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Solid citizen in the lab: digital imaging

By Karen Lusky

Experts tracking the uptake of digital pathology tend to talk about adoption curves and market penetration. But pathologist Eric Glassy, MD, has a way of cutting to the chase: “We’ve moved beyond the ‘gee whiz what do you do with it?’ era.”

Way beyond, to the point that it’s “soon to be indispensable,” predicts Dr. Glassy, medical director of Pathology Inc. in Torrance, Calif., which uses a digital whole-slide imaging system in its reference lab for case consultation, virtual immunohistochemistry, tumor board presentations, client case review, conferencing, and image analysis.

Indeed, the answers to “what do you do with digital technology in pathology?” continue to grow by the year (one vendor has identified 26 niche applications).

“In four to six years,” predicts Ulysses Balis, MD, associate professor and director of the Division of Pathology Informatics at the University of Michigan, “digital pathology will be in effect for the majority of use cases—and in 10 years, pathology will largely be all digital.”

The transition to digital is filled with opportunities, but there are also challenges to adopting digital pathology fully, as well as questions about how technology in pathologic diagnostics may ultimately play out.

As for opportunities, some pathology practices are finding that clinicians like getting on the digital bandwagon. Pathology Inc. used to send recut liver biopsy slides to GI specialists, Dr. Glassy says, but once the specialists “experienced the whole-slide image on their computer screen, they were sold and won’t look at the glass slides anymore. The same for urologists.”

Path Logic in Carmichael, Calif., which has been using digital images in pathology reports for 10 years, is now producing video reports (think YouTube), primarily for nephrologists, said Peter Kolbeck, MD, medical director and CEO of the practice, in a presentation at this year’s Executive War College, sponsored by The Dark Report. In the video, the pathologist uses a pointer to identify diagnostic lesions in the image and explain the rationale for the interpretation.

As for the time required to produce the video, Dr. Kolbeck says that for renal cases, it's probably faster to do a video report than to dictate and wait for the dictation to be done or to do templated reports.

Digital pathology solutions are also being designed to help pathologists more quickly distill clinical information and other radiology tests when signing out a case. McKesson's Horizon Anatomic Pathology Virtual Slide Tray, as an example, has been on the market for about a year, and has been contracted for by 10 hospital and reference lab customers, says Joseph Stabile, MT(ASCP), product marketing manager at McKesson Provider Technologies. The product has a console where the pathologist can view and perform everything from one computer screen, including viewing images from the radiology PACS (picture archiving and communication system), he adds. Thus, if the pathologist is looking at a breast biopsy, the digital slides and the mammogram are "just a few clicks away," Stabile explains.

"In addition to McKesson," says Bruce Friedman, MD, active emeritus pathology professor at the University of Michigan, "other companies are developing similar console products [that integrate digital pathology]."

A growing number of labs are taking advantage of computer-assisted imaging algorithms, which is where Dr. Glassy sees the real value in digital applications. "That may be computer-assisted quantification of breast markers, multi-stain analysis, ploidy, FISH analysis, automatic counting of mitoses, finding rare events such as acid-fast organisms, and even assisted diagnosis."

Medicare covers computer-assisted image analysis in some cases. "In general," says Charles Root, PhD, principal of CodeMap in Barrington, Ill., "immunohistochemistry and FISH computer-assisted analysis pay more because it's reimbursed under the physician fee schedule, which takes into account the cost of technology and other resource use."

For example, says Dennis Padget, president of DLPadget Enterprises in The Villages, Fla., the national Medicare global allowed charge for an independent lab for a non-hospital patient test sample for 88360 (manual quantitative or semiquantitative) is \$118.66, with a professional component of \$53.74 and technical component of \$64.92. By contrast, the global charge for 88361 (IHC computer-assisted) is \$150.40 (the PC is \$58.07 and TC, \$92.33), he notes.

Yet, even with the extra reimbursement, which helps, the cost of obtaining digital scanners can be a stumbling block for labs, especially in today's economy.

"The scanners are \$100,000 plus," says Paul Urie, MD, medical director of pathology and lab medicine at Intermountain Healthcare in Salt Lake City, which plans to adopt digital pathology within the next couple of years. And that price tag represents a big capital outlay if the multi-provider system puts them in several hospitals, Dr. Urie notes. In some cases, "you would like to put the scanners in smaller places where you can use them not only for anatomic pathology but also for clinical pathology—things like blood smears,

gram stains, body fluids—anything you can put on a slide. You could scan a slide and then have it reviewed by experts remotely. [Yet] it may be difficult to justify putting [a scanner] in a small lab that has one to three techs.”

BioImagene, whose investors include Siemens Venture Capital, has what’s called a “pay for click” approach. Using the model, “there’s no up-front expense, as we provide the software and equipment,” says Ajit Singh, PhD, CEO of BioImagene. The lab pays \$1 to scan a slide, and \$10 to analyze it with a computer-assisted algorithm. To date, BioImagene has FDA-cleared IHC algorithms for HER2 to identify candidates for Herceptin. Other IHC algorithms include ER/PR and p53 for breast cancer, Ki67 for breast, brain, and prostate cancers, CD138 for multiple myeloma, and CD3/CD20 for lymphoma.

Unlike the BioImagene model, Aperio charges a laboratory based on the throughput—slides scanned per hour—that a lab wishes to achieve, says Dirk Soenksen, CEO of the company. “For a fixed monthly fee, the lab can decide to scan at the guaranteed throughput ... for as many hours a day as it wants,” Soenksen says. Labs pay a fee every time they use one of Aperio’s digital algorithms to analyze a slide and generate a report.

Aperio has FDA-cleared IHC algorithms for HER2, ER, and PR used for breast cancer. It also has Ki-67, p53, and EGFR, which are not cleared by the FDA. The Aperio toolbox also includes packages for area quantification, cell quantification, microvessel analysis, rare event detection, and a new product, Genie Histology Pattern Recognition, Soenksen reports. Using the latter, pathologists new to imaging analysis can train the software using various examples of tissue types.

Can pathologists legitimately use digital images and non-FDA-cleared computer-assisted algorithms to make primary diagnoses? The answer to that question, says Soenksen, is often misunderstood. Vendors like Aperio have to obtain FDA clearance to market their products for clinical use, he points out. Aperio, in fact, has FDA clearance for using its product to interpret IHC slides on the computer monitor. Pathologists can choose to use digital pathology to make diagnoses if they validate it, as they would any new method, as required by CLIA. “Many labs have done that already with digital pathology,” Soenksen says.

Given the newness of digital technology, pathologists are faced with the question of whether digital images are equivalent to traditional microscopy. Thus far, the answer appears largely to be yes.

Shriram Jakate, MD, who signs out tertiary GI and liver pathology consultation cases using digital whole-slide scans, has felt a need to ask for glass slides in only two of 1,000 digital cases he has read over the past three years. His decision to do so in those two instances had nothing to do with limitations of the digital scan image, says Dr. Jakate, professor of pathology, gastroenterology, and hepatology and director of laboratory services at Rush University Medical Center, Chicago. In one case, the benign diagnosis was out of synch with the radiology report, which talked about a mass in the liver, though

the material Dr. Jakate viewed wasn't representative of a mass. "Ultimately, when the liver was resampled, it did show carcinoma," he says. "The other case was very complicated and I didn't receive a representative slide."

There are, however, situations in which digital whole-slide images aren't as good as viewing the specimen under the microscope, Dr. Jakate cautions. One example involves scenarios where the pathologist requires the Z axis or depth of field. "The microscope has the Z axis whereas the digital whole-slide scan is typically just an X and Y axis," he explains.

Though the depth-of-field limitation isn't common in Dr. Jakate's specialty (GI and hepatology), he can see it being a factor in some specialties. Cytologists, for example, "have a habit of going up and down in the focus to see the entire nuclear or cytoplasmic content," he says. Many vendors are, however, "now thinking of incorporating the Z axis into the digital scan where you scan the whole slide at one layer and scan it again at a slightly deeper layer," he adds.

Dr. Jakate also cautions against using digital images when looking for amyloid birefringence in tissue. When asked whether the Congo red is positive for amyloid birefringence, Dr. Jakate recommends the primary pathologist(s) review that on a glass slide. "I can't reproduce that on a digital slide scan since there is no ability to polarize and view the Z axis on the digital scan," he says. And the limitation affects the ability to look for any amyloid tissue on digital whole-slide images, he cautions. "You could potentially scan the image again with the polarizer, but the image may be too dim. Also, it requires the pathologist's intervention at some point. It's not something a technician could do. ..."

The University of Michigan's Dr. Balis believes that pigmented lesions in dermatopathology and lymphomas are probably best reviewed under the microscope before rendering a final diagnosis. "Pigment [in lesions] can have a higher density optically, which is also true for heavily stained lymph nodes that are very blue and dark. But in the future, better quality scans and pathologists' understanding of the artifacts will address" the problem.

So-called dog ears or areas on the glass slide where the tissue looks up can also be a problem when digitized, as they will produce a blurry spot that could, for example, obscure some glomeruli on a renal biopsy, or the area of cancer in an otherwise benign prostate biopsy, Dr. Balis cautions.

Glass slides may also be preferable when interpreting bone marrow aspirates or other areas of hematopathology that require oil immersion, Dr. Balis says. He notes that scanners have recently become available to carry out high magnification for use with oil immersion. "But they are cumbersome and not many places use them," he says, adding that vendors are aware of the need for improvements.

Cytopathology may pose one of the greatest challenges for whole-slide imaging, in Dr. Balis' view. That's because you have to scan the entire surface area of a ThinPrep or cytology preparation, and may have to capture as much as a 25- to 30- μ m-deep depth-of-field range, he points out.

Keith Kaplan, MD, associate professor of pathology at Mayo Clinic, and colleagues did a study in cytology, which hasn't been published yet, that demonstrated good concordance between digital and glass slides. "Any way you sliced or diced it," Dr. Kaplan says, "the limiting factor was related to glandular lesions, which are difficult using glass slides. With squamous lesions there was very high agreement between digital and glass slide."

Dahl-Chase Pathology Associates in Bangor, Me., which is ramping up with digital using BioImagene's system, has a high volume of cytopathology, says George Eyerer, MD, president of the practice. "I see our initial use of digital pathology for cytopathology to be sharing of cases with other pathologists, and also potentially using imaging software to identify certain characteristic cells, such as cells with viral inclusions. I do not think we will be using it for primary diagnoses at this point [for cytopathology]."

His 13-member group provides intraoperative pathology consultations to 17 Maine hospitals. In the interest of efficiency, the group hopes to have PAs on site to examine the specimens, prepare the frozen sections, and transmit the digital images while the pathologists remain in their offices reviewing the digital images and providing diagnoses.

Overall, Jeffrey Myers, MD, A. James French professor and director of the Division of Anatomic Pathology at the University of Michigan, cautions against jumping to conclusions about areas where digital may not work as well as conventional microscopy. "Special stains for microorganisms is an area where current technology is insufficient, but that will change. People speculated that digital pathology might not work well for small biopsies for making a diagnosis of carcinoma, but I haven't found that to be true. It works fine."

The Holy Grail in digital pathology is for laboratories to achieve full adoption of whole-slide imaging, Dr. Friedman said last February in a panel discussion with digital pathology vendors at the Molecular Summit, sponsored by The Dark Report. Aperio CEO Soenksen notes that early adopters are now saying they would consider making that leap, if the vendors could successfully address workflow integration and other issues.

"For example," Soenksen says, "some pathologists question whether they could use a mouse all day to navigate around digital slides, or whether they will need other navigation tools to interact with the files and images on the computer, such as joysticks or a specialized gizmo that has yet to be designed."

Dr. Myers sees the pathologist user interface as being the primary limitation to doing digital reads routinely. The problem is "you lose a few seconds with every load and [when] switching between images," he says. "I provide consultations to a lab in California, and sometimes it takes about 15 seconds to load an image. In 15 seconds, I

can look at a glass slide, make a diagnosis, and dictate the report. If you are doing 100 GI biopsies a day and it takes five seconds to load an image—that's just too long.”

“Vendors talk about the images being so beautiful or about cockpits that look like those in radiology or an airplane, to which I say, ‘I'm not a radiologist or trying to fly a plane. I'm trying to sign out cases,’” Dr. Myers says. “If you view radiology reports for selected cases, then being able to access those images quickly is useful,” but pathologists who do that for only two percent of their cases don't need an application that provides a 100 percent solution, he points out.

Ole Eichhorn, Aperio's chief technology officer, agrees that the user interface is critical. “It has to be comfortable and efficient”—the faster, the better, he notes. Eichhorn predicts the tipping point for full adoption of digital pathology will occur when the technology improves workflow. “That's what happened for radiology. We think it could be ... five years or so until that value proposition becomes clearly established and labs start broadly adopting digital for their entire slide workflow.”

Over time, additional reimbursement for digital pathology could also foster adoption, as it did in radiology, Eichhorn predicts. CodeMap's Dr. Root notes that Medicare does provide more reimbursement in radiology for three-dimensional reconstructions using CT or MRI. He thinks it will be interesting to see if a parallel occurs in digital pathology whereby Medicare would ante up more money for three-dimensional imaging or reconstruction. “There's no CPT code yet for the latter,” he says. (On the other hand, Dr. Root notes that the existing extra Medicare reimbursement for computer-assisted image analysis could go away once the technology becomes the standard.)

“If the federal government,” Eichhorn says, “would throw some money in the pot for digital, that might foster some adoption. But we have noted that faster adoption has occurred in countries outside the U.S., and that's partly due to pathologists being scarcer and more concentrated in big cities.” (Lack of FDA regulatory hurdles overseas is another reason, Soenksen noted in the Molecular Summit panel discussion.)

Rush's Dr. Jakate believes economic and market forces leading to hospitals consolidating or closing will ultimately be what pushes diagnostic digital pathology to the fore. Then people will realize how valuable it is otherwise, he adds. “We hear ... all the time where there are four hospitals, for example, in a network and one closes down or it closes the lab so all the tissue has to go to a more centralized place.” He foresees more of that, fueling the need for remote pathologic diagnosis done digitally.

Some pathologists fear the specter of their work being outsourced to China or India. But Mayo's Dr. Kaplan doesn't think that will happen, “given that about 90 to 95 percent of subspecialty pathologists are in the U.S.,” he says. Rather, he sees “a flip of that model”—that is, an opportunity for in-sourcing work to the United States. “Why couldn't I get credentialed at a medical center in China and digitally read their slides in Minnesota?” he asks.

Of course, how diagnostic digital pathology will ultimately evolve—and whether it will be supplanted to some extent by the next new technology on the block—remains to be seen.

Right now labs and pathologists interested in that next best thing have their eye on Omnyx (a joint venture between GE Healthcare and the University of Pittsburgh Medical Center), which is working on a comprehensive digital pathology system. The goal of the effort is to provide pathologists with a tool that focuses on making primary diagnoses, allowing pathologists to do what they do now with glass slides, says Michael Becich, MD, PhD, chair of the Department of Biomedical Informatics at the University of Pittsburgh.

Over time, digital imaging technology overall is likely to become much more sophisticated and move toward real-time scanning. Dr. Glassy can foresee a time when you “wave a glass slide under some black box and an image will pop up on the computer monitor.” The image could then “be analyzed, deconstructed, repurposed, quantified, and shared.”

“Maybe the focus should be before the glass slide is even created—the processing and staining of the biopsy,” Dr. Glassy adds. “That part hasn’t changed much at all for over 100 years.”

Pathologist Russell Kerschmann, MD, says currently “there is no compatible product for producing diagnostic-quality tissue images without first making a glass slide.” But he’s chairman of a company, Microscience Group, with a technology that could do away with glass slides completely. The company’s Digital Volumetric Imaging, or DVI, system, which has been used by a number of research institutions for many years, can capture a digital image of tissue directly from the cut surface of the tissue block.

How does it work its digital magic sans glass slides? First you fix the tissue in formalin and add a mixture of fluorochrome stains to the tissue block, he explains. Next the block is embedded in an epoxy polymer that contains a very black colorant. Then an automated microscope/microtome system sections the block, capturing images of the successive cut surfaces. “The resulting dark-field images are digitally transformed into diagnostic-quality H&E bright-field images,” Dr. Kerschmann says. For each sample, the laboratory can store a few two-dimensional images for analysis. Or you can capture “stacks of thousands of serial images ... to produce high-resolution tissue reconstructions.”

The system can do not only H&E but also potentially immunohistochemistry, and even FISH, Dr. Kerschmann says. As long as you can do “en bloc labeling with some fluorochrome-labeled probe, DVI can image it. We have even done special stains by putting different colors of fluorochromes in the tissue, or by producing ‘virtual special stains’ digitally by transforming the image in various ways.”

Given that DVI eliminates glass slides and most of the labor required to produce them, “each two-dimensional image becomes very inexpensive,” Dr. Kerschmann says.

If such a system were used in the clinical setting, the lab would still have to do grossing to “select, orient, and embed the specimen,” he adds.

To market the system clinically, Microscience Group would probably need FDA clearance, which would be easier to get if digital pathology were well accepted, Dr. Kerschmann says.

“In our estimation, pathology will follow the pattern set in radiology, where first the films were scanned and the radiologist read the digital version of the films. Then, as the next step, film was eliminated and the radiology imagers captured x-rays directly as digital images.”

Rush’s Dr. Jakate envisions a future with more and more pre-pathology evaluation of tissue, either using high-resolution optical viewing via endoscopy, bronchoscopy, or colposcopy, etc.—or by radiographic imaging. “That pre-pathology evaluation will provide a much better assessment of disease process than it does currently and may somewhat diminish the value of routine pathology as it is practiced today,” though digital imaging will continue to grow thanks to its many uses, he surmises.

Dr. Friedman predicts that eventually pathology, lab medicine, and radiology will evolve into a new “diagnostic medicine” specialty. Practitioners within this new field will be trained to interpret morphology, biomarker assays, and the various radiology imaging modalities to make a diagnosis. “Specialization will probably be along the lines of individual organs or categories of disease,” he says.

Precisely how the future will look technologywise no one knows. “But for now,” says Dr. Glassy, “it is exciting that digital pathology is real ... it works and works well.” And “it can be a compelling driver of business and diagnostic acumen.”

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