Therefore, the aim of this study was to systematically identify and evaluate United States patents and patent applications related to digital pathology. **Materials and Methods:** Issued patents and patent applications related to digital pathology published in the United States Patent and Trademark Office (USPTO) database (www.uspto.gov) (through January 2014) were searched using the Google Patents search engine (Google Inc., Mountain View, California, USA). Keywords and phrases related to digital pathology, whole-slide imaging (WSI), image analysis, and telepathology were used to query the USPTO database. Data were downloaded and analyzed using the Papers application (Mekentosj BV, Aalsmeer, Netherlands). **Results:** A total of 588 United States patents that pertain to digital pathology were identified. In addition, 228 patent applications were identified, including 155 that were pending, 65 abandoned, and eight rejected. Of the 588 patents granted, 348 (59.18%) were specific to pathology, while 240 (40.82%) included more general patents also usable outside of pathology. There were 70 (21.12%) patents specific to pathology and 57 (23.75%) more general patents that had expired. Over 120 unique entities (individual inventors, academic institutions, and private companies) applied for pathology specific patents. Patents dealt largely with telepathology and image analysis. WSI related patents addressed image acquisition (scanning and focus), quality (z-stacks), management (storage, retrieval, and transmission of WSI files), and viewing (graphical user interface (GUI), workflow, slide navigation and remote control). An increasing number of recent patents focused on computer-aided diagnosis (CAD) and digital consultation networks. **Conclusion:** In the last 2 decades, there have been an increasing number of patents granted and patent applications filed related to digital pathology. The number of these patents quadrupled during the last decade, and this trend is predicted to intensify based on the number of patent applications already published by the USPTO.

Key words: Digital pathology, image analysis, intellectual property, legal, patent, telepathology, whole-slide imaging

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INTRODUCTION

Digital pathology has been increasingly used for education, clinical practice, and research.[1] Digital imaging in the pathology laboratory has improved significantly with advances in computers, digital camera technology, and whole-slide imaging (WSI) scanners.[2-5] Digital imaging allows pathologists to become untethered from conventional light microscopes, which has resulted in increased use of telepathology applications. Development of image analysis algorithms has allowed pathologists to reproducibly provide more accurate quantification of histological and immunohistochemical biomarkers and offers the potential to capitalize on computer-aided diagnosis (CAD).

Major technological innovations related to telepathology and digital image applications were introduced during the last 2 decades.[6-10] Most of these developments have been captured in the form of patents.[4] Publically disclosed patents grant the patentee exclusive rights to an invention for a limited period of time, normally 17-20 years from the filing date of a patent application.[11] Patents represent a form of intellectual property. Understanding the patent system is crucial for the protection of intellectual property and to help overcome related infringements. Transactions involving patents, such as licensing, are known to drive technology development by enhancing the rate of development and increasing the efficiencies of a given technology market. However, litigation between companies in various industries regarding intellectual property has concluded with lengthy and costly lawsuits. Such "patent wars" place the future of innovation at risk.

Patents also play a central role in technology advancement.[12] The number of patents issued and related transactions, such as licenses or infringement lawsuits can be analyzed to understand and identify the state of technology development and market acceptance for a given technology. Patent landscapes have in fact been successfully used to identify and study-specific scientific and technological trends.[13] A similar evaluation of digital pathology patents may help summarize emerging technology trends, identify technology gaps, and possibly provide some insight into the future direction of this field.

This paper represents the first review of patents related to digital imaging in pathology. The aim of the review is to systematically analyze US patents and patent applications related to digital pathology, in order to evaluate current innovations in this field, and to identify potential future technological directions. Consideration of international patents, including patents recorded in the European Patent Office and the Japanese Patent Office, are beyond the scope of this review.

MATERIALS AND METHODS

Patents granted and pending applications that were published in the USPTO database prior to January 2014 were searched using the Google Patents search engine (Google Inc., Mountain View, California, USA). The USPTO database is publically available at www.uspto.gov (United States Patent and Trademark Office, Alexandria, Virginia, USA). The USPTO uses a classification system to categorize technologies.[14] A class field usually delineates one technology from another. A subclass field delineates processes, structural features, and functional features of the subject matter encompassed within the scope of a class. Every class and most subclasses have unique alphanumeric identifiers. However, the current classification does not include specific fields for "digital pathology" or "telepathology". Therefore, a more advanced search by using specific key words or phrases within the documents' text was necessary to identify patents and patent applications related to digital pathology. Keywords and phrases used to query the USPTO database are listed in Table 1. We did not search patents by company name (i.e. DMetrix), which narrowed the search to manageable proportions but may have resulted in excluding some relevant patents, especially those on the leading edge of innovation. Data related to the query results were downloaded using Papers software (Mekentosj BV, Aalsmeer, Netherlands) for further analysis. Duplicate and unrelated patents were excluded.

Each issued US patent can be identified by its unique seven-digit serial number (e.g. US Patent Serial Number 7426567). Similarly, published US patent applications currently pending are identified either by their eight-digit application numbers (e.g. US Patent Application Serial

Table 1: Keywords and phrases used to query the USPTO database*

"Computer assisted diagnosis" and "pathology"
"Digital image analysis" and "pathology"
"Digital imaging" and "pathology"
"Digital imaging" and "pathology" and "data security"
"Digital microscopy"
"Digital pathology"
"Telemicroscopy"
"Telepathology"
"Telepathology" and "data security"
"Videomicroscopy"
"Virtual microscopy"
"Virtual pathology"
"Whole slide imaging"
"Whole slide scanner" and "pathology"

*The term "DMetrix" was not queried, but is discussed in the results section.
USPTO: United states patent and trademark office

Number 13/893,942) or by publication numbers (e.g. US Patent Publication Serial Number 20130305138). In this study, patents that were granted are referenced as "patents" or by their US Patent Serial Number (e.g. patent 7426567), while patents that are still pending are referenced as "applications" or by their US Patent Application Serial Number (e.g. patent application 12/171618). The discussion section includes a brief description of the patent issuing process in the United States.

RESULTS

Quantitative Findings

Querying the USPTO database generated a total of 1,229 patents granted and patent applications. From these, we excluded 413 patents and applications that had no role in digital pathology. Thus, we identified 588 patents and 228 applications that were related to digital pathology. These included patents and applications covering technologies specific just to digital pathology, as well as patents and applications for technologies that were developed for other fields, but were still of use ("usable") in pathology. A patent specific to pathology refers to technology with applications almost exclusively in pathology. An example is a system for acquiring and reconstructing magnified specimen images from a computer-controlled microscope (patent 6404906). A general patent that is also usable in pathology refers to technology that was first applied in another field (e.g. radiology) and now has utility in pathology (e.g. system for streaming Digital Imaging and Communications in Medicine (DICOM) images - patent 7426567, or image registration and stitching for creating panoramic images - patent 7460730).

Of the 588 patents granted, 348 (59.18%) were specific to pathology, while 240 (40.82%) were general and usable in pathology [Figure 1a]. The query identified 228 applications, including 155 that were pending, 65 previously abandoned, and eight that were rejected. Of the 155

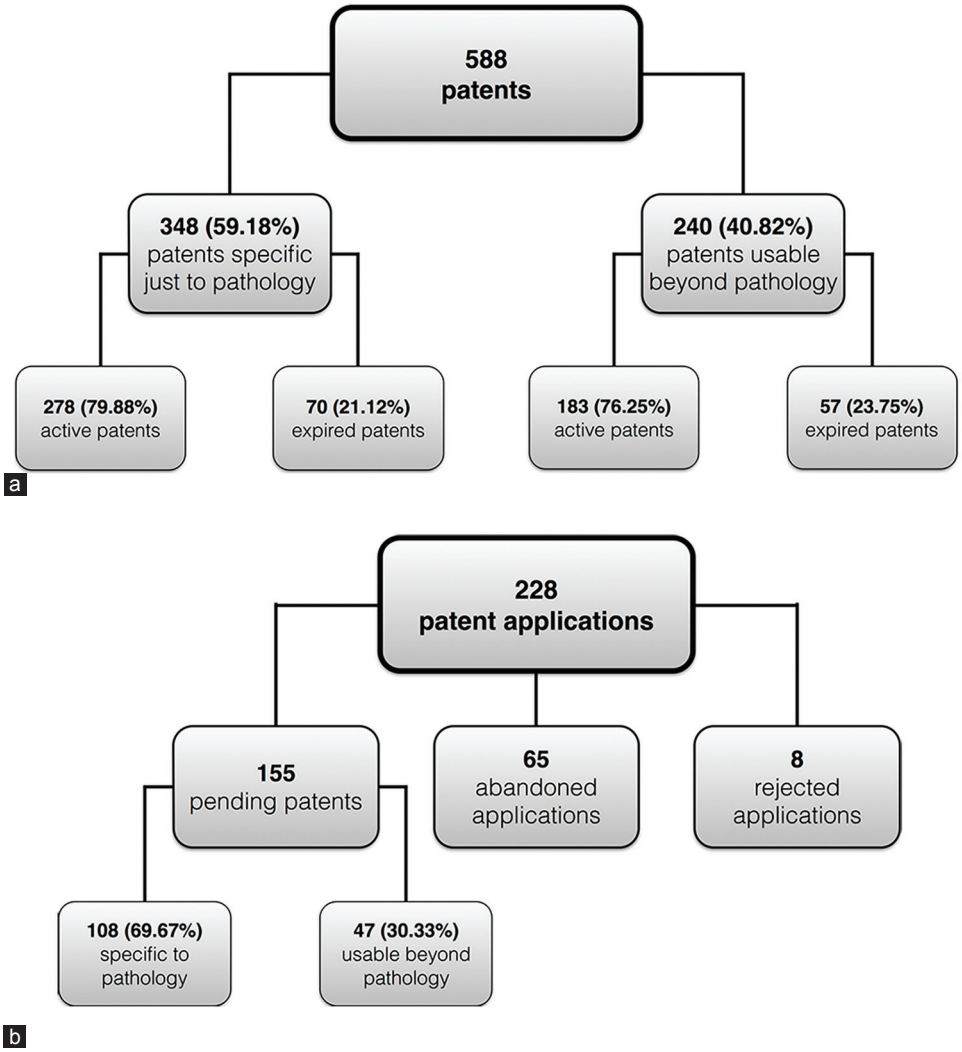

Figure 1: (a) Schematic representation of patents related to digital pathology. (b) Schematic representation of the status for all patent applications in digital pathology including pending and abandoned applications

pending patents, 108 (69.67%) were specific to pathology and 47 (30.33%) were usable beyond pathology [Figure 1b].

Of the 348 patents granted that were specific to pathology, 278 (79.88%) were still active, while 70 (21.12%) had expired either due to non-payment of maintenance fees (22 patents) or because their term ended (48 patents). Of the 240 general patents granted usable beyond pathology, 183 (76.25%) were still active, while 57 (23.75%) had expired either due to non-payment of maintenance fees (26 patents) or because their term ended (31 patents). For abandoned patent applications, 56 (86.15%) were specific to pathology and nine (13.85%) were more general usable beyond pathology. All eight rejected applications were for patents specific to pathology.

Our analysis revealed that the number of granted US patents specific to digital pathology increased almost four-fold in the last decade; 160 patents (45.97% of all patents specific to pathology) were granted during the 2001-2010 decade, while only 43 (12.35% of all patents specific to pathology) were granted during the prior decade (1991-2000) [Figure 2a]. This trend continued into the next decade, as there were already 133 patents issued between 2011 and 2013 (38.21% of all patents specific to pathology) [Figure 2b]. Our query identified only 16 digital pathology patents filed before 1991. This represents just 4.59% of all patents specific to pathology. A significant surge in the number of patents granted, specific to pathology occurred between 2001 and 2010, mostly related to telepathology and the introduction of WSI. An ascending trend was also noted for pending patents (108 total pending patents specific to digital pathology), matching the trend for the number of patents granted within the last several years [Figure 2c].

The total number of telepathology patents, excluding WSI-specific patents, was 97 (27.87% of all patents specific for pathology). While only 18 telepathology patents (5.17% of all patents specific to pathology) were granted during 1991-2000, 72 telepathology patents (20.69% of all patents specific to digital pathology) were granted during 2001-2010 (i.e. four times increase). Telepathology-related WSI patents spiked approximately eight times in the 2001-2010 decade; there were 48 patents (13.79% of all

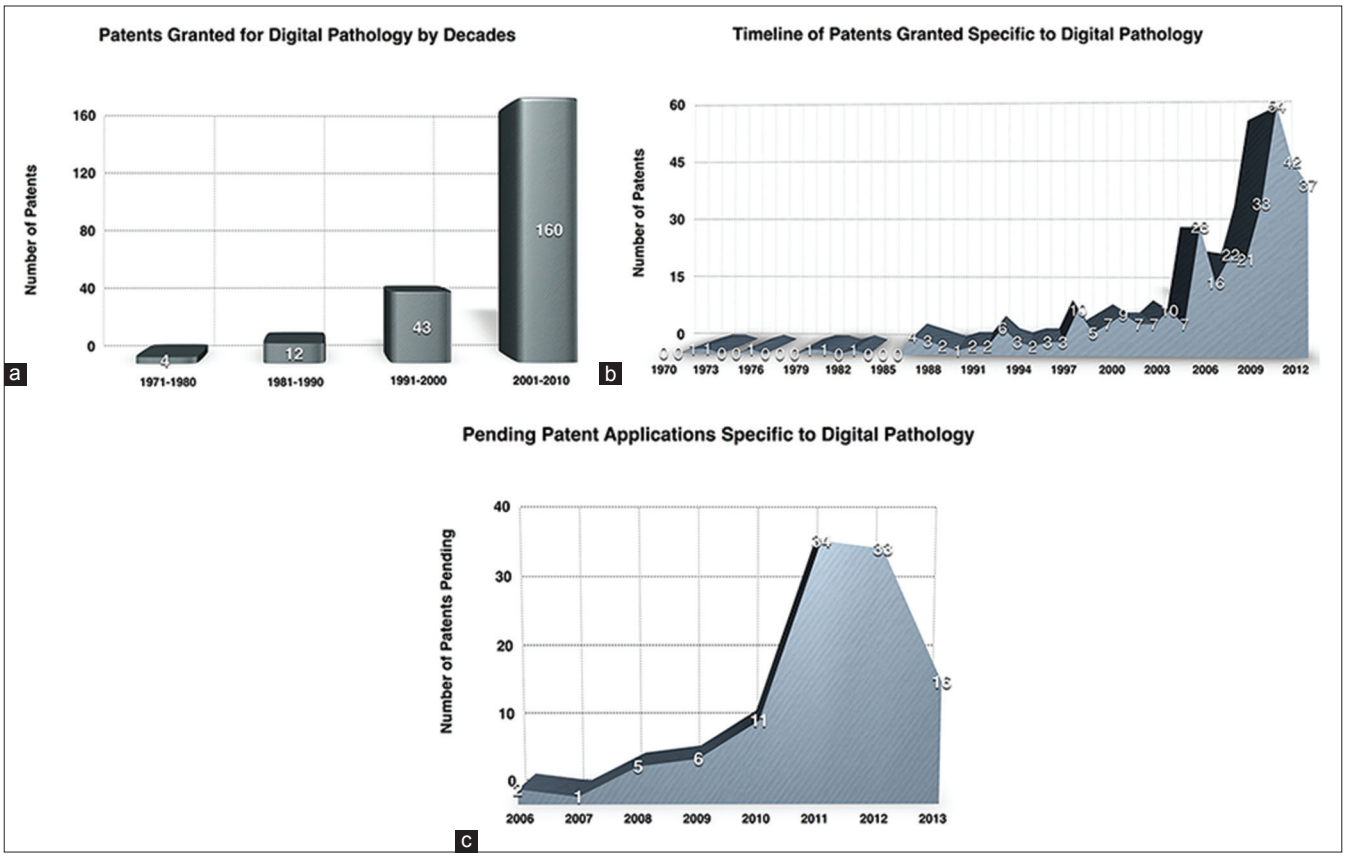

Figure 2: (a) Graph depicting the number of patents specific to digital pathology granted between 1971 and 2010, grouped by decades. Note the marked increase in the number of patents during 2001-2010. There were 160 patents (46% of all patents) granted during 2001-2010 compared to only 43 (12% of all patents) granted during 1991-2000. (b) Timeline of patents granted, that are specific to digital pathology. The graph shows a steep increase in patents over the last decade. The dip seen on the graph in 2013 is likely an artifact of the study due to the lag between the time patents are awarded and the time they are published in the USPTO public database. (c) Graph depicting pending patents specific to digital pathology. Similarly, the dip seen on this graph in 2013 is likely an artifact due to the lag between the time patent applications are made and the time they are published in the USPTO public database

patents specific to pathology) granted during 2001-2010, versus just six patents (1.72% of all patents specific to pathology) granted between 1991 and 2000. Initially, there were 28 telepathology patents (8.05% of all pathology specific patents) that were related to television and video microscopy technology.

The number of patents granted about image analysis was 117 (33.62% of all granted patents specific for pathology). This number increased significantly in recent years. Only 15 (12.82%) of these were granted between 1991 and 2000, while 39 (33.33%) patents were granted between 2001 and 2010 [Figure 3]. There were 56 patents (47.86%) related to image analysis granted in just a 3-year period (2011-2013). This number represents approximately 43% of all patents specific to pathology granted during this time frame. Moreover, 48 out of 108 (44.44%) pending patents specific to pathology are related to image analysis.

There were over 120 unique entities (individual inventors, academic centers or institutions, and private companies) that had applied for patents specific to digital pathology. The largest number of patents was issued to Aperio (Vista, CA). Aperio had 37 patents, which accounted for approximately 10% of all patent applications specific to pathology. Table 2 lists the top 10 initial assignees for patents related to digital pathology. Table 3 presents the top four companies, current owners of patents for digital pathology, as a result of mergers or royalty arrangements. A market review and detailed analysis of digital pathology companies was beyond the scope of this study.

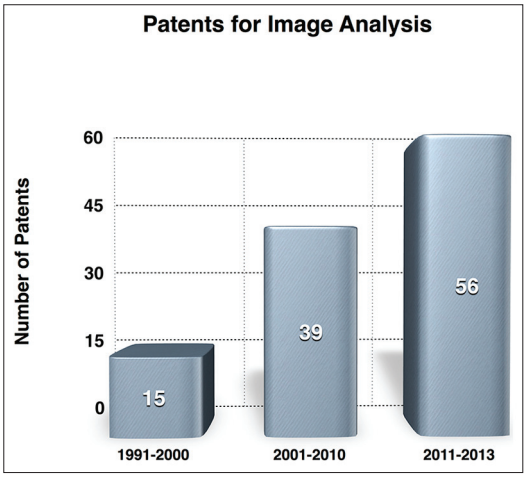

Figure 3: Graph showing the number of patents related to image analysis. The number of these patents spiked in recent years (2011-2013), representing almost half of all patents related to digital pathology granted during same time

Qualitative Findings

Patents were classified into the following technologies: Telepathology (including WSI), digital image analysis, CAD tools, and diagnostic networks. Patents referenced in this section are listed in the Appendix A (patents granted) and Appendix B (pending patent applications). These appendices do not represent a complete list of all of the patents included for review in this study.

Telepathology

Numerous telepathology innovations were reflected by patent applications. These could be divided into three modes of telepathology practice: Store and forward of static images, robotic dynamic microscopy, and virtual slides (WSI).[15] Many hybrid telepathology systems have combined these modalities in various combinations.

Store and Forward

The first telepathology patent incorporated low-resolution digital image store and forward as a graphics navigation tool (patent 5216596). Greater use was precluded by the low resolution of digital cameras in the mid-1980s. One patent described a system for sharing digital images over a network via standardized email messages created automatically by an image server (patent 7028075). The email included links to digital images stored on the server. Another patent described remote viewing of digital images via an automatically generated HTML web page by the host image server (patent 7319540). A recent patent

Table 2: Top ten initial assignees of digital pathology patents in the United States

Initial assignee	Number of patents awarded	Number of patent applications pending	Total number of patents and patent applications
Aperio Technologies, Inc (Vista, CA)	37	9	46
DMetrix (Tucson, Arizona)	29	5	34
Carl Zeiss MicroImaging AIS, Inc.	22	0	22
Olympus Corporation and Olympus America	16	6	22
Bacus Research Laboratories, Inc.	14	0	14
Ventana Medical Systems, Inc. (Tucson, AZ)	10	4	14
General Electric Company	11	2	13
Leica Microsystems and Leica Biosystems Imaging, Inc.	13	0	13
Sony Corporation	5	7	12
Tripath Imaging, Inc.	9	2	11

Table 3: Top four commercial digital pathology patent owners in the United States

Patent owners (initial assignee acquired by the current owner)	Number of patents awarded	Number of patent applications pending	Total number of patents and patent applications
Leica (Aperio)	50	9	59
Olympus (Bacus)	30	6	36
DMetrix (University of Arizona)	30	5	35
Ventana (Bioimagene)	15	5	20

application (application 12/171618) described an automated method to prefetch DICOM medical images from external DICOM servers and to store them on an internal image server. Other patent applications (application 11/778814) describe more complex ways of storing and forwarding images over networks, than simple email.

Video Microscopy and Telemicroscopy

Although early technology for video microscopy was borrowed from the field of television, we identified video microscopy patents specific for pathology. Carl Zeiss Jena GmbH filed a patent in 1971 for a means to automatically focus a microscope (patent 3721759). The described microscope had a video camera attached that was able to transmit video images to a monitor. A method to perform automatic focusing using video microscopy was also depicted in this patent. Other innovations were related to the control of a microscope stage (patent 4700298), control of illumination (patent 5018209), methods for synchronization of the image recorded by a video camera and the position of a microscope stage (patent 5216500), or development of a compact video-microscope (patent 6452625). This category also included patents that concentrated on video displays dedicated specifically for pathology images (patent 6208374) and compression of video images for transmission over a network, patented by Trestle Corporation in 2003 (patent 6606413).

Robotic Telepathology

Dr. Ronald S. Weinstein was awarded two "Telepathology Diagnostic Network" patents in 1993 (patent 5216596) [Figure 4] and 1994 (patent 5297034). These patents have a priority day of April 30, 1987 when they were initially submitted to USPTO. They describe systems used for rendering a diagnosis on a pathology glass slide by a remotely located pathologist. The systems incorporate robotically-controlled microscopes at the remote site equipped with video cameras for collecting video signals from the microscope, a bidirectional way of communication to link the microscope with a pathologist workstation that contains a monitor for viewing images received from the video camera, and a means for generating control signals which are sent back to the microscope. The system has a digital imaging component for mapping the tissue section, at low magnification, and providing a graphic interface map for tissue section navigation purposes. The low-resolution tissue map is viewed on a second video monitor. The remote pathologist can thereby remotely control the stage movement, magnification, focus, and illumination of the microscope, while remaining oriented to positional information on the precise relationship of the objective lens to the tissue section. Subsequently, other patents about robotic microscopy were awarded (patents 7215467, 7391894, 7432486, 7916916, and 8189897). Many commercial robotic telepathology systems are hybrid systems combining both static/store-and-forward imaging with robotic/dynamic real-time video imaging.

Transmission of Digital Images

Patents related to the transmission of digital images include compression and decompression technology. Although much of this technology was imported from other fields, we identified a few patents that were specific to pathology. These patents were filed by the same inventor (Jack A Zeineh), and assigned to Trestle Acquisition Corp. (patent 6606413) and Clarient Inc. (patent 7224839).

Whole Slide Imaging

Patents regarding WSI technology were classified for this purpose of this review based on various functions. These include scanning and image acquisition, image quality and focus, three-dimensional view (z-stacks), storage as well as retrieval and transmission of whole-slide image files over networks, slide navigation and remote control of instruments, graphical user interface (GUI), and workflow.[16] Select patents pertaining to these functions are discussed below.

Scanning and Image Acquisition

The first two WSI patents were filed by Bacus Research Laboratory Inc. in 1997 and 1998, and awarded in 2000 (patent 6101265) and 2001 (patent 6272235), respectively. They describe a WSI apparatus for image acquisition of an entire glass slide and presentation for viewing to a pathologist on a computer display. Subsequent patents described various techniques for digital image acquisition of whole glass slides including linear array; the majority of these are assigned to Aperio (patents 6711283, 6917696, 7457446, 8055042, 7978894, and 8385619). There is a patent about two-dimensional arrays assigned to Bio-Rad (patent 7692162) and another one describing a multiple sensor array with a single optical axis assigned to Aperio (patent 8164622).

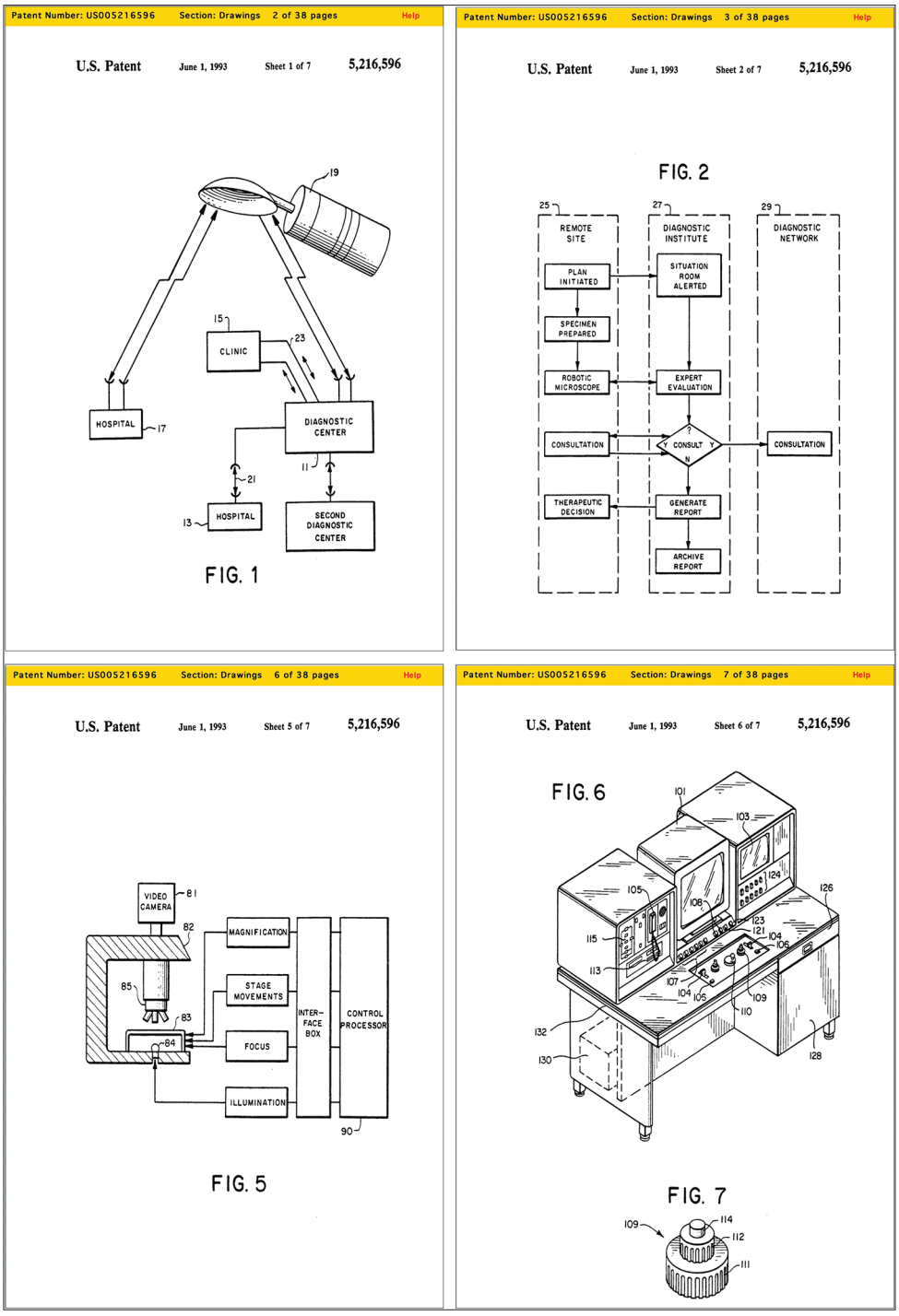

Figure 4: Selected drawings are shown from the patent "Telepathology Diagnostic Network" (patent 5216596) awarded to Corabi International Telemetrics, Inc. in 1993 (reproduced from the public database at www.uspto.gov)

Image Quality and Focus

A number of recent patents and patent applications from Aperio involved techniques to improve image quality, such as image quality assessment (patents 7668362, 8023714, and application 12/234446), quality assurance (patent 8165363), and optimization of image quality (patent 8103082). Given that cellular material attached to glass slides may exhibit a three-dimensional aspect (particularly cytology specimens), inventors developed mechanisms for automatic selection of multiple focal points to be able to capture the whole glass slide in focus. Patent applications directed at such prefocus and multipoint focus technologies were published between 2004 and 2011 by vendors such as Aperio (patents 7518652, 7646495, 7893988, and 8456522), Hamamatsu (patent 7801352),

and DMetrix (patent 7755841).

Three-Dimensional View (3D-View or Z-Stack)

Initially, one of the drawbacks of WSI technology was the lack of capabilities to acquire multilayered images that could digitally simulate the "up-and-down" fine focus that pathologists perform on their traditional microscope. This was addressed by the introduction of a technology from Bacus Research Laboratory Inc. called z-stack, the description of which is captured in a patent application from 2003 (patent 7596249). The technology continued to mature over the years. Aperio was awarded with the largest number of patents for three-dimensional view of a virtual slide, published in the database mainly within the last 5 years (patents 7463761, 7689024, and 8189891). Olympus has had two related patents, both awarded in 2011 (patents 7925067 and 8306300), aimed at improving z-axis navigation technology.

Image Management (Storage, Retrieval, and Transmission of WSI Over a Network)

Virtual slide images consist of large image files that can be stored on local workstations, external storage devices, or on networked storage devices. To be effective, WSI images have to be easily accessible and retrieved by pathologists remotely, over a local network, or over the Internet. Numerous patents and patent applications captured innovations related to image management. These include patents by companies such as Bacus Research Laboratory Inc. (patents 6674881, 7149332, 7542596, and 7856131), Aperio (patents 7035478, 7116440, 7602524, 7738688, 7826649, 7949168, 8010555, 8010555, 8086077, and 8094902, and applications 13/221759 or 13/337882), and 3DHistech KFT (patent 8203575). Aperio was awarded a patent about the "method for storing and retrieving large images via DICOM" (patent 8086077) [Figure 5 top panel]. This method was inspired by a patent originally developed for technologies outside of pathology called "System and method for constructing photorealistic mosaics", that has been cited in Aperio's patent (patent 8233740) [Figure 5 bottom panel].

Slide Navigation and Remote Control

Several patents and patent applications captured efforts to improve slide navigation, such as reconstruction of image trajectory (patents 7505616 and 7916913) from Carl Zeiss, as well as technology related to peripheral devices for slide navigation (application 12/664701) from Johns Hopkins University.

Graphical User Interface

As WSI technology matured, there was a need for improvements to the GUI. The main patent holders in this area are the University of Pittsburgh Medical Center (patent 8249315), Bioimagene Inc. (patent 8537181), and Omnyx (application 13/233575).

Digital Image Workflow

There were limited patents related to digital workflow issues. Our query identified one such patent application from Omnyx (application 13/233372).[17]

Digital Image Analysis

Although basic image analysis tools have been imported from other fields, there is a large number of innovations about digital image analysis tools in pathology that have been captured as patents. These patents span a wide variety of image analysis topics including segmentation, classification, pattern recognition, biomarker detection and quantification, quantitative fluorescence image analysis, multiplexing and multispectral image analysis as well as CAD.

Segmentation

Patents about segmentation algorithms in pathology were first filed in 1995 by inventors from an academic institution, Cedars-Sinai Medical Center (patent 5687251). In the last decade, patents related to automated and intelligent segmentation algorithms of digital images in pathology have been filed by commercial vendors such as General Electric (patent 8036462), Carl Zeiss (patent 8116543), and Sony Corporation (application 12/852096).

Pattern Recognition

Patents on pattern recognition have encompassed algorithms with applications largely for morphological identification in histology. This includes the use of pattern recognition for the identification of mitoses (patents 7979212) and the detection of epithelial from non-epithelial components in images of immunohistochemistry, from Ventana Medical Systems (patent 7941275 and application 13/079719). There is also a patent about blood cell identification and the generation of hematology profiles for peripheral blood smears (patent 4307376). Several patents about pattern recognition involve WSI (patents 7257268, 7502519, and 7844125).

Classification

Classification algorithms patents date back to late 1970s and early 1980s (patents 4207554 and 4404683). There are also numerous patent applications about classification algorithms that have been filed within the last decade. They include tools for cell class detection such as signet ring cells from NEC Laboratories (patent 8582860) and epithelial ovarian cancer cells (application 13/061530). The majority of these applications were filed in 2009-2010, and many were pending at the time of our query.

Biomarker Detection and Quantification

Several patents were awarded and patent applications filed that deal with automation of the image analysis process. They describe automatic finding of regions of interest, automatic detection of specific tissue regions or specific cells, and automatic quantitation of immunohistochemical stains (patents 7899624 and 8515683).

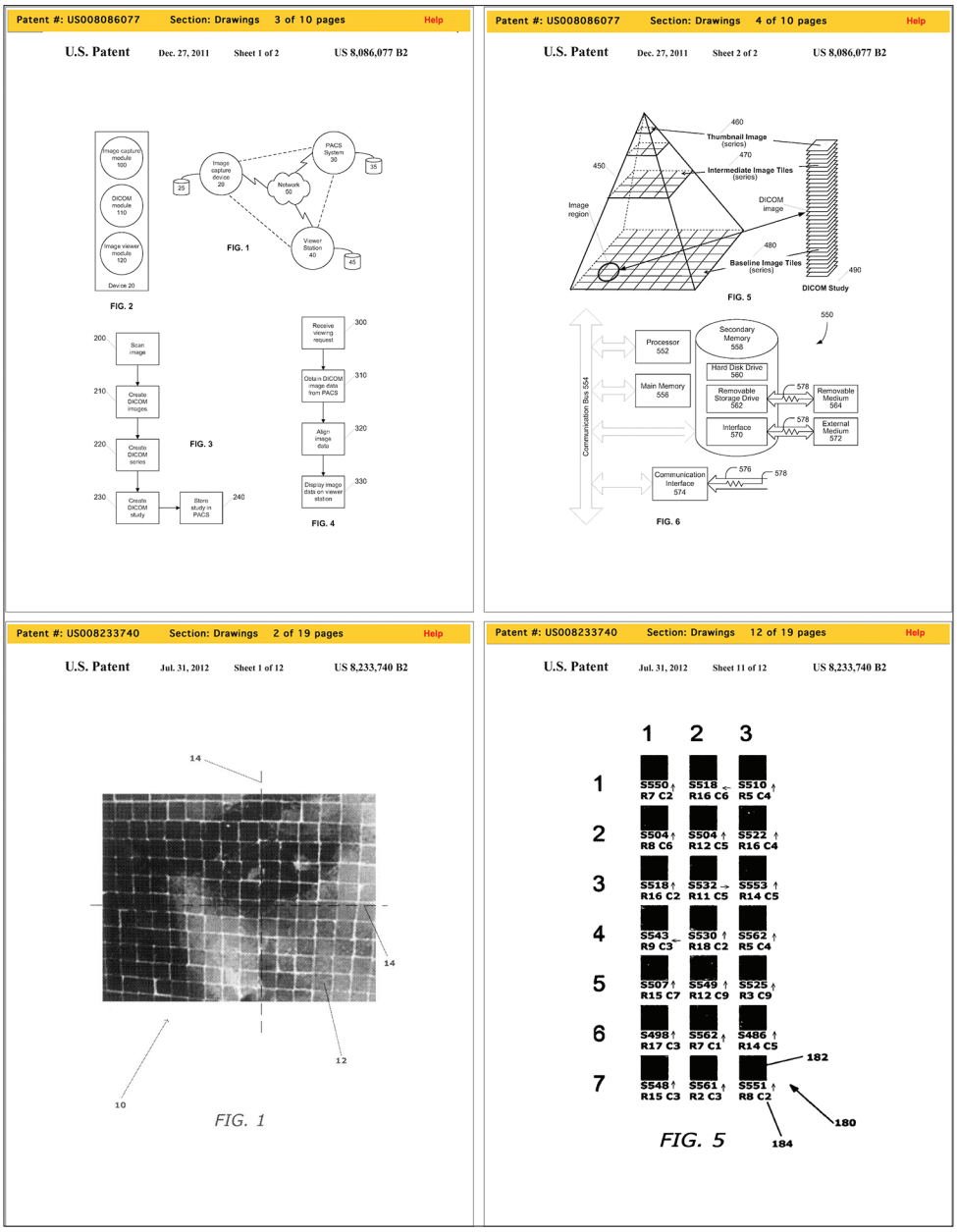

Figure 5: Top: Shown are drawings from Aperio's patent "Method for storing and retrieving large images via DICOM" (patent 8086077). They demonstrate a system for storing and retrieving images. Bottom: Shown are drawings from the cited patent (patent 8233740) in Aperio's above patent that describes a method to construct photorealistic mosaics (reproduced from the public database at www.uspto.gov)

Quantitative Fluorescence Image Analysis

The initial patents for automatic classification of cells using quantitative fluorescence were based on video microscopy (patent 7844125). However, in concert with the introduction of digital images in pathology and the development of fluorescent WSI scanners, there has been considerable development of fluorescent imaging analysis tools. Some of these patents or patent applications originated from the University of Oklahoma (patents 5733721 and 5741648) and Bioimagene Inc. (application 12/720582).

Multiplexing and Multispectral Image Analysis

Within the last decade, there were patents related to newer image analysis tools for the quantification of biomarkers. Some of these tools have been captured in patents describing methods for spectral deconvolution (patent 6618140) and quantum dots (patents 8244021 or 8290236). More recently, vendors began developing tools that allow multispectral and fluorescence analysis to be performed using whole-slide digital images. Such work has been disclosed in patents and patent applications from DMetrix (patent 7864379) and Applied Imaging (application 12/053515).

Computer-Aided Diagnosis

CAD patent applications have been very active mostly within the last 5 years (e.g. patents 7027627, 7027633,

and 8077958). One of the earlier patents in this area belongs to the University of Pittsburgh (patent 6278793). Newer patents incorporate automated algorithms for unsupervised detection and grading of various pathologies, such as Gleason grading of prostatic adenocarcinoma (patent 8139831).

In addition to the aforementioned patents, during our review we encountered several other patents describing innovative image analysis technologies in pathology. These include applications for automatic cytology screening and classification (patents 7446935 and 7764822). A method for testing proficiency in cytology screening has been patented by Neopath Inc. (patent 5797130). Recent patents also included innovations related to image analysis of tissue microarrays (TMAs). These comprise automatic processing of TMA scores (patent 8428887), co-registration of multi-channel images (patent 8131476), automatic quantification (patent 8068988), and automatic scoring (patent 8060348). A few patents specifically addressed the implementation of image analysis algorithms for WSI (patents 8116547 and 8199358). There were also patents regarding image quality assurance (patents 7818130, 8121383 and 8103082) that deal with the quality of digital images for image analysis.

Pathology Consultation Networks

Dr. Weinstein is one of the pioneers in pathology consultation networks. He designed one of the first complex networks of communication for pathologists. His innovations were captured in two early patents entitled "telepathology diagnostic network" (patents 5216596 and 5297034). Aperio later patented their "second opinion network" (patent 8565498), an implementation of WSI in consultation workflow, which incorporated communication means, along with consultation payment processing, to allow digital slide conferences between a referral source and consultant. Similar patent applications have been made for an integrated clinical consultation network of hematological specimens (application 13/069836). This particular application describes an integrated solution for image processing and digital image-based hematologic diagnoses, with server-based knowledge management and social network applications for professional communication. The patent also describes how laboratory reports can be generated automatically based on image-associated metadata, and how de-identified data can be mined for medical research.

"Collaborative Diagnostic Systems" (patent 7027633) is another example of a patent related to consultation networks. This particular patent describes built-in CAD tools for improved diagnostic accuracy and early detection of disease. The patent called "data processing and feedback method and system" (patent 7187790), owned by GE Medical Systems Global Technology Company LLC, extends the consultation and diagnostic network beyond pathology, to incorporate professional consultations at different levels of healthcare delivery. The patent "system for networked digital pathology exchange" (patent 8244912) assigned to Corista LLC describes a cloud-based method to facilitate the exchange of pathology studies.

Next Generation Digital Scanners

Dr. Ronald S. Weinstein was a cofounder of DMetrix, a spin-out company of the University of Arizona Colleges of Medicine and Optical Science. DMetrix initiated a two-phase research and development program in 2001. The Phase 1 objective was to design and manufacture a digital scanner that could digitize the image of a standardized 1.5 cm^2 tissue section in less than 1 minute. At that time, slide digitizing times ranged from 30 minutes to 3 hours using commercially available digitizers. University of Arizona scientists invented a solid-state array microscope, which was linked to a proprietary 8-channel CMOS sensor. The 1-minute scanning time was achieved in 2005. This solid-state miniaturized microscopy array optical scanner, the "DMetrix 20" scanner, was successfully manufactured and implemented at top University Medical Centers in the United States, including Case Western Reserve University (Cleveland, Ohio), the Massachusetts General Hospital (Boston, Massachusetts), and MD Anderson Medical Center (Houston, Texas). The initial pathology array microscope patent is the property of the University of Arizona and is licensed to DMetrix (patent 7116437).

The DMetrix phase 2 research and development program was aimed at developing a liquid lens-based digital slide scanner. There are numerous advantages to using liquid lenses including increased precision of z-axis focal point acquisition, since the focal point of each miniaturized microscope in the array is controlled independently, unlike the fixed focal points in a solid-state system.

With regard to this patent survey, it is noteworthy that most of the DMetrix patents are not retrieved by searching the USPTO database using the keywords and phrases listed in Table 1. In order to retrieve the large portfolio of digital pathology-relevant DMetrix, awarded patents, search the USPTO database using the word "DMetrix". As of February 18, 2014, there are 29 awarded patents, all of which are relevant to DMetrix digital scanners. DMetrix digital slide scanner patents are not retrievable using Table 1 key words and phrases with one exception. US patent 6905300 is retrievable using either the key word DMetrix or telepathology. Generally, DMetrix does not use the term digital slide scanner or digital pathology in the titles of its patents. The miniature microscopy array optics component of the DMetrix slide scanners may be employed for other purposes in laboratories, such as providing the optics for the digital

imaging systems in next generation sequencing (NGS) platforms used for rapid-throughput DNA analysis.

DISCUSSION

The vast majority of patents related to the field of digital pathology are called utility patents, or "patents on an apparatus or method". In order to be awarded, patent applications for utility patents have to meet three criteria: subject matter eligibility, novelty, and non-obviousness. In the US, a patent application can be filed as a provisional or a non-provisional application. A provisional patent application is used to establish a priority date. This provides inventors time to evaluate their technology before committing resources towards patent prosecution. A provisional application requires no set format or content, but typically includes a simple description of an idea, accompanied by one or more drawings. This type of patent application will not be examined by the patent office and automatically becomes abandoned after 1 year, unless a related non-provisional application is filed, in which case the non-provisional patent application may claim priority to the filing date of the provisional application. The non-provisional patent application requires a defined format and more components: an abstract, a description of the invention, a set of claims, any applicable drawings of the invention, a filing fee, and an oath or declaration. When reviewing a patent, it is important to pay attention to all of these components. The claims represent the most important component of a patent application; they define, in technical terms, the scope of protection granted by the patent. The description section is usually written with reference to the drawings that show the invention, and each claim (if more than one is made), should be entirely supported by the description. When a patent is awarded by the USPTO, a patent number is assigned, which is different from the initial patent application number or the patent publication number. The actual date of the patent is the date when the patent was issued, not the date when the patent application was filed. Current US patent law allows patents a term of 20 years from the date of the filing, compared to 17 years from the date of issue for patents awarded before 1995. A US patent only grants rights within the United States territories. When inventors want to get patent protection in other countries, they need to file a patent application in those countries as well.

In this study, analysis of patent applications filed with the USPTO and patents they granted related to digital pathology allowed us to gather information about prior advancements in this field, and to determine the current industry status as well as possible future trends. As this study was limited only to a search of the US patent database, these results and deductions may not entirely reflect global technology trends. Digital pathology is a disruptive technology that is transforming the practice of pathology.[18] Advances in computers and digital imaging reflected in the patents reviewed here demonstrate that there have been marked improvements in image acquisition and the quality of digital pathology images. Digital pathology patents have evolved from using static images to those that employed whole-slide images of entirely digitized (scanned) glass slides (so-called virtual microscopy). Innovative applications were patented that support the practice of telepathology and computer-assisted image analysis. This review of the USPTO database indicates that this technology was developed by inventors from both academic and industry sectors.

Patent owners are obliged, in return for patent protection, to publicly disclose the information of their invention, which in turn promotes further creativity and innovation. This may help explain why there are progressively more digital pathology patent applications in recent years. Patent prosecution (the process to secure a patent) is a lengthy process that can last from months to years. Applicants may abandon applications for various reasons including the technical feasibility of their claimed invention, rejections raised by the patent examiner, or financial reasons. Nevertheless, the abandonment rate for patents identified in our digital pathology study was 10.6%, which is low compared to the 30-45% overall abandonment rate noted with all USPTO applications.[19] Although eight patent applications specific to digital pathology were referenced as rejected in the USPTO transaction history, no public records were available to document reasons for rejection. After a patent is granted, the assignees are responsible for maintaining them by paying the required fees. After expiration, due to term or non-payment of fees, protection of the patent ends, and the invention enters the public domain. In certain circumstances, patents that were abandoned but not expired due to term can be revived upon payment of all required fees.

This review of USPTO patents demonstrates three main trends in the field of digital pathology. They include telepathology, creation of pathology consultation networks, and image analysis. Telepathology applications improved over time from video microscopy to virtual microscopy. These trends correspond to the growing number of publications, especially about telepathology,[20] noted in the literature. Patents about image analysis represent approximately one-third of all patents specific to digital pathology. These patents were clustered mostly toward the end of the timeline studied, between 2011 and 2013. Therefore, we expect to see an increased number of image analysis tools in the near future.

The first patent applications for robotic telepathology were filed by Dr. Ronald S. Weinstein in 1990 and 1993, and were assigned to his company, Corabi International Telemetrics Inc. These patents, entitled "Telepathology Diagnostic Network", were awarded a few years later in 1993 and 1994, respectively. They both have a priority date of April 30, 1987, the date they were first filed (initially as a single patent application) at the USPTO. Having been filed before June 8, 1995, the patent term was 17 years. This was adjusted up to 20 years for patents filed after June 8, 1995. These patents are an important milestone for telepathology. Recently, they expired, permitting dynamic robotic telepathology technology to be freely incorporated into WSI scanners. Consequently, WSI vendors have started marketing hybrid robotic WSI instruments. Major improvements in digital imaging were reported after the introduction of WSI technology. This is reflected by the large number of recent WSI-related patents and patent applications. The patent entitled "Method and apparatus for acquiring and reconstructing magnified specimen images from a computer-controlled microscope" owned by Bacus Research Laboratories Inc. (filed in 1997 and awarded in 2000) marked the beginning of WSI technology.[21] Since then, over 20 companies, organizations, and individual inventors have filed patent applications (total of 77 patents at the time of this study) related to this technology, 63 of which were already granted by the USPTO. Early innovations related to WSI technology concentrated on improving scanning and image acquisition. Later patents showed an increased interest in improving z-stacking capabilities, slide navigation, remote device control, GUI, and digital image workflow.

The dynamics of technology development in digital pathology are also exposed by the number of transactions involving related intellectual property. The growing number of agreements or licenses between companies and organizations that involve patents indicates an active growth phase for digital pathology. For example, in recent years Olympus America Inc. entered into a license agreement with DigiPath, Inc®.[4] Olympus America Inc. also entered into a non-exclusive worldwide licensing agreement with Omnyx, LLC, a joint venture of GE Healthcare and the University of Pittsburgh Medical Center.[5] Moreover, Olympus acquired Bacus Laboratories Inc. (Lombard, IL). More recently, Leica Microsystems (Buffalo Grove, IL), which owned 13 patents for digital pathology, acquired Aperio Technologies (Vista, CA), the initial assignee with the most patents for digital pathology. Therefore, we have made a distinction between the original patent assignees [Table 2] and the current patent owners [Table 3].

During this time period there have also been legal challenges related to digital pathology technology, where companies and organizations competed for market domination through ownership of critical patents. One of the early leaders in the field, Aperio Technologies Inc., filed and later settled its patent litigation with Bacus Laboratories.[22] Aperio Technologies also filed a lawsuit against Hamamatsu Photonics KK and Olympus America alleging that Hamamatsu's NanoZoomer technology infringed its US patents.[23] Unfortunately such legal battles may negatively impact the growth and development of digital pathology.

An essential role for the wide adoption of new technologies is played by standards. Patents can have a significant impact on standards development. A potential conflict between patents and standards may arise when the implementation of standards necessitates use of technology protected by patents. In order to minimize the risk of conflict and to assure an easy dissemination of standardized technology, standards setting bodies usually establish their own patent policy. For instance, participants in the DICOM WG26 development of standards are required to disclose patents and to license them according to the DICOM intellectual property policy.[24] As indicated in this policy, it is the responsibility of the parties involved in technology implementation to be aware of issues that may arise, and to make decisions based on consultations with their legal counsel.

In summary, this investigation demonstrates that there have been many patents and patent applications related to the field of digital pathology. The fact that the number of patents specific to use in pathology quadrupled in the last decade, bears testimony to the rapid advancements witnessed in this field. The bulk of these digital pathology patents have been about telepathology and WSI. More recently, we have witnessed an upward trend in technologies related to digital image analysis and CAD. Based on these observations, technological advances in the field of digital pathology are expected to increase. Therefore, we anticipate continued growth in the field of digital pathology as well as a concurrent increase in the number of patent applications, both in the United States and globally.

ACKNOWLEDGEMENT

Dr. Ronald S. Weinstein co-founded both Corabi International Telemetrics, Inc., (the first telepathology company) in 1985 and DMetrix, Inc., in 2001. Rights to the intellectual property of Corabi International Telemetrics, Inc. were acquired by Apollo Telemedicine, in 1991, a company in which Dr. Weinstein has stock options. DMetrix, Inc., underwent a corporate reorganization in 2011, when it was acquired by foreign investors. Dr. Weinstein sold his interests in DMetrix, Inc. As the co-inventor of array microscopy at the University of Arizona, Dr. Weinstein is entitled to receive royalties on his array microscopy patents (patent 7116437 and patent 7184610), through the University of Arizona Office of Technology Transfer, in Tucson, Arizona.

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Appendix A: List of select patents related to digital pathology

Patent number	Patent title	Assignee	Filing year	Issued year
3721759	Methods of and device for the automatics focusing of microscopes	Carl Zeiss Jena GmbH	1971	1973
4207554	Method and apparatus for automated classification and analysis of cells	Med-El Inc.	1978	1980
4307376	Pattern recognition system for generating hematology profile	Geometric Data Corporation	1979	1981
4404683	Blood cell identification and classification system	Omron Tateisi Electronics Co.	1980	1983
4700298	Dynamic microscope image processing scanner	Branko Palcic, Bruno Jaggi, Jan Nordin	1984	1987
5018209	Analysis method and apparatus for biological specimens	Cell Analysis Systems, Inc.	1986	1991
5216500	Simultaneously recording of video image and microscope stage position data	RJ Lee Group, Inc.	1991	1993
5216596	Telepathology diagnostic network	Corabi International Telemetrics, Inc.	1990	1993
5297034	Telepathology diagnostic network	Corabi International Telemetrics, Inc.	1993	1994
5687251	Method and apparatus for providing preferentially segmented digital images	Cedars-Sinai Medical Center	1995	1997
5733721	Cell analysis method using quantitative fluorescence image analysis	The Board of Regents of the University of Oklahoma	1992	1998
5741648	Cell analysis method using quantitative fluorescence image analysis	The Board of Regents of the University of Oklahoma	1996	1998
5797130	Method for testing proficiency in screening images of biological slides	NeoPath, Inc.	1995	1998
6101265	Method and apparatus for acquiring and reconstructing magnified specimen images from a computer-controlled microscope	Bacus Research Laboratories, Inc.	1997	2000
6208374	Video display systems	Second Opinion Solutions AS	1997	2001
6272235	Method and apparatus for creating a virtual microscope slide	Bacus Research Laboratories, Inc.	1998	2001
6278793	Image quality based adaptive optimization of computer aided detection schemes	University of Pittsburgh	1998	2001
6404906	Method and apparatus for acquiring and reconstructing magnified specimen images from a computer-controlled microscope	Bacus Research Laboratories, Inc	2000	2002
6452625	Compact video microscope	Leica Microsystems Wetzlar GmbH	1997	2002
6606413	Compression packaged image transmission for telemicroscopy	Trestle Acquisition Corp.	1999	2003
6618140	Spectral deconvolution of fluorescent markers	Amnis Corporation	2002	2003
6674881	Method and apparatus for internet, intranet, and local viewing of virtual microscope slides	Bacus Laboratories, Inc.	2001	2004
6711283	Fully automatic rapid microscope slide scanner	Aperio Technologies, Inc.	2000	2004
6917696	Fully automatic rapid microscope slide scanner	Aperio Technologies, Inc.	2004	2005
7027627	Medical decision support system and method	AccuramedLtd.	2001	2006
7027633	Collaborative diagnostic systems	David J Foran *et al.*	2001	2006
7028075	Method and system for sharing digital images over a network	FlashPoint Technology, Inc.	2002	2006
7035478	System and method for data management in a linear-array-based microscope slide scanner	Aperio Technologies, Inc.	2003	2006
7116437	Inter-objective baffle system	DMetrix, Inc.	2002	2006
7116440	Image processing and analysis framework	Aperio Technologies, Inc.	2004	2006
7184610	Miniaturized microscope array digital slide scanner	DMetrix, Inc.	2003	2007
7149332	Method and apparatus for internet, intranet, and local viewing of virtual microscope slides	Bacus Laboratories, Inc.	2004	2006
7187790	Data processing and feedback method and system	GE Medical Systems Global Technology Company, LLC	2002	2007
7215467	System and method for controlling microscope	Olympus Optical Co., Ltd.	2003	2007
7224839	Compression packaged image transmission for telemicroscopy	Clarient Inc.	2003	2007
7257268	Systems and methods for image pattern recognition	Aperio Technologies, Inc.	2004	2007
7319540	Systems and methods for remote viewing of patient images	Stryker Corporation	2006	2008
7391894	System and method for remote navigation of a specimen	Carl Zeiss MicroImaging GmbH	2006	2008
7426567	Methods and apparatus for streaming DICOM images through data element sources and sinks	Emageon Inc	2001	2008

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Appendix A: Contd...

Patent number	Patent title	Assignee	Filing year	Issued year
7432486	Microscope image acquiring system with separate microscope and imaging instrument controllers that operate cooperatively	Nikon Corporation	2007	2008
7446935	Cytological imaging systems and methods	Cytyc Corporation	2007	2008
7457446	Fully automatic rapid microscope slide scanner	Aperio Technologies, Inc.	2005	2008
7460730	Video registration and image sequence stitching	Microsoft Corporation	2005	2008
7463761	Systems and methods for creating and viewing three dimensional virtual slides	Aperio Technologies, Inc.	2005	2008
7502519	Systems and methods for image pattern recognition	Aperio Technologies, Inc.	2007	2009
7505616	System and method for reconstructing a diagnostic trajectory	Carl Zeiss MicroImaging AIS, Inc.	2006	2009
7518652	Method and apparatus for pre-focus in a linear array based slide scanner	Aperio Technologies, Inc.	2004	2009
7542596	Method and apparatus for internet, intranet, and local viewing of virtual microscope slides	Bacus Laboratories, Inc.	2006	2009
7542596	Method and apparatus for internet, intranet, and local viewing of virtual microscope slides	Olympus America Inc.	2006	2009
7596249	Focusable virtual microscopy apparatus and method	Bacus Laboratories, Inc.	2003	2009
7602524	Image processing and analysis framework	Aperio Technologies, Inc.	2006	2009
7646495	System and computer readable medium for pre-focus of digital slides	Aperio Technologies, Inc.	2009	2010
7668362	System and method for assessing virtual slide image quality	Aperio Technologies, Inc.	2005	2010
7689024	Systems and methods for creating and viewing three dimensional virtual slides	Aperio Technologies, Inc.	2008	2010
7692162	Imaging of two-dimensional arrays	Bio-Rad Laboratories, Inc.	2007	2010
7738688	System and method for viewing virtual slides	Aperio Technologies, Inc.	2004	2010
7755841	Liquid-lens variable-control optics in array microscope	DMetrix, Inc.	2008	2010
7764822	System and methods for rapid and automated screening of cells	GE Healthcare Niagara Inc.	2008	2010
7801352	Image acquiring apparatus, image acquiring method, and image acquiring program	Hamamatsu Photonics K.K.	2006	2010
7818130	Automated method and system for setting image analysis parameters to control image analysis operations	Cellomics, Inc.	2005	2010
7826649	Data management in a linear-array-based microscope slide scanner	Aperio Technologies, Inc.	2008	2010
7844125	Systems and methods for image pattern recognition	Aperio Technologies, Inc.	2009	2010
7856131	Method and apparatus for internet, intranet, and local viewing of virtual microscope slides	Bacus Laboratories, Inc.	2009	2010
7864379	Multi-spectral whole-slide scanner	DMetrix, Inc.	2006	2011
7893988	Method for pre-focus of digital slides	Aperio Technologies, Inc.	2009	2011
7899624	Virtual flow cytometry on immunostained tissue-tissue cytometer	Hernani Cualing, *et al.*	2006	2011
7916913	System and method for reconstructing a diagnostic trajectory	Carl Zeiss MicroImaging AIS, Inc.	2009	2011
7916916	System and method for remote navigation of a specimen	Carl Zeiss MicroImaging GmbH	2009	2011
7925067	Focusable virtual microscopy apparatus and method	Olympus America Inc.	2009	2011
7941275	Method and system for automated detection of immunohistochemical patterns	Ventana Medical Systems, Inc.	2005	2011
7949168	Data management in a linear-array-based microscope slide scanner	Aperio Technologies, Inc.	2010	2011
7978894	Fully automatic rapid microscope slide scanner	Aperio Technologies, Inc.	2010	2011
7979212	Method and system for morphology based mitosis identification and classification of digital images	Ventana Medical Systems, Inc.	2005	2011
8010555	System and method for managing images over a network	Aperio Technologies, Inc.	2007	2011
8023714	System and method for assessing image interpretability in anatomic pathology	Aperio Technologies, Inc.	2007	2011
8036462	Automated segmentation of image structures	General Electric Company	2007	2011
8055042	Fully automatic rapid microscope slide scanner	Aperio Technologies, Inc.	2008	2011
8060348	System and methods for scoring images of a tissue micro array	Harvey Ellis Cline, *et al.*	2006	2011
8068988	Method for automated processing of digital images of tissue micro-arrays	Ventana Medical Systems, Inc.	2005	2011

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Appendix A: Contd...

Patent number	Patent title	Assignee	Filing year	Issued year
8077958	Computer-Aided Pathological Diagnosis System	University of South Florida	2007	2011
8094902	Data management in a linear-array-based microscope slide scanner	Aperio Technologies, Inc.	2011	2012
8103082	Optimizing virtual slide image quality	Aperio Technologies, Inc.	2010	2012
8116543	System for and method of intelligently directed segmentation analysis for automated microscope systems	Carl Zeiss MicroImaging GmbH	2009	2012
8116547	Signal to noise ratio in digital pathology image analysis	Aperio Technologies, Inc.	2010	2012
8121383	Automated method and system for setting image analysis parameters to control image analysis operations	Cellomics, Inc.	2010	2012
8131476	System and method for co-registering multi-channel images of a tissue micro array	General Electric Company	2006	2012
8139831	System and method for unsupervised detection and gleason grading of prostate cancer whole mounts using NIR fluorescence	Siemens Aktiengesellschaft	2008	2012
8164622	System and method for single optical axis multi-detector microscope slide scanner	Aperio Technologies, Inc.	2007	2012
8165363	System and method for quality assurance in pathology	Aperio Technologies, Inc.	2008	2012
8189891	Viewing three dimensional digital slides	Aperio Technologies, Inc.	2010	2012
8189897	Program-controlled microscope and method for externally controlling microscopes	Carl Zeiss MicroImaging GmbH	2005	2012
8199358	Digital slide image analysis	Aperio Technologies, Inc.	2009	2012
8233740	System and method for constructing photorealistic mosaics	Alan Steven Roth	2007	2012
8203575	Method and system for accessing a slide from a remote workstation	3Dhistech Kft.	2008	2012
8244021	Quantitative, multispectral image analysis of tissue specimens stained with quantum dots	Ventana Medical Systems, Inc.	2007	2012
8244912	System for networked digital pathology exchange	Corista LLC	2010	2012
8249315	System and method for improved viewing and navigation of digital images	UPMC	2007	2012
8290236	Quantitative, multispectral image analysis of tissue specimens stained with quantum dots	Ventana Medical Systems, Inc.	2011	2012
8306300	Focusable virtual microscopy apparatus and method	Olympus America Inc.	2011	2012
8385619	Fully automatic rapid microscope slide scanner	Aperio Technologies, Inc.	2011	2013
8428887	Method for automated processing of digital images of tissue micro-arrays	Ventana Medical Systems, Inc.	2011	2013
8456522	Achieving Focus in a Digital Pathology System	Aperio Technologies, Inc.	2011	2013
8515683	Method and system for automated detection of immunohistochemical patterns	Ventana Medical Systems, Inc.	2011	2013
8537181	Modes and interfaces for observation, and manipulation of digital images on computer screen in support of pathologist's workflow	BioImagene, Inc.	2010	2013
8565498	Second opinion network	Aperio Technologies, Inc.	2008	2013
8582860	Signet ring cell detector and related methods	NEC Laboratories America, Inc.	2009	2013

DICOM: Digital imaging and communications in medicine, LLC: Limited liability company, NIR: Near-infrared, UPMC: University of Pittsburgh medical center

Appendix B: List of select pending (at the time of the study) patent applications related to digital pathology

Application number	Patent application title	Assignee	Filing year
11/778814	System for physician directed digital medical image data transmission between medical institutions	Philip L. Johnson, Kenneth W. Batson, Joe B. Dressler	2007
12/053515	Multi-Exposure Imaging for Automated Fluorescent Microscope Slide Scanning	Applied Imaging Corp.	2008
12/171618	Automated DICOM pre-fetch application	Apteryx Inc.	2008
12/664701	Manipulation device for navigating virtual microscopy slides/ digital images and methods related thereto	The Johns Hopkins University	2008

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Appendix B: Contd...

Application number	Patent application title	Assignee	Filing year
12/720582	Method of detection of fluorescence-labeled probes attached to diseased solid tissue	Bioimagene, Inc	2010
12/852096	Systems and methods for segmenting digital images	Sony Corporation	2010
13/061530	Method of diagnosing or prognosing epithelial ovarian cancer	Carl Arne Krister Borrebaeck *et al.*	2009
13/069836	Network image review in clinical hematology	Peter W Nordell *et al.*	2011
13/221759	System and method for managing images over a network	Aperio Technologies, Inc.	2011
13/233372	Histology workflow management system	Omnyx, LLC	2011
13/233575	Digital pathology image manipulation	Omnyx, LLC	2011
13/337882	Storing and retrieving large images via DICOM	Aperio Technologies, Inc.	2011

DICOM: Digital imaging and communications in medicine, LLC: Limited liability company