New scope for trial drives FDA verdict

Valerie Neff Newitt

June 2017—The new FDA-enabled milestone in pathology—approval in April of whole slide imaging for primary diagnosis—allows pathology to dip its toe into the technological revolution that has already transformed other fields. Widespread adoption will take time, training, and money, but it no longer awaits breakthrough approval.

“It allows us to say there is a competent device that, when we give it a slide, will give us back an image consistent with what we would see through light microscopy,” says John Gilbertson, MD, director of pathology informatics, Massachusetts General Hospital. “And when one slide is scanned by many different scanners, will those images be the same? The answer is yes. And that is a big deal.”

Having worked in digital pathology for almost 20 years, Dr. Gilbertson predicts “a golden age of pathology,” one that unleashes driving forces.

“We will be able to apply computational power and network our activity, both driving forces behind innovation, discovery, and productivity in the modern world in virtually every industry. Now we can also apply that to pathology for the very first time.”

Dr. Taylor

This noteworthy moment is due in part to an exhaustive Philips study that paved the way to the FDA’s approval of the Philips IntelliSite Pathology Solution for primary diagnosis. Clive Taylor, MD, PhD, a professor of pathology at Keck School of Medicine of USC, was involved in the design of the study, which was much broader in scope than earlier whole slide imaging investigations.

Comparing it to a 2013 study by Bauer TW, et al. (Arch Pathol Lab Med. 2013;137[4]:518–524), Dr. Taylor explains, “The Philips study was intended to be a very large comparison of primary diagnosis by glass slide versus whole slide digital imaging, using the same pathologists to look at both diagnoses and to make the comparison against the original reference diagnosis of record. The Bauer study did some of those things as well, but it was a much smaller study—about 600 cases—and was limited to only subsets of disease.”

Dr. Taylor says one key differentiator of the Philips study is that it was designed with input from the FDA regarding the specifics required before broad approval could be granted. The study had to hit almost all organ systems, with the exception of non-formalin-fixed, paraffin-embedded hematopathology cases, frozen sections, and cytology, across 2,000 cases.

“While diagnostic subcategories in pathology are similar in terms of diagnostic principles, they also have significant differences in diagnostic applications. The FDA felt, and most people agree, there needed to be a validation to prove this process works for breast, prostate, lung, and so forth—not just one or two organ systems,” Dr. Taylor explains.

There were also discussions about what the case mix should look like, which led to agreement on a required number of cases for major organ systems and a smaller number of cases for smaller organ systems that may be encountered less commonly and considered less critical.

Asked if validation guidelines for the study differed from the CAP's validation guideline published in 2013 (Pantanowitz L, et al. *Arch Pathol Lab Med.* 2013;137[12]:1710–1722), Dr. Taylor says, "The CAP guideline study was different in the sense that a consensus panel reviewed the literature on digital pathology diagnosis and came up with a series of 12 recommendations. Yet I should say that in putting the Philips study together, those guidelines were essentially all embraced in the proposal, in terms of how the process was introduced into each of the reading institutions for the purpose of the study and in the intended use of the digital slides once they get out there into practice." The value of the CAP guideline is credibility, Dr. Taylor says. "They reflect the work of a broad group of experts who enumerated sensible steps to be taken before embarking on digital pathology. Validation of the device itself was an additional dimension. Again, Philips reviewed that same literature that CAP reviewed in considering what they had to do to create a device that is safe and reliable and consistent."

The clinical study design required that there be
four clinical sites (Cleveland Clinic, University of Virginia, Miraca Life Sciences, and Advanced Pathology Associates, Rockville, Md.) to read the 2,000 cases. There were 27 pathologists involved: four to complete case enrollments, four to oversee validation, 16 to read cases, and three to adjudicate. In total there would be 16,000 reads with four pathologists reading both glass slides and digital slides for each case, with a four-week wash-out period in between.


Dr. Rubin

Brian Rubin, MD, PhD, of the Cleveland Clinic Lerner Research Institute and vice chair for research, Cleveland Clinic Laboratories, explains the role he played in the Philips study at his site. "I selected slides in the organ systems we were assigned and pulled consecutive cases over a specified time period. The FDA wanted consecutive cases so there could be no cherry-picking to identify easier or harder cases; they wanted to avoid any bias that could be introduced that way. So we indeed ended up with a true snapshot—a broad swath of the normal things pathologists diagnose."

After pulling pertinent slides, Dr. Rubin undertook quality assurance steps to make sure the slides fulfilled search criteria, documented the cases, and then provided the slides to the scanning technician for additional QA before actual scanning.

"The beauty of this test was the slides were not just scanned," he says. "They were put into trays and the readers read them either optically under light microscopy or digitally. Four weeks later they did the exact same cases with the other modality. And yet there was not one single case where all four pathologists got it wrong by digital reading but got it right by light microscopy. Not even one. It proved the point of non-inferiority."

Furthermore, there were few cases in which the readings were discordant. Esther Abels, director of regulatory, clinical, and medical affairs at Philips Digital Pathology Solutions, says: "The overall difference in major discordance rate, compared with the main diagnosis, for digital-optical was 0.4 percent with a two-sided 95 percent confidence interval of -0.30, 1.01. As the upper limit of this confidence interval was less than the non-inferiority margin of four percent, manual digital diagnosing by a pathologist using PIPS [Philips IntelliSite Pathology Solution] is non-inferior to diagnosing by a pathologist using the optical microscope."

Asked if digital pathology imposes any limitations on pathologists, Dr. Gilbertson says, "There are still limitations to some of these devices. For example, we still get only one focal plane out of them right now, though that will

change at some point."

"There are always limitations to what pathologists can do," Dr. Rubin adds. "It's never black and white; there is always a gray area. We discovered digital microscopes don't clarify the gray area any more than traditional microscopes. What is tough under light microscopy is just as tough with digital microscopy. Nothing makes me say, wow, this is an area that is significantly improved, or significantly worse. It is really equivalent."

While one might reasonably assume U.S. acceptance of digital pathology will parallel the European experience, Russell Granzow, general manager of Philips Digital Pathology Solutions, says the U.S. is likely to have a unique experience. "Acceptance is driven even more strongly by ROI [return on investment] in Europe. Each country has its own reimbursement paradigm. As such, there is no single 'European experience.' The UK has the NHS dynamics, Spain has regional dynamics, Nordics are early adopters, etc."

One certain driver shared by parts of the U.S., Europe, and the rest of the world, however, is a shortage of pathologists, which means, Dr. Gilbertson says, "there are going to be major disruptions somewhere. Countries like India and China try to do medicine without having available pathologists. They will change the model, not only because they have to but because they can," he says, given that digital pathology makes it possible to share slides worldwide.

With increased adoption—and the inevitability of one technology giving birth to another—comes expanded needs, particularly for image storage and management. Granzow says Philips is already developing new solutions for image management critical to the storage of digital pathology images, which are about 10 times larger than radiology images.

"Our system is designed for rapid, multisite, secure image viewing. It will be an open system, and as new digital imaging and communications standards are developed for effective data exchange of pathology images, we will adopt and deploy them to ensure interoperability," Granzow says. It is becoming increasingly important to be a data integrator, he adds. "We will bring together longitudinal patient data, radiology, pathology, and genomics with EMR data to enable effective decision-making in, for example, multidisciplinary tumor board sessions."

Stronger artificial intelligence capability for digital pathology is of paramount importance to those interviewed. "One of the big milestones in medical history was the introduction of the microscope 170 years ago," Dr. Taylor says. "Prior to that, disease was diagnosed by looking at the whole patient. But everything changed when we could look at organs, tissues, and cells through the microscope. The next big change is happening now. Digital pathology will lead to an intelligent microscope that will give assistance to the pathologist in looking at and interpreting microscopic slides. It won't replace the pathologist, but it sure will provide incredibly powerful assistance in how a pathologist functions."

Dr. Gilbertson

Computers can do many things light microscopes don't do, Dr. Rubin notes, such as image quantification. "I am looking forward to not having to count stuff," he says light-heartedly. "That is something we as humans are not very good at, yet computers are great at that sort of thing."

Dr. Gilbertson is sure that it won't be long before the pathology community will be unable to imagine a time when pathology was without digital pathology. "The ability to actually share slides, to compute on slides, to enable a health care system to have the right slides of the right patient to the right pathologist at the right time is a really

big deal. At Mass General we are 100 percent subspecialized, but many facilities are not. So just being able to get a slide from various parts of the country to that expert pathologist when needed is beyond huge.

“The very infrastructure around pathologists is increasingly capable,” he adds. “The expense to scan and store an image is coming way down. The time it takes to scan has come down too, and the rescan rate has dropped dramatically. At some point the advantages completely overwhelm the disadvantages of it.”

Dr. Rubin thinks there was little surprise that digital imaging was found to be non-inferior. “We all had this feeling that ‘this is it.’ The time had finally come for this study to answer the basic question: Are digital pathology and light microscopy equivalent? The answer,” he says, “is a resounding yes.”n

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