Better than glass slides? Digital pathology's challenge

Valerie Neff Newitt

September 2019—The FDA's clearance this year of a second digital pathology system for primary diagnosis is likely to lead to lower costs and greater innovation and interoperability, say digital pathology advocates.

A multicenter study led the FDA in May to clear Leica Biosystems' Aperio AT2 DX System for clinical diagnosis in the United States.

Laboratories in the U.S. have been slow to adopt digital pathology for primary diagnosis since the FDA's approval in 2017 of Philips' IntelliSite Pathology Solution, the first system to be cleared for primary diagnosis.

Dr. Asa

"And yet digital pathology has been around for almost 20 years," says Sylvia Asa, MD, PhD, former chief of pathology of University Health Network (UHN), University of Toronto, where she now consults, and a consultant at University Hospitals of Cleveland. At UHN, she was an early adopter of digital pathology for primary diagnosis. "At the beginning there was extreme antipathy, intense doubt. People said, 'You're going to make mistakes. You're going to get sued.' There was no faith in the technology. But back then many people didn't even have cell phones." And times have changed, she notes, with the world becoming digital in the past two decades. "A traditionally conservative pathology approach has slowly moved forward. We all use electronic medical records and lab information systems and rely on IT. Now the challenge is to prove that digital pathology is actually better than glass slides."

Asked what the differences are between the Philips and Leica systems (Dr. Asa is a Leica medical advisor and board member), she says: "Philips scanners are excellent, the image quality is superb, and the system offers a full package that, if you have no need for customization, works beautifully. However, in a big lab center with multiple applications, it's a challenge because the Philips system doesn't work well with other players. While Leica offers an open system [though cleared as a closed system for use in the U.S.], also with excellent slide quality, it is not quite as plug-and-play as the Philips system. So that also presents a challenge."

Her point, she says, is that every vendor has strengths and weaknesses. "Some scanners on the market are really adaptable for special slide formats, such as large slides for whole mount sections, but neither Leica nor Philips accommodates those." (CAP TODAY requested but was unable to obtain an interview with a Leica Biosystems representative.)

A second system cleared for primary diagnosis in the U.S., even with a limitation, is a plus for pathology, Dr. Asa says. "Like anything in life, more competitors in the field give the purchaser more opportunity to pick and choose what fits them best. And competition spurs innovation."

Esther Abels, co-chair of the regulatory and standards task force of the Digital Pathology Association and DPA secretary, is vice president of regulatory and clinical affairs and strategic business development at PathAI in Boston. She was director of regulatory, clinical, and medical affairs at Philips Digital Pathology Solutions when its system was going through, and gained, FDA clearance. "Adoption is a slow process, unfortunately," she says. "Most labs and pathologists are not picking it up quite yet because full digital pathology system integration is a

demanding undertaking that requires a lot of investment, monetarily and procedurally."

Still, the new clearance will have a positive effect on digital pathology, Abels says, though not necessarily in terms of immediate adoption. "I think it will build comfort and confidence around digital pathology, not just for users but for the FDA as well. As more people use digital pathology in clinical practice, the FDA becomes more comfortable easing some of its strict processes."

Having reviewed the FDA summary files, Abels says both of the cleared systems are being verified and validated as closed systems, each composed of a scanner, viewing system, and monitor. "The FDA sees this as one entire system, one device, all locked into one approval. So labs and pathologists must have these three subsystems as a whole to replace their microscopes. And they have to test it end to end, from scanning all the way up to the display." A second cleared system is a strong next step to changing all of that, she says.

"And I hope a third cleared system comes soon, because once the FDA sees three vendors can [reach clearance status], they may become more comfortable with breaking up the entire device into different subsystems, allowing interoperability between devices." The FDA is now working with the Digital Pathology Association on artificial intelligence, including having discussions on whether more interoperability and more standardization can be achieved. "That will make a major impact on adoption," Abels says.

Thomas W. Bauer, MD, PhD, pathologist-in-chief, Department of Pathology and Laboratory Medicine, Hospital for Special Surgery, New York, NY, has been a long-time user of digital pathology. Dr. Bauer was previously head of an "e-pathology" division at the Cleveland Clinic where the team validated the ability to interpret microscope slides for primary diagnosis, frozen sections, and consults, and demonstrated that the interpretation of whole slide images is not inferior to interpretation of microscope slides. The clearance of a second system is the start of competition among industry vendors, he says. "As additional scanners are approved, we would expect that competition in the industry would drive down costs. That's really what this particular approval will mean to the everyday pathologist."

Dr. Bauer agrees that the latest clearance is a sign that "the FDA, a conservative institution, has recognized the safety and efficacy of digital imaging. This should increase confidence in the entire process among pathologists."

Many pathologists, like Dr. Bauer, already have full confidence in digital pathology, in part because it has been used successfully for primary diagnosis for years outside the United States. "Those of us who have been to meetings and have heard early adopters from Europe and Canada have witnessed a lot of good reports. The data has been very enlightening and encouraging," Dr. Bauer says.

Dr. Asa can speak directly to that. UHN, where she was head of pathology, was formed through the merger of three hospitals, two of which were across the street from one another and the other a mile away. "We built a consolidated department of pathology with all staff and equipment in one centralized location. But we had to have a pathologist for frozen sections at the more remote hospital," she says. In 2004, she and colleagues tried to overcome the remote challenge by using a robotic microscope, but they found it slow and cumbersome. "So we went to whole slide imaging in 2006 when we recognized that this technology worked. We made the argument that a pathologist would look at the slides and if a slide was not suitable, a pathologist would make that call. Unlike the FDA, Canada was okay with that logic. So that was our starting point. We had a need, and digital pathology was the solution."

It became the solution, too, for Ontario's northernmost hospitals that do not have pathologists on site. "That was the start of our expansion. By 2008 the technology was used across northern Ontario, though only for urgent assessments."

By 2011 technology had become available for massive throughput, so UHN started to use an Aperio digital pathology system for primary diagnosis. (Leica subsequently bought Aperio.) And it began using digital pathology to supply subspecialty pathologists to hospitals where all pathologists were generalists. "It meant we didn't waste time with wrong diagnoses, didn't waste money on the wrong drugs, and didn't have patients sitting in hospital

beds waiting for second opinions. All of these things affected the finances of the institution," Dr. Asa says.

She and colleagues worked first with Aperio, then with Leica, on workflow and with their laboratory information system vendor (Cerner) to achieve a better and more streamlined process.

"Slides would get stained, come off the coverslipper, go to the scanner, get scanned, then integrated into the lab information system as a case," she says. "The case was then sent automatically to the work list of the pathologist best able to handle that specific case. We didn't need any more of a business case than this. We said, 'Buy the equipment and we will get you faster, better, cheaper pathology.'"

Many pathology departments in the U.S. have a tougher time than their Canadian counterpart making a similarly compelling business case. Even in Canada, "the big challenge is to go to full primary diagnosis," Dr. Asa says. "You have to be able to prove a benefit because the same pathologist, in the very same place, is going to read the slide whether it is glass or whole slide imaging. You're swapping one technology for another, and that alone doesn't make the business case."

Terese

Sam C. Terese, president and CEO of Alverno Clinical Laboratories in Hammond, Ind., is one American laboratory executive who is bullish on digital pathology for primary diagnosis, and says making a cogent business case is likely different for every lab, depending on size, purpose, and expectations.

"We made the decision from a digital pathology perspective in 2017, right around the time of the Philips FDA clearance. Almost immediately we identified the benefits, and we started the process of transition," he says. "It works in our model because we are a large, centralized, integrated lab that works with 35 to 40 hospitals. There is value to us because we ordinarily move about 2,500 blocks, about 5,000 to 6,000 slides, each and every day, literally driving them in a car to the local pathologist for interpretation. With digital pathology, all of that goes away." Instead, they will scan 1 million to 1.4 million slides annually. "We have that benefit of scale," he adds.

Because Alverno is an early U.S. adopter of full digital pathology, the ongoing transitional phase has its challenges. For example, "There are not a lot of other folks who can tell you how they're doing this. So we're creating our process as we go," Terese says. "It took us a good year of evaluation, engaging with our pathologists, and building that necessary comfort level so we don't have anyone saying, 'I can't do this digitally. I must have glass.' All of our approximately 50 pathologists are on board."

The next step involved the contracting and acquisition details related to setting up the physical environment. "It's not a low-cost initiative," he says. "Right now we have eight scanners, with four more coming at the end of the year. We had to get agreements done, and go into installation mode. Things had to be delivered; things needed remodeling."

And there were snags along the way. "For example, we bought computers but the video cards were not big enough or fast enough, so we had to revisit that," Terese says. "Then the room for the scanners had too much heat. We had to modify the air conditioning so that we didn't overheat the equipment. We found that as the room cooled, we suddenly had condensation. We had overlooked humidity, so we had to install humidistats to correct the situation." These and many other minor complications came up. "We are used to being innovators so they didn't bother us too much, but in other labs they could be very concerning," Terese says.

After the environment was perfected, the next questions became, "How can we really evaluate this? What are the

validation steps? Nobody really knew. So again, we had to create a validation process and work through it." Then came the rollout. "We are doing it in three phases. We started phase one in the second quarter of this year; the first three hospitals went live Aug. 15."

While Terese agrees that new vendors in the marketplace will alter pricing for the technology, that is not what he sees as most significant to digital pathology adoption. "What will give it 'lift' is the future state, which is more about artificial intelligence, and real enhancement to the practice of pathology," he says. "How far away is that? Not far. We are likely to see AI for digital pathology next year. Everything from an innovation standpoint is moving so quickly. We are on the Philips system, and they already have a number of initiatives and partnerships in place. I think that is where they define the future as well."

Abels agrees, saying algorithms are likely to be the push digital pathology needs. "Pathologists are becoming aware that algorithms plus pathologists are more accurate than operating alone. Algorithms can help pathologists reach results that are more accurate and precise. They will also help oncologists to make better informed decisions on treatment. And in the future we could expect artificial intelligence tools identifying new biomarkers, which in turn will help in the development of targeted medication."

Dr. Asa, too, sees the strength of digital pathology tied to AI, because she believes artificial intelligence is the driver that will make digital pathology profitable. "Pathology groups will invest in AI if it shows a significant impact on their day-to-day work, something that will save time and money and improve quality. Some companies now are developing algorithms that can screen prostate biopsies for cancer—normally a tedious job requiring a lot of pathologists to screen a lot of slides. In some institutions that adds up to a full-time pathologist. So there is a clear business case to buy an AI app for that purpose." Even better, she says, is that it will ensure quality. "Because no matter what you say, after you've looked at your 15th prostate biopsy, you might miss something. The machine doesn't get tired at the end of the day."

Dr. Bauer

Dr. Bauer foresees AI not only defining the future of digital pathology but also changing pathology practice. "Quantitative image analysis is very effective at identifying rare events. For example, identifying Reed-Sternberg cells in a lymphoproliferative lesion, counting mitoses, identifying microorganisms, screening lymph nodes for metastatic carcinoma, classifying dysplasia in inflammatory bowel disease or the esophagus, recognizing granulomas—these kinds of things are extremely tedious for pathologists. It has already been shown that image analysis systems can identify metastatic carcinoma in a lymph node and are good at scoring HER2 staining on breast cancer, for example.

"And I can foresee that these algorithms will be slightly adjustable," Dr. Bauer continues. "An algorithm, if calibrated to be very sensitive, will have lower specificity and therefore will identify false-positives. Pathologists would then have the opportunity to reject items determined to be false-positives. On the other hand, if the algorithm keeps presenting negative cell after negative cell, it might be appropriate to adjust down the sensitivity and increase the specificity. Within limits, the pathologist should be able to adjust the sensitivity and specificity based on what is clinically important for the particular observation."

Will it stage cancers? The short answer, he says, is yes. "For example, there is no reason why an algorithm couldn't identify a lymph node. So you could have a complex resection case that has 30 microscope slides, and scan them all. Then a combined image algorithm and the LIS could tell you how many lymph nodes there are, how many look like they are positive, and then, based on how the slides were labeled, it might start filling in your synoptic report."

While waiting for AI to spawn such realities, digital pathology advocates are adopting, taking advantage of, and innovating with digital pathology. Dr. Asa says she uses digital pathology to better connect with patients. "Digital pathology makes it easy to do. Now when patients come to my office I can show them the whole slide image on the computer screen, point out things of significance, and tell them what they mean. Sitting with patients and reviewing their pathology is a critical element that brings us to the patient and makes patients understand the importance of what we do. And that has always been a big challenge for pathology." Dr. Asa sends patients home with a copy of their digital pathology report and slides on DVD.

"When it comes to digital pathology, I have two mantras," she says, "and they say it all: Digital pathology allows you to get the right patient specimen to the right pathologist at the right time. And the result is faster, better, cheaper pathology."

At the Hospital for Special Surgery, an exhaustive effort is afoot as Dr. Bauer awaits a new scanner. "Adding scanning to the workflow adds a step to the way we usually handle microscope slides. So that entails some cost—you have to buy a scanner and it requires more tech time." For the whole system to work, he says, other ways to improve efficiency have to be found. "Driving everything toward digital can really enhance that. The integration between the process of pathologists looking at slides, interacting with the LIS, and interacting with the electronic medical record is cumbersome in most hospitals. But we are going to implement a workstation where a pathologist will log on, click on a case in a work list, and then be able to see the case, the whole slide images, and patient information from the LIS and from the EMR, all at the same time. That will definitely improve efficiency. And as a pathologist interprets a case and signs it out, that pathology report then can be distributed to the LIS."

He and colleagues are looking forward to integrating all that with the picture archiving and communication system, or PACS, used for viewing radiographic imaging studies. "We are working now with our LIS and PACS vendors so that when a pathologist signs out a case using whole slide images, selected images can be loaded on the PACS. That way, treating physicians will be able to see and navigate the slide from which the diagnosis is based, and at the same time radiologists can see, side by side, radiographs, MR/CT scans, and the corresponding histology slide. We think we are out in front on this and recognize that it is the future."

Abels, too, is looking forward, in her case to progress within a proposed collaboration between, among others, the FDA, the Digital Pathology Association, and the Medical Device Innovation Consortium.

Abels

"We are exploring forming a temporary alliance with many different stakeholders with the goal of synergizing larger-scale projects," she explains. "For example, we would like to standardize things that you would need in an end-to-end workflow, or that would make proficiency testing easier. We would like to harmonize data sets that everybody can have access to and will enable greater market access. We also hope to create more clarity on regulatory pathways. And we're trying to harmonize those efforts between various stakeholders to optimize interoperability integration and implementation."

Terese says that over the next several months, Alverno will continue to transition sites to full digital pathology. "By Q1 of 2020 every glass slide will be scanned. Histology, special stains, IHC—everything," he says. "To be clear, when we started the transition, we started doing primary screening for all primary diagnosis. It is a 100 percent conversion. Few places have made that leap."

Terese suggests the following to others who will someday take steps to fully adopt digital pathology:

- Build the framework that you need to get buy-in up front. "If you do not have pathologists' buy-in to use it and adopt it, you will never succeed. It will always be a battle. Understand that it's their work. They are putting their names on this. Engage with them and listen to them."
- Understand what makes sense from a business perspective. "Digital pathology may not make sense for everybody. Be clear in terms of what you hope to accomplish. For us, it was not only about the logistics of moving glass. We also wanted to impact turnaround times. And we wanted to make it easier for pathologists to collaborate and give second opinions."
- Be realistic. "If you are going to be an early adopter, it's not going to be a smooth process; you will have to figure out things as you go. Make sure that who you partner with—Philips, Leica, or whoever may be there in the future—is willing to work with you and help you jump in, move forward, and meet your targets."
- But be a tad fearless, Dr. Bauer says. "Three years ago I was skeptical that it would ever be rational to scan every slide. But I've changed my tune about that. Now I am enthusiastic about changing the workflow and making it efficient enough that you would want to scan every slide. Costs are coming down and industry is progressing, making it much more feasible now. To tell you the truth, it's been easier than I ever expected."

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