The digital future of histopathology: where we are today and where we are heading

Pathologists have been using their tool of trade, the microscope, since the early 17th century, when it was first described by Antony van Leeuwenhoek and Robert Hook.1 Today, with the advent of the Internet and new technologies that have allowed cameras to digitalise images, new products are being developed that have and will impact the way the pathologist will practise. This article describes situations and scenarios where digitalised images and telepathology have provided useful solutions on the workflow of today’s pathologists and the future impact with whole-slide imaging systems and proteomics-based molecular tissue imaging systems.

As a matter of clarification, we can further subdivide digital pathology imaging into following subcategories.
1. Static laboratory information system (LIS) based imaging.
2. Telepathology:
   a) static
   b) dynamic
   c) hybrid.
3. Whole-slide imaging (WSI):
   a) virtual microscope/virtual slide
   b) collaborative telemicroscopy.

Static laboratory information system (LIS) based imaging
The implementation of the digital camera in the cut-up room allowed for easy documentation of resected specimens and digital documentation of paper-based requests. Many current microscopes also have adaptors that allow direct connection to digital cameras, which capture microscopic images documenting histological areas of interest. This method is far faster and more efficient than traditional film-based cameras.2 The cost saving, improved access at time of reporting and publication quality of digitalised images has made it a success in many laboratories. The success was established not only in clinical arena, but also in the fields of education, image archiving and conferencing. As a matter of interest, it appears, at least from the latest survey data published by Dennis et al,3 that most of the pathologists in the UK possess digital cameras mounted on the microscope, but are not too familiar with potential telemedicine use of those.

Furthermore, these types of images then can be integrated into the image-enhanced report (see Figure 1). Many of the current laboratory information systems (LIS) vendors are beginning to offer this capability as an option to existing customers. Boutique reference laboratories have been doing this for years, as an edge on competitor laboratories. The impact of this strategy can be seen by the eroding outpatient biopsy market in the areas of hematopathology, genito-urinary, and gastrointestinal divisions of hospital laboratories.

Telepathology
Telepathology can be defined as a way for pathologist to consult with other physicians using the remote electronic connection, either Internet or dedicated servers. Initial telepathology systems were primarily static and web-based systems that were asynchronous but had sampling issues (dependency on the sender to recognise diagnostic areas). The dynamic telepathology systems that followed allowed not only the local users of the system to control the stage, but also...
the remote pathologist (see Figures 2a and 2b). However, these dynamic systems are too costly and cumbersome to use and are not integrated with the LIS. Some of the main issues with dynamic telepathology (compared to a trained user on the microscope) are that the interface is still relatively slow, there are issues with focusing and one still needs a person on the other end to lay the slides on the stage.4 This technology, however, is extremely valuable for places where one or several pathologists have to cover several services at the same time,5,6 or for real-time video conferencing (non-diagnostic usage).7

**Figure 2a** UPMC Dynamic Telepathology System (below)

![Olympus AX80 with Motorized Stage](image1)

8 glass slides

**Figure 2b** UPMC Dynamic Telepathology System user interface (below).

![User Interface](image2)

Newer systems that are currently used have a hybrid model of the two discussed above. The University of Pittsburgh Medical Center (UPMC) and the Palermo collaboration has produced an excellent practical case for implementation of hybrid systems for telepathology, which allowed the pathologists from the University of Pittsburgh to provide a real-time support for complex transplant biopsies in its Palermo clinic. It is, however, extremely important to outline that success was based not only due to the system itself, but in large part due to meticulous organisation of the service. For instance, every time a case was logged in the system, asking for a consultation, a pathologist who was on-call for telepathology would receive a digital page. This allowed for instant consultations on demand, and provided the highest quality of healthcare deliverable.8

Despite its relative success, neither the static nor the dynamic telepathology systems became integrated with the LIS. This fact did not allow for direct billing and reporting in telepathology. One could argue, however, that capturing images in the LIS does allow for consultations on those (for instance – see also Figure 3) as one could ask a colleague ‘Please go into the case #1234, and tell me what you think’. Invariably, since these types of consultations were done within the same system/hospital, the result was sharing the glass slides.
Whole-slide imaging (WSI)

As stated previously, much of the information needed to represent the entire slide is not being captured by the static images or, although seen via the dynamic telepathology cannot be automatically captured, or rather can be captured in its eternity only as a data stream (by way of screen capture or similar MPEG formats).

Therefore, the practice demand has driven the field to the creation of WSI systems; they are the end answer to most, if not all, of the problems outlined above. This resulted in the creation of websites dedicated to histopathology of particular organ systems, enabling the users to control and browse the digital slide.

So what is the WSI? It consists of a modified microscope mounted on the high-speed robotic stage. It was first pioneered by InterScope Technologies, resulting in a method that allowed for the replication of histologic glass slides for use in diagnostic pathology. Shortly after, several companies (Aperio, Baccus, Dmetrix, InterScope Technologies, MicroBrightField, and Trestle Corporation) were offering virtual slides powered by virtual microscope software for viewing two-dimensional images on computer monitors. WSI was adopted across the pathology and clinical community, with varying uses.

WSI allows for use of the images thus created for multiple purposes. Educational interface and use is readily apparent; here at University of Pittsburgh, we have eliminated the glass-slide teaching set, allowing trainees access to a virtual slide teaching set at http://interscope.hillman.upmc.edu/Eduslide. In the past, the problems were breakages of glass slides, the inability of trainees to look at the same slide simultaneously, etc.
Quality assurance (QA) initiative is a second-tier use for WSI. In essence, the creation of a virtual slide upfront eliminates moving precious glass slides, decreases loss of slides, and eliminates mistakes from slide refilling.\textsuperscript{13}

Teleconsultation is also enabled. For two or more pathologists (we tried with 27 people logged into the same case simultaneously), it allows multiple users to conference about the same case and also discuss it in real time, either via the telephone (old-fashioned teleconferencing) or via voice-over Internet or chat engines. The current viewer also allows users to view two different areas of the same slide or different slides for comparison; this feature is not available on any microscope and becomes an exceedingly convenient feature if, for example, one compares immunohistochemistry-stained and haematoxylin and eosin-stained slides (see Figure 4).

Figure 4 Comparison feature in the GUI developed by Interscope technologies™ that allows the user to compare two areas on the same or different images

As a converse usage of the last, classic glass-based referral cases now can be scanned and, once the slide is returned to the originating hospital, the consultation institution still retains a permanent record of the material that was returned. If however, one sends a consultation out, a virtual slide can be created, thus allowing the originating institution to still retain a permanent record, were the glass slide sent out to be lost, broken or never returned.

Once one has a virtual slide, the other issues are apparent – there is a need to fulfill all of the requests just delineated. As first, one needs a graphic user interface (GUI) that would allow for exact cataloguing of the slides and integration of those into a virtual case (in the same way as we use glass slide trays). Then this GUI either needs to get integrated with existing LIS in the institution, or become a LIS itself.

Although there are several viable solutions for creating the virtual slides (Aperio, Baccus, Dmetrix, and Nikon Coolscope), Interscope (recently merged with/purchased by Trestle Corporation) is the only player that developed a GUI along the lines of demand stated above.\textsuperscript{14}

We feel that the current technology allows pathology laboratories to start migration into the digital era, by adopting the WSI technologies. As the speed of the slide capture improves, everyday diagnostic applications are coming in the near future, but use of these technologies for QA, educational, and consultation services are already applicable today.\textsuperscript{15–18}

What are the next steps that WSI would need to fulfill to become a successful pathology (all-in-one) platform? Companies need to allow for proteomics/molecular pathology sample-based imaging, and tissue microarray slide imaging also needs to be integrated, with [the?] interface to research LIS as well as clinical LIS.\textsuperscript{19–20}

As the field advances, it is becoming more and more apparent that WSI is not here to replace the classic microscope;\textsuperscript{21} it is here to supplement it and advance it and, more importantly, at least in the opinion of the authors, it is here to stay.\textsuperscript{22}

As the end point, we are providing additional references and links for readers to investigate the field further on their own.
Reference URLs for digital imaging, telepathology, and whole-slide imaging

Example of current telereports
http://www.pathology.pitt.edu/lectures/consult/

AP cases
http://www.pathology.pitt.edu/lectures/consult/case02/case02.htm
http://www.pathology.pitt.edu/lectures/consult/case03/case03.htm

Educational application for pathology trainees
http://path.upmc.edu/cases/dxindex.html

Telepathology URL
http://www.pathology.pitt.edu/telepath/

References

