Whole slide imaging for primary diagnosis: ‘Now it is happening’

Valerie Neff Newitt

May 2017—When the Food and Drug Administration granted permission to Philips to market its whole slide imaging system for primary diagnosis last month, it was a “big deal” of the highest order.

“Yes, this is a very big deal,” says Liron Pantanowitz, MD, a professor of pathology and biomedical informatics at the University of Pittsburgh Medical Center. “This event will provide the impetus to drive digital pathology forward for clinical use in the U.S., and allow us to catch up with our colleagues around the world who are ahead of us in their digital transformation journey.”

Eric Glassy, MD, president of the Digital Pathology Association and medical director of Affiliated Pathologists Medical Group, Rancho Dominguez, Calif., agrees. “Until last month the U.S. was the only industrialized country without an approved whole slide imaging system. Clearly, primary diagnosis is the holy grail of pathology. Now, after 15 years of very hard work, multiple clinical studies, and a great deal of collaboration, the FDA decision validates that effort and affirms that digital pathology is equivalent—not inferior—to a microscope.”

Dr. Becich

Michael Becich, MD, PhD, chairman and distinguished university professor, Department of Biomedical Informatics, University of Pittsburgh School of Medicine, is a pioneer of the digital pathology movement and has been working in this space for 20 years. He recalls when the utility of virtual microscopes was just beginning to be recognized. Only a few visionaries “believed it would ever be a reality for primary diagnostics. A lot of people thought it would just be a ‘toy’ for conference support or research,” Dr. Becich says. “They were wrong. Now it is happening. This moment is extremely satisfying.”

Dr. Becich predicts continuing emergence of digital pathology along with technology that will mine increasingly more patient information. “The crude oil of all of medicine is related to laboratory data generated on patients and their care episodes,” Dr. Becich says. “The digital framework has always been clinical tests, the numbers. Genomics is mainstream and now digital imaging, too. Those three things, together with the clinical brainpower of a pathologist and an engine to look deeply at data and find trends, will create a mammoth force for precision medicine.”

This seminal moment would not have happened were it not for progressive pathologists, championed by the Digital Pathology Association and the CAP, and the efforts of Philips and other companies. They worked in concert with a collaborative FDA team willing to meet, discuss, and eventually approve a WSI downgrade from a class III (high risk) to a class II (moderate risk) de novo device, to forge a simplified regulatory path. Philips’ IntelliSite Pathology Solution is now the first and only FDA-cleared WSI system for primary diagnosis. But experts agree Philips’ predicate device may soon be joined by follow-on devices from other manufacturers as enthusiasm and investments pick up in the wake of the de novo classification.

“Kudos to Philips for being first, and to the industry for having the fortitude to get there,” Dr. Becich says. “We will

see a lot more activity in this space, including from us in Pittsburgh. Definitely."

Glassy

Dr. Glassy says other vendors now see an easier pathway. "What was validated by the FDA was more than a single solution; it was a whole system of technology—remote viewing, diagnosing away from the microscope. This is bigger than just Philips, although they did a tremendous amount of work."

Much of that work grew from the FDA's concern—shared by detractors of the digital movement—that digital pathology might present a risk of misdiagnosis owing to such issues as images in poor focus, improper lining up of images, improperly scanned images, and more, says Dr. Glassy. But Philips' diligence and the DPA's educational efforts have shown the concerns to be largely unfounded. "There are risks with a microscope, too," Dr. Glassy says. "We explained to the FDA the risks a pathologist has in normal practice when reviewing and reading cases on our own. We made it clear that pathologists know when an image is bad. Using a scanner will not change that. Additionally, manufacturers have improved algorithms and are making sure that scans accurately reflect what's present on glass slides."

Granzow

Philips undertook an enormous task in its push for clearance, say Russ Granzow, general manager of Philips Digital Pathology Solutions, and Esther Abels, director of regulatory, clinical, and medical affairs at Philips Digital Pathology Solutions and chair of the DPA regulatory and standards task force.

"We've been working on this for so long, it's become part of our DNA at Philips for the past five years or more," Granzow says. "The FDA worked very hard with us. There was daily contact with Esther, reviewers, senior management. They wanted to make this decision and to make it the right way."

That decision was largely dependent on a large clinical study of about 2,000 surgical pathology cases—one of the largest studies ever conducted to compare the use of digital pathology to optical microscopes.

Abels

"We used four different facilities [Cleveland Clinic, University of Virginia, Miraca Life Sciences, and Advanced Pathology Associates, Rockville, Md.], and four reading pathologists per hospital—16 pathologists, ranging from

general pathologists to specialists—all reading the same cases at their institutions," Abels explains. In total there were about 16,000 reads across 2,000 cases. "An adjudication committee—a panel of three independent pathologists—reviewed whether findings on these digital cases, including difficult cases, were different from sign-out cases," Abels says.

Study results showed that diagnoses made based on Philips' WSI system were comparable to those made using glass slides and demonstrated the point of non-inferiority.

"We tried to get full and representative coverage," Granzow says. "The goal was to show non-inferiority between the microscope and all use cases for anatomic pathology, as opposed to simply biasing it toward just breast or prostate. Pathologists must feel confident that digital pathology can be adopted into daily practice."
"One of the reasons it had not been adopted until today," Abels adds, "is pathologists didn't feel they could fundamentally adapt their workflow around digital pathology. Now they have the opportunity to do that."

While news of the clearance has had its own level of energy, continuing excitement is found in the benefits to follow. Dr. Glassy says the FDA's stamp of approval gives pathologists a new comfort level in enjoying those benefits. "Remote diagnosis is a liberating use of technology. The world is now a pathologist's office, keeping in mind issues with CLIA licensure, of course. The FDA has lifted the travel ban that pathologists have been under, keeping them in offices or laboratories to read out cases. We have been untethered."

Dr. Pantanowitz says the approval will make it easier to share cases, balance workload, and centralize services, and it will support subspecialty practice. "It will also allow us to embrace next-generation applications—such as image analysis, streaming analytics, and computational pathology—much sooner than anticipated. Once these digital pathology systems are 'hooked up' for clinical use and operational, they can even begin to be deployed within larger enterprise image ecosystems—for example, vendor neutral archives."

Clinicians and patients stand to gain from greater access to experts, faster turnaround times, improved accuracy, and computer-aided diagnoses, Dr. Pantanowitz says. "I am hoping this milestone will drive down the cost of these systems, create new revenue opportunities for pathology labs, promote digital imaging specialists, and encourage innovation that will reshape pathology."

Some worry that digital pathology approved for primary diagnosis could end up replacing pathologists, Dr. Becich says, but he doesn't see it that way. "Today it is all about managing data drawn from imaging, longitudinal laboratory data, electronic health records, and so forth. Now more pathologists will embrace computational pathology; we will see pathology informatics as a discipline grow and diversify in ways to help us all. It will include the deeper research enrichment that comes from computational pathology's ability to bring its own data. And that bodes well for precision medicine."

In making its announcement, the FDA called for special controls to ensure "precision, reliability, and clinical relevance . . . safety and effectiveness for this digital imaging system."

"DPA has been in discussions with the FDA regarding exactly what these are, what level of detail is required. It is a lot of work," Dr. Pantanowitz says. "Before, it was not tangible, only hypothetical. Now we actually do have a class II device. As part of the submission, Philips was required to address a proposal of the special controls, and the FDA will provide final guidance. With the de novo authorization published in the FDA's de novo database, the special controls are made public and apply to WSI devices. Finally someone is doing this."

Pantanowitz

But he cautions that the regulatory challenge with WSI is not over. “How are we going to evaluate the safety and effectiveness of all the new devices on the market? There is work to be done, such as developing phantoms and related tools to aid with validation and regulatory evaluation.” And while FDA clearance for “one locked-down system is great,” he says, it raises questions about future interoperability—“will we be able to mix and match products?”—and the capacity to advance this field—“will open systems and artificial intelligence tools ever be permitted?” Moreover, pathology laboratories produce more than surgical pathology slides, he adds. “We still need FDA-approved digital pathology systems for cytology, non-FFPE hematology, and microbiology slides before we can claim to be ‘fully digital.’”

Granzow says Philips has seen widespread adoption by reference laboratories in Europe and expects the same will happen in the United States. He also says computational analysis is becoming more accepted overseas as companies roll out important algorithms. “Truly, digitalization is the first step, not the end,” he says.

Dr. Glassy knows the journey ahead is challenging but suggests the route already traveled has brought pathology to an important harbor. “We all knew this would happen and we would get here. But that it happened in my lifetime—that is truly fantastic.”
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