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THE DIGITAL PATHOLOGY DIVIDE

With two $100 million-plus financings this year, investment in digital pathology is surging, largely driven by the technology's potential to identify tissue-based biomarkers for applications in precision medicine. But the number of initial use cases is limited and clinical uptake of the technology by hospitals and reference labs has been slow. What will impel large reference labs and hospitals to adopt this technology to a greater extent?

▶ RACHEL LAING, SOPHIE PELTRE, AND MARIE KERISIT, BIONEST PARTNERS, AND MARK RATNER

The hardware for digitizing pathology slides began to emerge in the early 2010s. Some early user interest existed, mostly within the life sciences/research community: the area was first developed in Europe by Definiens, which the MedImmune unit of drugmaker **AstraZeneca PLC** acquired in 2014 for $150 million to aid in the identification of biomarkers in tumor tissue. Prior to the emergence of the cloud and development of increased computing power in the last five years, however, the notion of introducing digital pathology at scale was fraught.

Royal Philips NV began selling the first commercial digital image scanner in 2017. At the time, less than 1% of global diagnostic slide volume was scanned, out of about a billion slides generated annually. Within 18

months that grew to 5-6%, says David West, CEO of **Proscia**, a software maker which originated as a project at Johns Hopkins University in 2014. Today, the number is somewhere around 10%, he says. "You are looking at a technology trend that is taking slides created for diagnostic purposes every year that otherwise would be sitting collecting dust on shelves, and turning that into rich, valuable and accessible information," he says.

Many of the historical limitations of digital pathology hardware have been overcome, including the ability to visualize, store, and transmit terabyte-size images. The security necessary to maintain confidentiality while storing and transmitting these large images has also improved. Tracking the overall emergence of digital health, start-ups focused on developing artificial intelligence (AI)-infused software have also begun to proliferate in the last four to five years. Now, multiple hardware suppliers are entrenched and the focus of the field is squarely on software. (Again, for the most part in life sciences research applications, although European regulators have issued a handful of CE-IVD marks for diagnostic uses.)

As these events have occurred, the user profile for digital pathology tools has bifurcated. The life sciences research market is fairly well penetrated, but on the clinical/diagnostic side, hospitals and laboratories remain slow to engage with the technology. Life sciences research represents about two-thirds of the spend in digital pathology today—for the scanners, software, storage, and requisite computing power. The routine diagnostic world of large reference labs and hospitals is about one-third of the spend.

That said, the clinical market is growing faster, says West. He thinks that the proportion of users should flip in about a three-year period.

The Emerging Clinical Market

Interest in digital pathology within the clinical space has accelerated compared to the last six months of 2020, says Monica Santamaria-Fries, MD, Digital Transformation Officer at Proscia. Santamaria-Fries practiced with the Permanente Medical Group for over 30 years, most recently as assistant chair for the Permanente Medical Pathology group comprising 130 or so pathologists in 20 facilities, before joining Proscia in October 2020.

COVID was the major accelerator, Santamaria-Fries says. Before the pandemic, clinical laboratory departments may have had one or two scanners and were partially digitized. But as soon as COVID hit, they saw the imperative to be fully digitized. Not necessarily to be more efficient, but to be able to provide patient care in a continuous, linear way (social distancing rules had hamstrung operations, in some cases allowing only two pathologists to the lab, depending on the state) and to protect its physicians. The FDA also eased the burden on pathology labs. In April 2020, it issued a guidance authorizing greater access to digital pathology devices for remote reviewing and reporting of pathology slides during the COVID emergency.

Dealing with the pandemic has prompted a shift in culture in the pathology community. "To remain relevant, they have become more aware of the need to be part of the digital era," says West. Although he and others do not expect the emergency use authorization for pathology software to remain in place, "it certainly accelerated the technology development," he says, allowing providers of digital pathology tools to build technology and prove the value of their products and services (*see Figure 1*).

A number of other catalysts were also percolating beneath the surface. Most notable is the falloff in the number of pathologists entering the field and the demographics of those professionals. "It's stunning how everything has shifted towards an older population," says Santamaria-Fries. According to Medscape's *Pathology Compensation Report* 2021, 26% of US pathologists surveyed were 60 years old and over; 54% were 50 and over and only 7% were 34 and under. At the same time, the cancer caseload is rising—up 43% from 2007-2017 and, according to West, the per-pathologist workload is up 42% in the US over the last decade.

The problem is worse outside the US. In the UK and other places in Europe, the imbalance of workload and staffing is apparent: the turnaround time of a biopsy may be weeks because not enough pathologists do the work. The UK's National Health Service published a report on its laboratory staff noting that 3% of labs had enough staff to meet demand. "It is a premonition of what's going to happen here." Santamaria-Fries says.

As that pressure is being felt, a handful of digital pathology use cases are emerging—applications like breast cancer prognosis and prostate cancer detection with grading algorithms. Low reimbursement rates for testing are also pushing laboratories to improve efficiencies.

"I'm starting to see and hear an acknowledgment that this is not shifting one tool for the next for the sake of modernization," says Santamaria-Fries. "It's deeper than that, enabling your practice to be more efficient operationally both at the department level and the individual level, and setting yourself up for success and being able to bring in computer applications, maybe not completely now, but in the future."

Patterns of Adoption

"Sometimes people say that because radiology went digital, therefore pathology will too," says Leo Grady, PhD, CEO of **Paige.AI Inc**. The three-year-old company arose out of Memorial Sloan-Kettering's center for digital pathology, which MSK had started to build out in 2015. Grady says the radiology comparison is an oversimplification. "Radiology went digital 20-25 years ago in a very different technology landscape for very different reasons," he says. Pathology going digital is a much more intentional process. And at a different time, as AI technology was not available when radiology went digital.

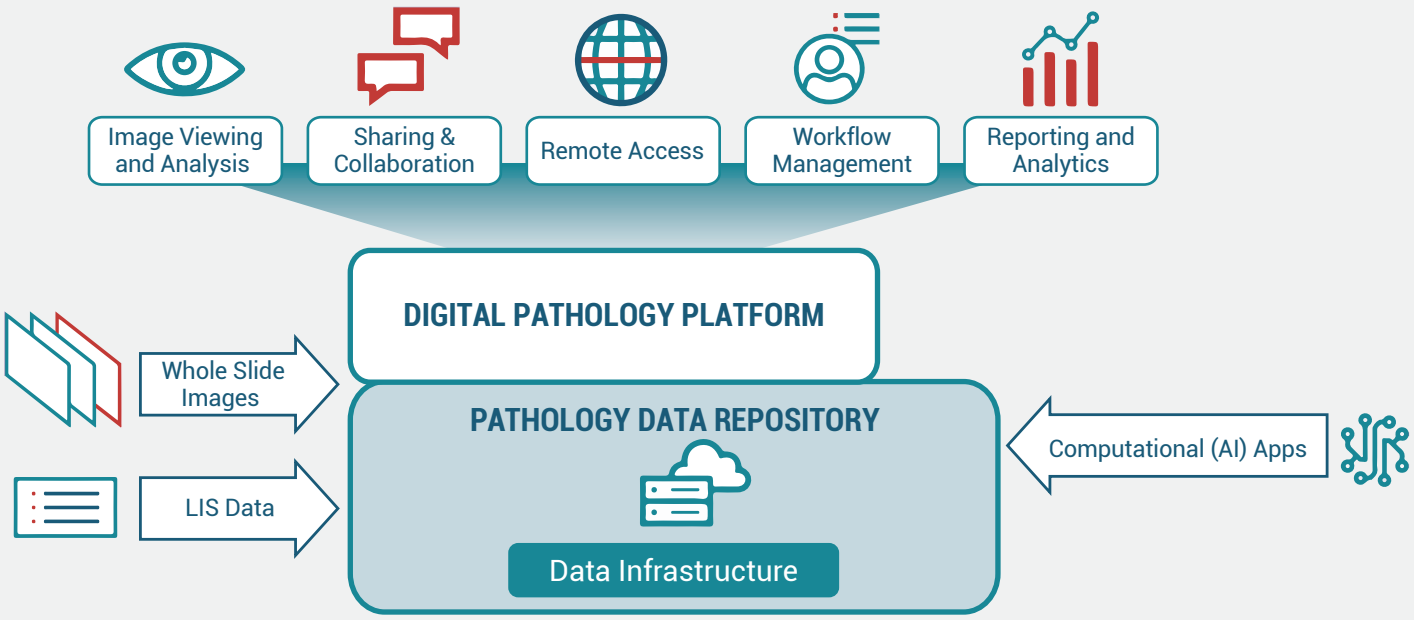
Grady spent the early part of his career applying AI to radiology. He worked at HeartFlow Inc., which developed a cloud-based cardiovascular diagnostic test. The raw materials for that test were the cardiac CT image, which was sent to the cloud, analyzed using software, then returned to the hospital through a web interface. "A lot of the infrastructure I built at HeartFlow is similar in concept to what we are doing at Paige," he says.

But radiologists always had a safety net because the treating physician could also get a biopsy. A pathologist's diagnosis is different: it is the gold standard, the basis for treatment and what insurance pays for and does not pay for. "The bodies involved look at pathology as a higher-stakes medical discipline," Grady says.

The same is true of comparisons to the adoption of genomics, which was more of an add-on technology to a laboratory's work. "The existing lab infrastructure makes this a different kind of bet," says Andy Beck, PhD, CEO of **PathAI**. Slides and stains are already being used in every trial. "I think the uptake can be faster than with other technologies," he says.

That said, it's still hard for many hospitals to point to much evidence that the transition to digital pathology matters for patients, Beck says. "It takes a pretty good value proposition to make something change that's been done the same way and pretty effectively for many years," he says. "That there hasn't

Figure 1
The Digital Pathology Ecosystem



Source: Proscia

been widespread adoption has to do with the return-on-investment case not being strong enough. There has to be a big delta to show the value: focus on digitization for convenience and workflow efficiencies is not enough."

That's looking at just the process of digitization versus interpretation on glass slides and not clinical applications that involve AI, he acknowledges. The appeal of AI is that it enables hospitals, laboratories, diagnostics providers, and pharma to focus on new insights.

Tissue contains a wealth of information. In oncology, for example, it can reveal a great deal about a patient's tumor, its microenvironment, and the patient's overall health. By digitizing that information, a pathologist has the capability to systematically identify, at scale, those characteristics of the patient's tumor and the microenvironment around it that are going to be more conducive to whether a given treatment will work. "The opportunity is to leverage that information in a way that is quick to compute, is nondestructive to the tissue, and can be done in a standardized way for everybody, then integrating that information from the tissue with the genomics, the immunohistochemistry and other biological information," says Grady.

Plus, digital pathology fits into an already existing multi-modality information paradigm of molecular and tissue information. And in that sense, the pathologist stands at the center of diagnosis—a further impetus to transition to digital technology, to keep pace with the trend throughout healthcare systems (*see box, "Considerations in the Transition to Digital Pathology"*).

The Center of All Things

"You can have a hospital without geriatrics or without pediatrics but you can't have a hospital without pathology," says Carlos Cordon-Cardo, MD, PhD, Professor and Chairman for the Mount Sinai Health System Department of Pathology in New York. Pathologists today assist in patient stratification, planning, and monitoring by analyzing the range of organ damage, and also bringing various cellular and molecular findings. "Most of personalized medicine starts with us," Cordon-Cardo says.

Part of the pathologist's role is to apply subjective reasoning to the analysis of tissues based on very specific changes that are difficult to quantitate. Pathology is therefore a logical area for which to develop highly accurate predictive algorithms that will integrate clinical variables, molecular profiles, specific biomarkers, and also histology and cellular features that through image analysis can produce quantitative analyses and measures. This body of information, when trained, will in turn produce, through deep learning, new, better algorithms.

Cordon-Cardo founded **PreciseDx**, a recent Mt. Sinai spin-out. "We have developed a new approach based on computational and systems pathology that attempts to produce a mathematical characterization of the phenotype," he says. The computational pathology team that has now formed PreciseDx has been in existence from the beginning of the 2000s. But they held off until the technology in PreciseDx was ready, he says.

Digital pathology can easily step in and help pathologists complete straightforward reads that are time or labor intensive. "Mt. Sinai is particularly good at mapping what a pathologist does now and how to assist them," says David Rubin, PhD, Managing Director at **Merck & Co. Inc.**'s venture capital arm, Merck GHIF, which has invested in PreciseDx.

Dividing cells are a hallmark of many cancer types. A pathologist may have to look at several different regions in a tissue sample and individually count 500 cells looking for

Considerations in the Transition to Digital Pathology

Both the initial planning/preparation and implementation of digital pathology in a laboratory are complex processes. Planning includes understanding the overall laboratory needs, identifying the topmost problems to be solved, determining who can make the case to administrative bodies to get funding, identifying the best technology options on the market, and understanding the regulatory environment. Making the transition will involve a large, multi-factorial team including the heads of pathology and informatics as well as front-line pathologists, histologists, laboratory directors, and administrative leadership. The IT department is a key piece of this enablement, as it will be able to provide expertise in technology selection and what is needed in terms of cybersecurity or interoperability, so that an image can be routed to the right pathologist and the right work list, securely and in accordance with the institution's IT policies.

After deciding on scanners and software, the team must align with laboratory regulations, determine the regulatory environment in the particular location to know what amendments to laboratory policies and procedures are required, and validate the system to make sure the laboratory is going to be able to continue to deliver the care at the level it had before, including demonstrating equivalencies or noninferiority of the new system. (That takes time, and the bigger the organization, the longer it takes.) Then comes training and making the adjustments to workflow that will increase efficiencies.

> Once this technology is ubiquitous in the clinical setting, it will have the ability to identify needles in haystacks and prioritize patients who may in fact have a condition that would be missed otherwise.

those that are dividing (in a mitotic state). That task of identifying mitotic cells is difficult, but easy for machine learning, after training, to accomplish, Cordon-Cardo says. "We count mitotic cells better than anyone," he says.

Building on that, PreciseDx has produced a unique architecture of specific building blocks based on areas of clinical significance that pathologists know are important, such as the shape of the nuclei, density and size of the cells, and the topology of the tumor in its environment. It will help in patient safety, will pay for itself in reproducibility and accuracy, and will enhance the expertise of the surgical pathologist both by bringing scalability to routine tasks and reducing errors, he says. "This is actionable information that will improve the clinical workflow and potentially gives the patient a better chance for cure by opting for the better treatment strategy," he says.

While applying this platform to train an algorithm in prostate cancer, PreciseDx also determined that its breast cancer algorithm was highly specific and sensitive with a great deal of predictability. "We centered on that as our first program for PreciseDx," Cordon-Cardo says. His team is continuing to work in prostate and melanoma and is also interested in developing an algorithm based on the number of inflammatory cells and biomarkers in immuno-oncology—a project of obvious interest to Merck, which sells the IO drug *Keytruda*.

Their work extends beyond oncology. "Our automated platform allows us to build approaches in different pathologies," Cordon-Cardo says. The Mt. Sinai group has published an algorithm identifying the tau protein and tangles in Alzheimer's—work that has progressed to the point of being able to start stratifying based on quantitation at the tissue level, Cordon-Cardo says. In another study using a biopsy of peripheral nerve on the leg, the researchers have been able to produce a potential score for Parkinson's Disease based on the identification of alpha synuclein and other characteristics of the tissue of the nervous system impacted by Parkinson's disease.

According to Cordon-Cardo, PreciseDx has just obtained the first reimbursement code for an AI-guided diagnostic tool. "That is a new development in computational pathology," he says. To date, going digital by itself has not had correlational CPT codes for reimbursement. Nor do any AI applications currently have any CPT codes. (A limited CPT code, 88361, exists for morphometric analysis, tumor immunohistochemistry to identify breast cancer prognostic markers [estrogen, progesterone and Her-2/neu] using a computer assisted technology.) "The technology needs to prove itself above and beyond the standard of care to justify new codes," Santamaria-Fries says.

Multiple digital pathology companies, including Paige and Proscia, are working in prostate cancer.

Although prostate cancer is morphologically obvious and fairly straightforward to distinguish, the clinical diagnosis takes several steps, starting with an elevated PSA score, then a urologist randomly taking samples of the prostate in a dozen or so locations, after which the lab has to cut multiple specimens from the same procedure, the vast majority of which are going to be benign. "It's a needle in a haystack problem," says West. But for a computer, it's basic pattern recognition capability to distinguish where that tumor is. "It's high utility to the pathologist, who just has to quickly look at the slide that is likely to have cancer and screen out the rest," he says.

Prostate, breast, and skin cancers (including basal cell carcinoma and melanoma) are low-hanging fruit for clinical diagnostic applications of digital pathology. *Paige Prostate Clinical*, for example, as well as *Paige Breast Clinical*, are CE-IVD cleared. Proscia has announced plans to submit its *DermAI*, which looks to distinguish between cancer diagnostic categories like basaloid or squamous or melanocytic, to FDA (but has not provided a timeline for doing so).

The seemingly straightforward ability to share images across multiple institutions is also low-hanging fruit. "It may not sound too exciting, but most of the systems out there are for a closed laboratory in a hospital setting, not for a group with multiple labs across the country or for extending consults to multiple groups," says Chris Garcia, MD, Medical Director, Clinical Informatics, at **Laboratory Corporation of America Holdings** (Labcorp). Indeed, large reference labs like Labcorp that grow through acquisition need to factor into their planning a degree of operational decentralization, to account for legacy systems in the businesses it acquires. Digital pathology has been implemented at Labcorp for some time, mostly in the quantitative biomarker space, for markers like Her2 in breast cancer.

Labcorp has also invested in or collaborated with a number of digital pathology companies including PathAI and PreciseDx.

Looking to the Future

"Game-changing medical-value algorithms will likely require a longer and more arduous path to market for routine clinical use," says Michael Rivers, Vice President, **Roche Digital Pathology**, which sells digital pathology solutions to both life sciences research and clinical customers. "I think it's important to pave the way with a variety of solutions that bring incremental value to the lab workflow and diagnostic process."

As the field moves forward, software developers will draw new insights from AI to help drug developers better identify the right patient subsets who will benefit from therapies, says Beck, whose company in May raised $165 million from a syndicate including strategic partners **Bristol-Myers Squibb Co.** (BMS), Labcorp, and Merck (see *Figure 2*).

PathAI has the right business and financing approach to do that, Rubin adds. "Their model starts with pharma connections," he says. "If you have novel technology and you can partner with cutting-edge pharma and learn and play in the sandbox with those scientists, it's a great way to develop biomarkers," he says.

In immuno-oncology, for example (an area of interest for many pharmaceutical companies including Merck and BMS), new potential pathologic mechanisms of response and resistance could help to explain why IO drugs can be so transformative in 30% or so of patients in certain diseases. "It's very hard for efficiencies to have the same impact on patients," Beck says. "That's not the real driver of impact."

Moreover, once this technology is ubiquitous in the clinical setting, it will have the ability to identify needles in haystacks and prioritize patients who may in fact have a condition that would be missed otherwise. "That's an important future application and advantage of having AI supplementing diagnosis," Beck says, to identify patients who may actually harbor a rare genetic mutation or some other disease that may show a particular benefit from a new therapy that targets rare subtypes of common diseases.

Pathologists are turning to digital tools because they want to grow their business by providing expertise anywhere in the world. Remote viewing enables a faster sign-out experience, West says, and adds to the ability to generate data that might be monetizable in partnership with pharma. The diagnostic applications are "sort of icing on the cake, but potentially can become the cake itself in the long run," he says.

"We think quite a bit of money will go into both categories," Rubin predicts, adding that more tech companies will then get into the game, developing cheaper scanners with open architecture. They will also come in to support with IT tools, infrastructure, database systems, and laboratory information management systems. MTS

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Figure 2

Recent Financings in Digital Pathology

Company (date)	Amount ($M)	Round, Participants
PathAI (May 2021)	165	Series C co-led by Capital Partners & Kaiser Permanente. Other investors included General Atlantic, Tiger Global Management, 8VC, Adage, Biospring Partners, General Catalyst, KdT Ventures, Polaris Partners, Refactor Capital, Bristol-Myers Squibb, Labcorp, & Merck Global Health Innovation Fund.
Paige (March 2021)	125+	Series C co-led by KKR, Casdin Capital and Johnson & Johnson Innovation. Additional investors include Catalio Capital Management, existing investors, and funds.
Ibex Medical Analytics (March 2021)	38	Series B led by Octopus Ventures & 83North, with additional participation from aMoon, Planven Entrepreneur Ventures, & Dell Technologies Capital.
Proscia (Dec. 2020)	23	Series B led by Scale Venture Partners, with participation from Hitachi Ventures.

Source: Company press releases