Digital path’s star rises from the mists

Anne Paxton

October 2023—In living up to its promise as a new technology that will revolutionize clinical care through greater ease, speed, and accuracy of diagnosis, digital pathology has been sluggish. While many analysts, starting at least two decades ago, forecasted that digital pathology would elbow aside glass slides for good, that milestone is still far out of reach.

As health economist and chief executive officer of the New York City-based digital pathology company Paige, Andy Moye, PhD, puts it bluntly: “In probably 90 to 95 percent of the cases in the U.S., a pathologist still makes the diagnosis of cancer the way they did it back in 1910: by looking at a glass slide under a microscope.”

Mark Lloyd, PhD, vice president of pathology for Fujifilm, says he wouldn’t be surprised to hear that perhaps only five percent to 10 percent of hospitals have moved beyond using only glass slides to offer pathologists digital pathology capability. In fact, Dr. Lloyd thinks those percentages are overstated. What is the market share for the clinical use of digital pathology? “I think it would be generous to say it’s five percent. In the U.S. specifically, digital sign-out is extraordinarily low.”

However, he views Fujifilm’s purchase last January of the digital pathology business from Inspirata as an important signal, among others, that digital pathology’s star is rising. Fujifilm, a $26 billion company with 80,000 employees and already highly experienced in digital radiology, “believes the needle is moving. They’ve voted on digital pathology as being that next major digital transformation.” This indicates maturity of digital pathology in the clinical market, he says.

There are signs that, in line with Dr. Lloyd’s belief that the needle is moving, digital pathology is doing more than occupying a niche in the clinical diagnostics landscape:

- Two years ago, the FDA approved for marketing the first product to combine digital pathology with artificial intelligence, Paige’s Prostate Detect. In June and July of this year, Paige launched its suite of breast and colon cancer digital pathology products for which the company is seeking approval.
- Paige announced last month it would collaborate with Microsoft to build “the world’s largest image-based artificial intelligence models for digital pathology and oncology.” Configured with billions of parameters and incorporating up to 4 million digitized microscopy slides across multiple types of cancer, the new AI model is “orders of magnitude larger than any other image-based AI model existing today,” the company says.
- Fujifilm’s new Synapse Pathology PACS, a “vendor agnostic” software, delivers digital images for diagnosis 1.7 hours faster than glass slides, the company says, and is the

only such software with “substantially equivalent” 510(k) FDA clearance with multiple scanners to market in the United States. Designed for large medical facilities across multiple locations and compatible with the products of multiple scanning vendors, Synapse Pathology became available in March this year.

- On the adoption front, Mayo Clinic is starting the third phase of a several-year digital pathology initiative, the aim of which is to replace glass slides for clinical diagnosis. “They’re setting up an entire platform, a kind of marketplace where they can collaborate and where all different kinds of digital data can be shared and maybe where you could create, for example, algorithms based on AI,” says Esther Abels, MSc, a precision medicine and biomedical regulatory health science expert and former president of the Digital Pathology Association.

Partnerships among digital pathology companies, facilitating streamlined digital workflow between scanners, image management software, and artificial intelligence tools, are proliferating, DeciBio Consulting says.

In its “Digital and Computational Pathology Market Report—First Edition: 2023–2028,” released this May, the company reports that about 40 digital pathology partnerships were announced in the first four months of this year.

DeciBio views partnerships as key to ensuring access to digital pathology capabilities in the clinical setting. Senior DeciBio product manager Katie Gillette cites the example of Fujifilm, which, with its acquisition of Inspirata, now has the largest number of partnerships in the digital pathology space as the market continues to evolve to better address customers’ needs. Other digital pathology companies, such as PathAI, Paige, Proscia, Mindpeak, Nucleai, Owkin, and Visiopharm, have also made partnerships for interoperability and research a priority, she adds.

DeciBio estimates the worldwide clinical digital pathology market in 2023 at about $270 million and growth of 15 percent per year, reaching $550 million in 2028. The U.S. is estimated to account for about 40 percent of that and to grow in line with the market.

In the report, projected growth in the U.S. market is broken out by customer segments. Within academic medical centers, where clinical use of digital pathology is most advanced, expected growth is close to 12 percent per year. In community hospitals, which are a much smaller segment of the market today, higher growth of 15 percent per year is projected, driven by initial adoption of scanners and image management systems in community hospital systems that don’t have the infrastructure now, Gillette says.

“Based on the feedback from the academic medical centers, AI tools for primary diagnosis and therapy selection are expected to be key growth drivers,” she says.

Andy Moye, PhD (left), chief executive officer of Paige, with David Klimstra, MD, Paige co-founder and chief medical officer. “At the end of the day, we believe this field is sort of the last frontier in digitization,” Dr. Moye says of pathology. [Photo by Jennifer Altman]

Some leading reference labs are more digitized than others, she says, “but even some of the largest have not fully digitized their workflows. Very few of any kind of institution—even the leading ones—are fully digitized.”

Measuring digital pathology’s adoption in U.S. hospitals is difficult, Gillette says, because there is no consensus on what “all digital” means. “Even in some of the institutions that are most bullish on digital pathology, there are still specific pathologists, labs, or subspecialties that do some or all of their cases manually.” They may say, for example, “‘Today, most of our sign-outs are digital’” or refer to efforts to establish a fully digital workflow without specifically indicating which parts of their workflows and which slides are digitized, she says.

Based on survey results, primary interviews, and secondary data, DeciBio estimates that about 10 percent of academic medical centers and less than one percent of community hospitals currently use digital pathology to support routine primary diagnosis.

A digital pathology workflow has multiple components, Gillette notes. “You need the slide scanner hardware, then you need the image management software to be able to view and annotate work and manage a patient’s case. You may use image analysis tools, and you may also need storage in the cloud.”

“There’s the whole digital pathology ecosystem that exists outside of that. And it takes a lot of change management and implementation to get digital pathology up and running.”

Many of the clinical lab respondents to DeciBio’s survey said they had scanners, for example. “But when you dive into it,” Gillette says, “they may have the scanner but are only scanning the most confusing cases, the cases that needed an external consult, or the cases they wanted to take home. Even if they have adopted an image analysis tool, they may be scanning just the small fraction of suspected prostate cancer cases they think would benefit from the algorithm.”

Gillette

People see the promise of the scanners and look forward to the AI tools that are to come. “But if you look at an individual pathologist level, the vast majority are definitely not fully digitized.”

Interoperability among these components is a logistical pain point, Gillette and other analysts agree. It can be difficult to get the technologies to work together seamlessly in a meaningful way, she says, yet laboratories value having the freedom to choose from among the vendors.

Digital pathology’s most significant impact is on lab workflow and clinical outcome, DeciBio’s report notes. “There’s generally a lot of optimism around the role that digital pathology can play on the operational and clinical side of things,” Gillette says. “Are there opportunities to run an annotation or analysis that previously took me two minutes to do manually?” Doing it in 90 seconds per case may not sound much different, but at scale the difference can be meaningful, she says. “And that difference is one of the big drivers for the commercial reference labs.”

As to image analysis, “If you are looking at PD-L1 or HER2, especially for HER2-low, there tends to be less concordance between pathologists when they’re reviewing the same slides, especially for the edge cases,” Gillette says. “And there’s a perception that if you’re able to improve concordance” and better identify patients for select drugs, “that has the potential to improve clinical outcomes, maybe in the longer term.”

Return on investment is less clear, with lack of reimbursement the obstacle.

“What is the inflection point that really drives digital pathology when the voluntary use of digital pathology becomes must-use and the nice-to-have tool becomes a must-have tool?” Gillette asks. “Reimbursement plays a big role there; it’s lacking and labs don’t want to do tests that aren’t paid for.” She predicts that “some types of algorithms will begin to make digital pathology a must-have rather than a nice-to-have. What it will take to get there is, to me, the biggest question.”

In her early career, Esther Abels primarily worked for pharmaceutical companies and also for clinical research organizations, executing studies for pharmaceutical companies.

Shifting into diagnostics, she spearheaded an initiative to reclassify whole slide imaging devices from highest-risk to moderate-risk class, and in Europe she led Visiopharm to become the first to get European in-vitro diagnostics regulations clearance for digital pathology and algorithms. Later, Abels founded SolarisRTC (RTC for research trials clinic), a digital health advisory company that specializes in digital pathology and is based in Boston.

She sees Mayo Clinic’s digital pathology platform as a major innovation and believes other institutions, too, would like to adopt digital pathology but are often dissuaded by the return on investment. While digital pathology will cost money to install, if the expense is capitalized over five years, the investment will pay off, she says. “Using all these algorithms, digital pathology ultimately helps you to be more efficient and precise, and you can reduce downstream costs.”

Interoperability can be perceived as a hurdle, Abels says. What now is understood is that FDA’s current thinking is, she says, “You cannot simply swap out a scanner for any other scanner, so when a vendor offers a scanner to a hospital to aid in diagnostic decision-making, they also need to offer the whole slide imaging system and monitor display. In addition, you have to have an algorithm that is linked to it cleared on the specific system.”

In the interest of a smooth digital pathology workflow, Abels hopes the industry can collaborate and standardize connections between devices to avoid incompatibilities. One first small step in that direction, she suggests, is

distorting an image to increase robustness of an algorithm. This eventually could lead to a reduction in the verification and validation testing required before an algorithm is allowed on the market, she says.

Abels

Asked what facet of digital technology is most likely to be misunderstood or underappreciated, Abels cites the need to trust a machine. “Going from a microscope one is used to working on to digital is a big change.” She compares it to a first ride in a self-driving car: “It’s kind of scary to fully trust that the algorithm that takes over from you really knows what it’s doing, because it’s never trained on every situation that happens. And it’s the same with pathology.”

More transparency on where the data is coming from would help, in her view. “Industry could educate better. If the user understands how the algorithm is trained, what kind of analysis has been done, where the data is coming from, whether it’s diverse enough, then I think it can be accepted more easily.”

“We shouldn’t be afraid that digital pathology or AI can replace the process of human diagnosis,” Abels says. “The workforce is decreasing, measurements are tedious; repetitive tasks that can be taken over by an algorithm give you as a pathologist more time to look at more complex cases. So I see it as an expansion of your brain power.”

Reimbursement is being addressed but has gotten off to a shaky start with the category III digital pathology CPT codes, she says. “They’re add-on codes,” and “we have already identified a few cases where it is missing opportunities. We need to go for a new setup of the system for digital pathology because, as I understand it, the CPT codes currently out are not covering the entire digital pathology workflow.”

In collaboration with the Digital Pathology Association Foundation, she hopes to launch a study that will show that results for digital pathology are as good as with the microscope but more efficient. “This is a steppingstone for algorithm CPT codes. We’re looking for centers that want to participate but also investors to fund these projects so we can show the return on investment for this technology. And that will help devise new CPT codes, especially for algorithms.”

Pathologists should embrace digital pathology technologies, Abels says, in part to ensure that algorithm development is not steered by people without a good understanding of pathology. “Without that, I think that digital pathology will start to replace pathologists’ jobs—or at least start bringing harm to patients.”

Digital pathology’s adoption in Europe was faster, she notes, in part because the regulation of IVDs came later. “They’re also allowed to have scanners with other viewers and other displays, which the FDA doesn’t allow in the U.S.”

Fujifilm’s Dr. Lloyd says the United Kingdom, for example, leads the United States in adoption in part “because the government is providing a lot of funding to expedite digital health and make sure that hospitals are starting to implement it to benefit patients.” (In 2020, the U.K. announced an extra £50 million in funding to scale up the work of the existing Digital Pathology and Imaging Artificial Intelligence Centers of Excellence, which were launched in 2018.)

Amid the buzz about digital pathology, some pathologists have reservations.

“Digital pathology can be really useful. It can count numbers of positive cells for biomarkers better than humans

and create consistent results," says Dorothy Wong, MD, chair of pathology at Regional Medical Center of San Jose in California. "But in other areas we have to leave it to the pathologist to diagnose and determine tumor origin. And in being able to see things low power and high power that I don't think a computer can do, the pathologist is irreplaceable. "

Dr. Wong was briefly contracted to help train computers to arrive at algorithms for reading digital slide images and found it unrewarding and ethically questionable. "I started to feel I was teaching a computer to replace me and to replace all pathologists with the cheapest option available." At the time, she adds, "There were efforts to find overseas radiologists and other specialists to replace licensed health care professionals in the U.S. And I think there are all sorts of problems with that, including medicolegal liabilities and also taking away that extensive experience, training, and education."

If a computer is missing something, she asks, "Who's responsible for that? You're liable and maybe you haven't looked at the case as extensively as you would have without it. There's a disconnect when you become too comfortable with AI. Are you on autopilot then? Are you even a pathologist at all?"

"We should not be supporting the health care system and hospital systems with the cheapest option available," she insists. "It's the devaluing of health care as we know it."

The upfront cost of digital pathology systems is another problem, she says. "Where are people going to get the funding to purchase digital pathology and the software? A lot of hospitals have these archaic LIS systems and digital pathology is likely to be another kind of detached system, which is very cumbersome." If digital pathology is an add-on service, she argues, insurers and patients are unlikely to want to pay for a redundant process.

Those issues aside, Dr. Wong notes, it is efficient to have digital versions of glass slides for consultations with clinicians or pathologists. Clearly valuable, she says, is "the ability to share images and maybe use digital versions for storage when otherwise we would have just had a bunch of glass slides that could randomly break depending on your storage conditions. So there is a lot of utility to digital pathology; it just has to be under the control of the pathologist."

New products such as Paige's Prostate Detect would likely be of interest to many groups, Dr. Wong says. But they probably wouldn't be able to get such a purchase approved by their hospitals because "there would be a lot of extra costs and there's no CPT code for them." A reimbursement solution is necessary, she says, "and there has to be significant oversight when it comes to the diagnostics. At the end of the day, you still want pathologists looking at your material to diagnose your case. I don't think that's going to change. People who are trying to go into this space and change health care do not know what they don't know about pathology."

In the earliest years of digital pathology, when Dr. Lloyd was involved in projects from 1998 to about 2008 at Moffitt Cancer Center in Tampa, Fla., "Digital pathology was gaining a lot of momentum in research.

I could see some of the first digital pathology tools and technologies beginning to grab hold in a research environment, and I had the opportunity to direct a digital pathology shared-resource facility, and that was phenomenal."

Motivated to see digital pathology mature into a large-scale clinical tool, soon he had started his first company, bringing together slide-scanning instruments, image management software, and algorithms. That progressed later to his company Inspirata, the digital pathology business that is now part of Fujifilm under Dr. Lloyd's management.

"We are focusing on enterprise imaging," Dr. Lloyd says, envisioning a suite of projects to include "everything from gross images in dermatology to endoscopy to intraoperative surgery to radiology and cardiovascular imaging and pathology imaging. That is the kind of scale we are looking at at Fujifilm."

Radiology was ahead of pathology in going digital, he notes, because PET and CT scans were natively digital,

whereas pathology has always started with creating a glass slide and will not be changing the technical component of creating a specimen. “We still make a slide and then we take an image of it. So our value proposition in pathology is very, very different.”

Addressing the fear of replacement some pathologists might have, Dr. Lloyd says: “It’s not the replacement of pathologists that I think any pathologist should be worried about. I am not at all a proponent of ‘Let’s just switch the lights on, now you’re digital—let’s get rid of these microscopes.’ That makes no sense to anyone.”

Dr. Lloyd

Rather, alleviating some of the menial tasks and drawing on the promise of artificial intelligence with digital pathology, “we now have a tool that can help physicians do something they couldn’t do themselves.” To Dr. Lloyd, “That’s like the killer application of digital pathology.”

On the other hand, although he is principal investigator on three grants involving AI work, he is concerned that AI is overhyped in the media, particularly as it reports on ChatGPT. “I don’t want to dampen anyone’s enthusiasm about the potential for AI. But I would caution them that this might not be the reason to buy digital pathology today, unless you have a use case where you and your organization have validated an AI technology that you really believe in.”

Pathology is very much a blackbox to people, says Paige’s Dr. Andy Moye.

“What gets the press are multi-cancer early detection breakthroughs or liquid biopsies to attack cancer and screen for it, or a new drug that came out.”

“But at the end of the day, we believe this field is sort of the last frontier in digitization,” he says. “Medical records have gone digital, radiology has gone digital, cardiologists are going digital. So this whole space will also move to digital, and the tools that are available, like AI, will help pathologists to do their jobs.”

Dr. Moye distinguishes between digital pathology, AI, and computational pathology. “Digital pathology is the use of a scanner to take a glass slide and make it a digital image,” he says. “‘Computational’ means using computation to provide an answer about what’s on the screen, what’s on the tissue,” and AI provides tools that can provide further answers. “We use machine learning or artificial intelligence techniques to build algorithms that enable that and give the information to the doctor. AI is a tool to be used—just as you would interrogate the antibodies with a chemical using immunohistochemistry.” Through training and data sets—Paige has robust data sets, he says, with partner Memorial Sloan Kettering—“we create an algorithm that with very high sensitivity and specificity provides an answer about what’s on that tissue.”

With AI, he says, that answer can be not only “There’s cancer” but also “That’s at least grade seven.”

“You can also find patterns in tissue that pathologists were never trained to see, meaning the machine can pick up patterns showing the patient has a genomic mutation or microsatellite instability.” Paige has an algorithm that’s trained on mRNA expression to predict whether a patient has HER2 expression, he notes.

Reimbursement can be a formidable obstacle but also a powerful ally, Dr. Moye says, citing radiology as an example. In the 1990s, radiology was still analog. Then disincentives were imposed.

“Basically, Medicare said, ‘If you continue to bill analog, we’re going to deduct 20 percent of your reimbursement.’”

That drove most of radiology to digital, he says, adding that studies show it takes two or three years to recoup the cost of converting to digital diagnosis. “Almost always, there is a positive net present value to going digital, but you have to have the capital to invest in it.”

The CPT category III codes for digital pathology are being reported now by laboratories that use digital pathology for primary diagnosis. “Ultimately CMS will ask how many people are using this code, and hopefully they’ll assign a reimbursable number to them.”

Two factors may shift the tide in digital’s favor, Dr. Moye says. One is that pathologists are coming out of medical school where most classes are taught using digital pathology. Second, since there is a shortage of pathologists now, pathologists who are willing to work only remotely are not likely to be overlooked for the open jobs.

“I think that’s going to be the biggest driver over the next year or two. The hospitals and health care systems are going to have no pathologists,” and possibly little recourse except to rely on telemedicine.

The fear of being replaced by digital pathology is off base, Dr. Moye says. “When radiology went digital, there was this same fear, but in fact the number of consults exploded and the number of radiologists exploded. The number of radiologists has tripled. The reason is that the digital environment, the digital ecosystem, has made that number giant. So now images move everywhere.” His view is that digital pathology might be healthy for the profession.

“AI does a few things for us. First the simple detection of cancer, what type of cancer it is. Whether you’re looking at lobular or ductal, it provides information about the mitotic count, it counts them up quickly and easily. It saves a lot of time.” With other algorithms, “we provide the AI that does very typical quantitative analysis for HER2 that most pathologists have to report on. Then we provide an algorithm called HER2Complete and it helps pathologists with the HER2-low dilemma.”

“We’re a full workflow solution for pathologists and labs that extends to research and pharmaceuticals and life sciences, but clinical care is the core of our business.”

The U.K.’s National Health Service is sponsoring a two-year prospective study by Paige, slated for completion in 2024. “What we expect to come out of that study is the cost-effectiveness of using AI tools like Prostate Detect on the health system,” he says. “That usually helps to dictate whether a health system or a payer is going to pay for it. We’re excited about the results of that. We think using something like Prostate Detect will save the payer money in the long term because you’re not missing cancers, you’re catching them earlier, and you’re getting the right results.”

Dr. Moye has two messages for pathologists, health care executives, and laboratories.

“One, AI is not coming. It’s here. I’ve had conversations with pathologists and lab directors who say, ‘Wow, that’s going to be really cool in a few years.’ I’m like, ‘Guys, this is FDA approved right now. And we’ve treated 7,500 patients who have been impacted by our AI this year.’”

“Second, AI is just a tool. It’s just like IHC and PCR and special stains and anything else in a laboratorian’s toolbox. It’s a tool to enable pathologists to do their jobs in a way that they probably couldn’t before and that provides more information and better care. It’s not taking anyone’s job.”

Anne Paxton is a writer and attorney in Seattle.