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Putting Digital Pathology Under the Microscope

[Clinical Lab Products - April 2009](#)

by **Renee DiIulio**

As systems add value beyond the digital image, their adoption will spread further and faster.

For pathologists, the wow factor of digitizing images has not been enough to push its widespread adoption. Having been "raised" looking through a microscope, busy pathologists have not wanted to take the time and expense to acquire and learn to use a new system that didn't offer many perceived advantages over the old one. But technology marches on, and the challenges inherent to storing, streaming, sharing, and analyzing considerably large digital image files have begun to be conquered. As digital pathology systems become more functional, they add value beyond what the microscope can offer and become must-haves for pathology laboratories.

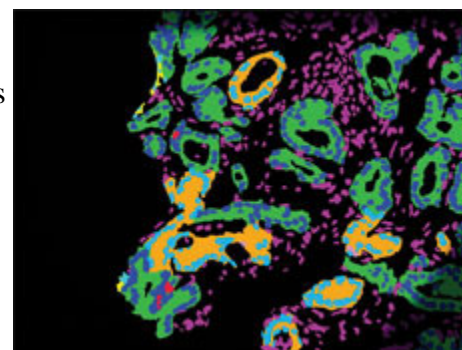


Before pathologists could even begin to be sold on digital pathology, however, vendors had to master image quality. Physicians want to be able to diagnose and consult directly from the screen, which today's systems allow them to do without special hardware. "Many customers tell us that the quality of a digital slide is as good as what they can see when looking at the corresponding glass slide through a microscope," says Dirk G. Soenksen, CEO of Aperio Technologies Inc, Vista, Calif.

Slides Versus Digital

Aperio is involved in a clinical study comparing diagnoses made on a glass slide versus a digital image. "We want to prove that you will get the same diagnosis using a digital image as with a glass slide, and based on the early results, that is turning out to be the case," Soenksen says.

Improved image quality, combined with the capability to transmit that quality, enables telepathology. Pathologists can work remotely. Workflow can be balanced among a team. Consultations with peers and specialists can be accomplished quickly, easily, and conveniently. Pathologists do not have to share glass slides during collaboration. Patients do not have to wait for slides to be couriered or shipped to the reading pathologist or for the pathologist to drive in. Slides do not have to be returned, nor are they likely to be lost.



"Imagine a room with 10,000 slides. If a slide is filed incorrectly, it's lost," Soenksen says. Searching electronically is not only easier, but it also becomes a tool. Users can create histopathology databases by compiling images that meet specific search criteria. "A valuable database enables the intelligent retrieval of information and sets the stage for using digital slide repositories for clinical decision support," Soenksen says.

Image 1

Electronic patient data, whether integrated through a hospital or laboratory information system, can therefore help to improve patient diagnoses. It can also help to improve workflow.

"Only a relatively small percentage of a pathologist's time is spent looking through a microscope. A lot of time is spent preparing the case, double checking the inputs for errors, and building the report," says Gene Cartwright, PhD, CEO of Omnyx, Pittsburgh. Integrated patient data reduces this time as well as decreases the risk of manual errors and improves storage capabilities.

Analytical tools bring even more advantages. "The ability to analyze digital slide images has the potential to increase the accuracy and reproducibility of quantitative clinical measurements, improving patient care," Soenksen says.

"There are some algorithms available today that offer significant improvements because the computer can quantify things that are hard to quantify visually," Cartwright concurs. Digital analysis, for instance, can quantify stain intensity or scan an entire slide for rare events.

Reproducible measurements help to ensure consistency across pathologists. "If three or more pathologists look at a slide, you often have three different answers. But an automated system is consistent," says Ajit Singh, PhD, CEO of Biologene, Cupertino, Calif. Digital analytics offer consistency not only across pathologists but also across time.

"Once digital imaging becomes the norm, clinicians and researchers can go back to the digital backup for reference. And if they have a digital image library, they will be able to sort by ID number, bar code, or other identifier and go as far back as the digital archive permits to review what they think may have been a prior reoccurrence," says Christopher Higgins, group manager for clinical digital imaging in the scientific equipment group of Olympus, Center Valley, Pa.

Legend for slide images shown above:

1. Aureon's new test, Prostate Px+, incorporates digital analysis to better identify subsets of prostate cancer patients.
2. Comparison of stains, such as this H&E, is easier digitally, where windows can be opened side by side.
3. This digital image of a leukemia blood smear is magnified 100x.

In the future, pathology informatics may clarify issues not only for physicians and researchers but also for patients. An image may help put to rest an anxious patient's concerns more effectively than a wordy report.

"If a physician were to receive a report from the pathologist complete with images, it could aid in patient education. The receiving physician could use the images in discussing the patient's situation, and having an image to look at might make it easier for the patient to understand what the doctor is explaining," Higgins says. Pictures can sometimes tell a better story than the report.

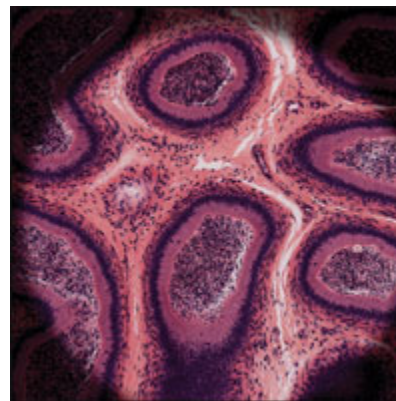


Image 2

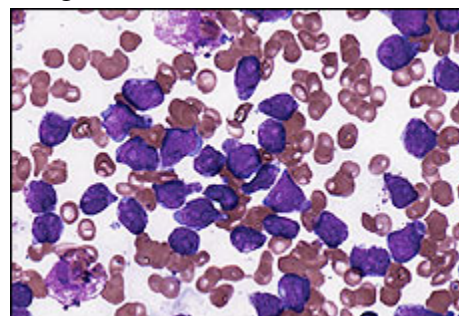


Image 3

The Pathology Cockpit

Clinical situations may also be clearer for the pathologist sitting in the pathology "cockpit." Instrument screens are replaced with computer screens, which display patient demographic and case data, pathology images and data, and other necessary information, such as radiology or clinical laboratory test results. Everything pathologists need to make a confident diagnosis is at his fingertips.

"I don't think there is much of a learning curve. It is designed to be intuitive, and the image is presented to look identical—as much as possible—to the microscope image," Cartwright says. Pathologists will likely have to make some adjustments to get acclimated to digital diagnosing, but training on the hardware and software does not prove a great challenge.

"The slide scanning systems used to digitize microscope slides and create whole-slide images have become push-button systems that are easy to use. Pathology image-management software is similar in features and complexity to the image-management—PACS—software used by radiologists," Soenksen says.

Most systems work rapidly, scanning and digitizing data in 2 to 10 minutes. This, in most instances, is fast enough, Cartwright suggests. "Faster scanners will provide an advantage until we get down to about 10 to 30 seconds, but I don't think speed has been preventing widespread adoption [of digital pathology]," Cartwright says. Rather, concerns about enterprise-level capabilities have slowed acceptance. Yet here again, technology has made advances, and today's systems are incorporating the technology and value that will make them enterprise solutions.

Aperio's Complete Solution

Aperio offers a complete digital pathology solution incorporating ScanScope slide scanners, Spectrum image management (PACS) software, advanced visualization software, image-analysis software, and multiple services. The company has plans to submit an application to the FDA for clearance of its digital pathology system as a diagnostic tool. The system has already been approved for specific clinical applications, such as IHC HER2, IHC ER (estrogen receptor), and IHC PR (progesterone receptor) image analysis.

The company has focused on providing a complete solution with options designed to meet the specific needs of a laboratory. Four slide scanner selections offer choices for low-volume (one slide at a time) to high-throughput laboratories (120-slide autoloader capacity). Management and analytical software enables digital slide viewing and conferencing, workflow management, data archival, intelligent retrieval, and image analysis. Applications cover drug discovery, cancer research, telepathology, peer review, and secondary consultation.

Users reap their return on investment in time and cost savings related to greater efficiencies in workflow, reduced shipping costs, decreased errors, and improved accuracy. "[Pathologists can] improve digital microscopic image review and analysis by providing whole-slide digital images and enabling the user to view multiple images simultaneously," Soenksen says.

The ability to compare areas of interest on slides that have undergone different stains side by side on screen improves data gathering and decision-making. "If you wanted to compare H&E to another stain, you have to look at the H&E glass slide, remember what a specific cell looked like, then find that same cell on the next glass slide and compare that to the remembered image of the H&E slide. That's very

difficult," Soenksen says. Digital pathology alleviates this challenge. "It's relatively easy to do with digital pathology and is a new way of looking at information," Soenksen says.

Aureon's Prostate Pathology

That new way will penetrate every aspect of decision-making and help to usher in personalized medicine. "Pathologists may look at a prostate cancer specimen and say it looks strange or not very differentiated, and we can take those subjective observations and translate them into specific quantitative measurements. Digital pathology can see things the human eye can't see and can also provide a much greater degree of differentiation between different samples," says Vijay Aggarwal, PhD, CEO of Aureon Laboratories Inc, Yonkers, NY.

Aureon's new test, Prostate Px+, incorporates digital analysis to better identify subsets of prostate cancer patients who may all share the same Gleason grade. "The test is based on CAD analysis of tissue samples and therefore is more objective, more reproducible, and able to provide a higher degree of predictive power than could be obtained with a traditional technique, such as immunohistochemistry or the visual examination of tissue," Aggarwal says.

The test can therefore "more accurately predict which patients diagnosed with prostate cancer will go on to experience metastatic disease and disease progression," Aggarwal says. The results help clinicians settle on a course of treatment that more accurately reflects the risks of the patient's particular disease.

The diagnostic biopsy sample can also be used for the Prostate Px+ (no special handling required), and turnaround generally takes about 5 days. Measurements are reflected as a single score that relates to the patient's probability of progression. Factors incorporated into the algorithm include clinical data and the spatial, mathematical analysis of tissue histology and molecular biomarkers associated with disease progression, such as androgen receptor.

"The question is not, 'Does this patient have prostate cancer or not?' but, 'How aggressive is it, and what is the appropriate therapy and management of disease?' " Aggarwal says.

Imaging Breast Cancer - Analytics from BioImagene

BioImagene's PATHIAM Imaging Software for HER2/neu Application helps to answer similar questions regarding breast cancer patients. The system recently received FDA 510(k) clearance for the scanner and associated software used to detect and provide a quantitative measurement of HER2/neu. Results help to determine if the patient is a candidate for treatment with the breast cancer drug Herceptin.

Up to 160 slides can be processed in batch mode on the iScan digital slide scanner. Labs can structure their workflow to allow the pathologist to begin reading as soon as the first image is available or to compile all the scans for distribution according to user-set rules. "You can load balance dynamically and match the load to expertise when and where needed," Singh says.

Objective analytics help to better differentiate patients into Herceptin and non-Herceptin categories. "There are approximately 10 to 15 percent of cases which are falsely interpreted as 3+ when they should have been interpreted as 2+, and those patients will get Herceptin when they should have had a second test to confirm," says Rob Monroe, MD, PhD, chief medical officer of BioImagene.

The consequences can range from the intangible results of inappropriate treatment to monetary waste. "It costs \$80,000 for a full course of treatment, and the cost to the patient can lead to congestive heart failure and cardiac arrest," Monroe says.

Prostate Px+ has been designed to provide "consistent and reliable scores that fall within that gray area to prevent false positives," Monroe says. Additional functions include validated protocols, digital archiving and retrieval, flexible reporting, and easy integration with LIS systems.

Digital Scope

Olympus also offers systems across the spectrum of pathology laboratory needs, from scopes for clinical use to advanced digital imaging systems for research and education. For instance, the NanoZoomer Digital Imaging System, currently for research purposes, can scan up to 210 slides at 20x or 40x using both brightfield and fluorescent imaging. A smaller version handles six slides at a time. WebSlide Server 3.0 software organizes the digital data. Viewing and analysis software extend the capabilities.

"We can have 100 students look at the same slide for a very specific case, and they can all view the slide and see the same image. The traditional way is to distribute 100 different slides to students to look at through their microscopes. What are the odds that the morphology will be the same on slide 1 as slide 100?" Higgins asks.

When looking at a digital slide, everyone sees the exact same image and receives the same education. Stored electronically, the slides are accessible remotely, 24 hours a day.

As digital pathology systems expand their value beyond the digital image, they become more useful tools in all settings: education, research, and the clinical laboratory. Even more than the wow factor, it is these advantages that will pull pathologists away from the microscope.

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Renee DiIulio is a contributing writer for CLP.

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