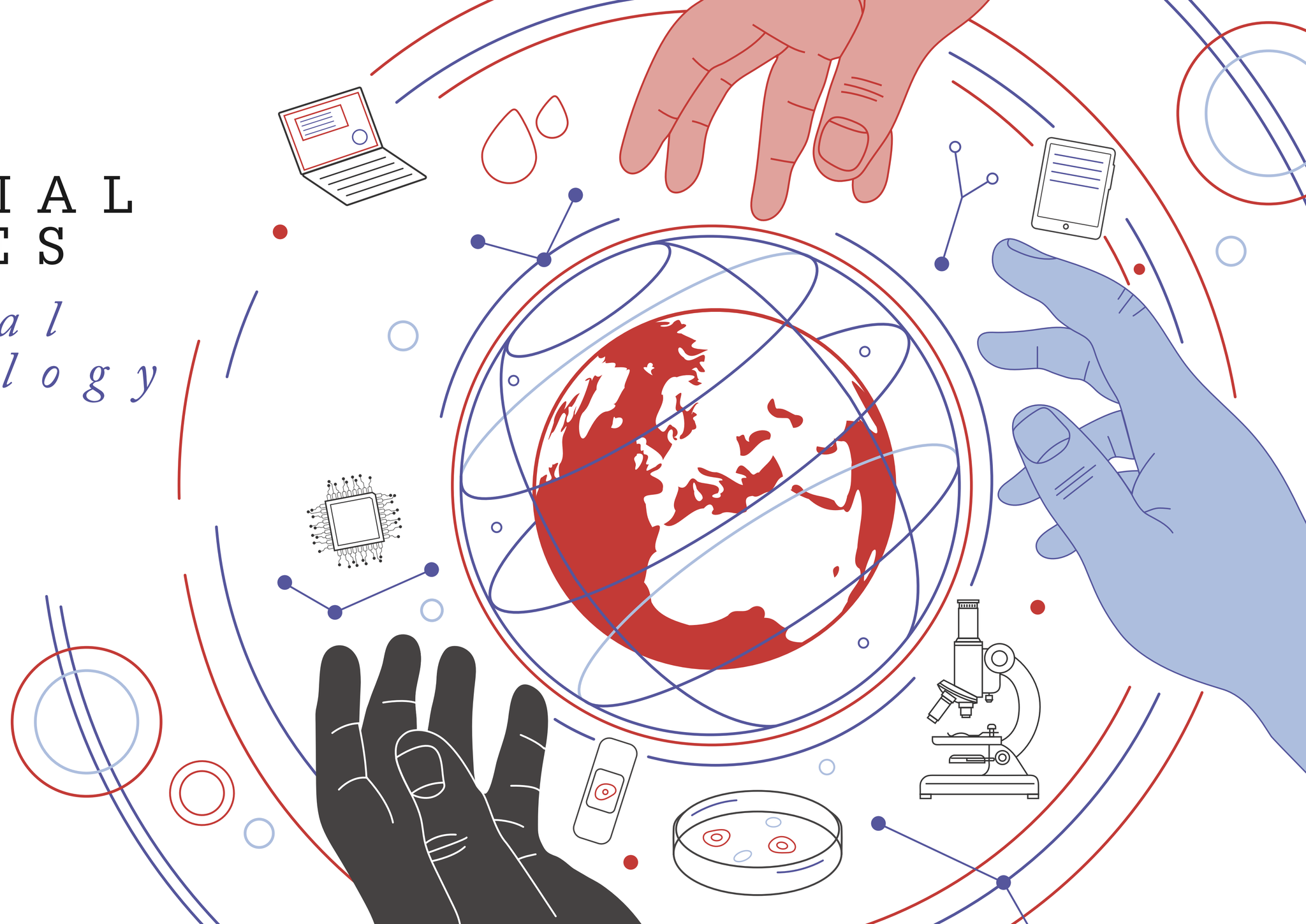
the Pathologist

SPECIAL SERIES

Digital Pathology



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IN MY VIEW

Success Through Centralization?

The path to realizing digital pathology's true value

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Digital pathology's benefits have been widely discussed – from alleviating staffing shortages to accelerating turnaround times; from increased consistency and accuracy to innovative teaching tools. But, in practice, those benefits have proven elusive. Why?

At its most intensive implementation, digital pathology has the potential to support primary clinical diagnosis. At a less intensive level, it can be used in targeted precision medicine applications, particularly in the area of immunohistochemistry tissue diagnostics. In all cases, though, the burdens of digitizing often outweigh the benefits – mainly because responsibility for the system's performance rests with the local laboratory. Though many companies have created effective tools for managing slide images and streamlining workflow, they have done little to relieve the most time-intensive burden: the creation, validation, and maintenance of image analysis tools and diagnostic algorithms.

To comply with Clinical Laboratory Improvement Amendments (CLIA) regulations regarding laboratory-developed tests (LDTs), an artificial intelligence (AI) diagnostic algorithm must be thoroughly tested and maintained. Quality assurance procedures must be created and users provided with regular, comprehensive training. Digital pathology equipment must be purchased and the informatics expertise needed to integrate it into laboratory and hospital information systems must be established. The overhead necessary to support these activities is prohibitive for most laboratories in the current reimbursement environment. A potential solution: AI algorithms offered as LDTs on a national scale. To take advantage of this capability, clinical laboratories would send slides or digital images to a service provider and receive a clinically appropriate diagnostic result. This would leverage current digital pathology product strengths while mitigating the challenges associated with DIY solutions.

Geoffrey Metcalf

For instance, local laboratories have limited ability to design and execute a clinical study of sufficient power to verify and validate a lab-developed algorithm in line with CLIA requirements. Based on patient volumes at a typical hospital or regional laboratory, the investment of time and money needed would be prohibitively expensive. Leveraging national economies of scale, a central service provider could develop an algorithm and test it in a clinically robust study that could be published in leading peer-review journals available to the entire medical community. This approach would not only yield a clinically superior product, but also eliminate the "black box" nature of DIY algorithms. It would also eliminate the organizational and financial challenges associated with DIY digital pathology solutions. Creating and maintaining image-based AI solutions is costly, time-intensive, and requires informatics expertise not every organization has. Testing them requires expertise in study design and access to clinical samples, which may be difficult or expensive to procure. And, as digital imaging equipment and staining technologies evolve, algorithms must be re-evaluated and updated to keep pace. Quality assurance procedures must be created and maintained and employee training programs implemented. All of this would need to be achieved within the current clinical diagnostic reimbursement environment. Without additional funding, it is not surprising that few laboratories can generate the financial ROI to justify a DIY digital pathology approach.

A centralized digital pathology service offered on a national scale would offer crucial additional benefits. For instance, purchasing efficiency is critical – so this approach enables the creation of a family of solutions local laboratories can procure efficiently. Most laboratories prefer to consolidate their purchases through as few vendors as possible; a centralized digital pathology provider could offer a "one-stop shop."

The provider would also be able to amass a powerful database that could be leveraged in support of clinical studies. A key characteristic of image analysis is that it generates large amounts of data. This data could support sophisticated clinical studies impossible to implement at the local level. Additionally, the data could be used in ways not otherwise possible, such as more robust evaluation of cut points and treatment decisions. For example, finding strong correlations between patient response to immunotherapy and currently available diagnostic data has been challenging. When studying such a complicated and dynamic clinical question, the larger the database the better. Imagine if a centralized provider – for instance, of PD-L1 AI solutions – stored the de-identified data from all of the samples it processed over time. Such a database would house an extensive range of clinical diagnostic data for tens of thousands of patients. When merged in a research setting with patient outcome data, it could yield true medical breakthroughs.

The final advantage to using a centralized send-out digital pathology solution is image storage and technical infrastructure. To achieve the degree of accuracy required for an AI solution to be practical across a wide range of samples, the image and resulting data files must be highly detailed, nuanced, and layered. This leads to not only large files that need to be carefully tracked, stored, and backed up for lengthy periods, but also millions of small files that must be effectively managed. This demands vast storage capacity and a highly redundant and available file system built around these specific needs. It also requires uniquely optimized, high-performance computational power to achieve the desired output in a viable amount of time. Any of these factors alone would be a major endeavor for a typical laboratory – but combining them into a cohesive, secure, compliant, and reliable ecosystem is an immense, complex undertaking. In my view, it is only by offering centralized solutions that we can get all labs on board with digital and computational pathology.

Meredith James

"The pathologist's goal is to provide treating physicians with the facts and tools they need to manage their patients. Artificial intelligence could be an important tool in fulfilling that mission – and only a centralized digital pathology provider would have the expertise, reach, and economies of scale to leverage that capability."

A local laboratory might be able to create an AI solution for a single indication, such as NSCLC, but this solution would not apply to other PD-L1 indications. It would probably not be wise for a laboratory to invest the time and money to develop a solution that is only applicable to a portion of its needs. Only a centralized service solution would deliver the economies of scale needed to support the creation of a family of PD-L1 solutions to meet the operational needs of local laboratories. And only a centralized service could promptly update its capabilities to keep up with the evolution of clinical care. Quickly adding new indications, stains, or digital scanners is only feasible for a large service solution provider.

In the immuno-oncology field, PD-L1 reactivity is only a portion of the clinical picture. Immunotherapy's effectiveness depends on both the PD-L1 reactivity of the tumor cells and the immune microenvironment. Current tests provide only a PD-L1 result because it is relevant in selecting FDA-approved therapies and it is the only reimbursable result. The fact that additional information about the tumor microenvironment (TME) is not typically available does not mean that it is not clinically relevant; it only means that the additional IHC stains required to identify macrophages and lymphocytes in the TME are not reimbursed.

What if the TME could be assessed without any additional time or cost on the part of the clinical laboratory? Though not commercially realistic using manual review techniques, an advanced AI algorithm could achieve this goal. AI is far superior to the human eye in detecting patterns that allow cells to be identified and classified across an entire tissue sample. What if a digital pathology solution could not only accurately detect PD-L1 reactivity, but also count and locate macrophages and lymphocytes and assess levels of tissue necrosis? Would an oncologist treating challenging patients benefit from this information? Although medical decisions must be based on clinically rigorous study data, the migration of ideas from research to FDA-cleared treatment typically takes decades. Oncologists perpetually find themselves in a grey area between cutting-edge research and fully validated, FDA-cleared treatments. The pathologist's goal is to provide treating physicians with the facts and tools they need to manage their patients. Artificial intelligence could be an important tool in fulfilling that mission – and only a centralized digital pathology provider would have the expertise, reach, and economies of scale to leverage that capability.

Roberto Gianani

IN MY VIEW

Opening Doors to AI-Enabled Pathology

Finding a low-resource route to AI-enabled digital pathology

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The COVID-19 pandemic changed what we define as "normal" in our lives – and many of those changes may be permanent. Take, for instance, digital pathology, which allowed us to continue working while avoiding unnecessary exposure during lockdown. Its adoption may have been rapid, but our use of digital tools will continue long after the crisis is over. Pathology is not new to the digital world – it has been over two decades since the introduction of whole-slide imaging (WSI) scanners. But as the world grappled with a deadly pandemic, digital pathology rose to the occasion and traveled like wildfire around the globe.

Digital pathology lets pathologists in their homes connect to colleagues in any part of the world in an instant. Once the glass slides are digitized using WSI scanners, the images can be sent anywhere for second opinions, remote diagnoses, or educational purposes – removing physical barriers that cost time and money. Digitizing also ensures long-term slide preservation, whereas glass slide quality can fade over time and necessitate re-staining. And, of course, digitization opens the door to automated, artificial intelligence (AI)-enabled disease diagnosis and prognosis models in laboratories with sufficient resources and infrastructure. These automated methods can pick up small pathologies that are more easily missed on a busy slide in a busy lab. In the near future, AI-enabled digital pathology tools will achieve diagnostic and prognostic capabilities beyond the scope of traditional microscopy.

Developing countries contain more than two-thirds of the world's population – and more than half of its cancer and endemic disease burden. Pathologists are scarce everywhere, but the situation is especially grave in the developing world. Digital and computational pathology can help – but AI-enabled techniques are beyond the reach of most low-resource organizations. Moreover, regulatory barriers and staff training present further challenges to adoption.

But all hope is not lost. Low-resource organizations can start their journeys toward digital pathology by leveraging resources from the open-source community. Many organizations offer free access to their WSI archives (for instance, The Cancer Genome Atlas, The Cancer Imaging Archive, the Digital Pathology Association's Whole-Slide Imaging Repository, and more), although rapid downloading and local storage of these large datasets still presents a challenge. Another option is to use a microscope connected to a camera. A pathologist can photograph a region of interest for a particular pathology and then annotate it to train an automated AI model using open-source software (for instance, QuPath, ImageJ, Cytomine, Orbit, ASAP, or others). In this way, pathologists can make disease models even without high-tech scanners, large hard drives, or high-speed Internet.

Worldwide, one thing is clear: developing countries are the biggest source of data that must be preserved to make reliable disease models, analyze trends, and predict outcomes. Information is the fuel on which modern algorithms run – and the foundation on which the future of precision medicine depends. If we take responsibility for saving this data now, pathologists, patients, and technology innovators all win. Let's work together to open the door to a new era of diagnostic medicine for all of humanity.

FEATURE

Pathobot: Deep Learning for Humans and Machines

When it comes to seeking out similar cases and second opinions, the pathology community is always ready to help – even the artificial members!

By Michael Schubert

When you'd appreciate a quick second opinion, what do you do? You might check with on-site colleagues or reach out to others via your smartphone. But, as COVID-19 continues to spur the rise of telepathology, social media is an increasingly popular platform for sharing and discussing deidentified cases. "Social media makes my life more exciting," says Celina Stayerman, a pathologist at Laboratorio TechniPath in Honduras. "And though I'm the only pathologist where I work, I'm never alone." Olaleke Folaranmi, of Nigeria's University of Ilorin Teaching Hospital, adds, "Some challenging cases I have posted to social media have posed great learning points for us. For example, the Nikolsky sign is negative in toxic epidermal necrolysis, but positive in disseminated varicella."

Within this vibrant international community of pathologists on social media, hierarchies are flattened and a new kind of organizational structure has emerged – around hashtags. Jerad M. Gardner, a pathologist at Geisinger Medical Center in Pennsylvania, explains, "After organizing the first live Tweet group at the United States and Canadian Academy of Pathology (USCAP) meeting in 2015, we realized we needed a formal list of subspecialty hashtags, e.g., #breastpath, #dermpath, and #gipath (1). The USCAP Social Media Subcommittee compiled this ontology (2), submitted it to Symplur, and we've all been using it since."

"Pathologists liked the bot so much, they contributed their own data to help improve its performance."

Years later, this structure attracted attention from computational fields. "We wondered if the hashtag-labeled photomicrographs on social media were data that could teach an artificial intelligence (AI) simple histopathology tasks," says Andrew Schaumberg, a postdoctoral fellow at Brigham and Women's Hospital in Massachusetts. "It turned out to be more complicated than the three-month summer project we anticipated…"

Fast forward to 2020 and this international group of 30 pathologists, computational scientists, and neuroscientists have published their study (3). Their work produced "pathobot," an AI-driven bot that searches social media to connect pathologists with similar cases. From pathology AI to 3D-printed smartphone-to-microscope mounts, we catch up with the group's endeavors to increase access to pathologists worldwide.

How it all began

Schaumberg cites a colleague as his inspiration: "Mariam Aly introduced me to Twitter, and I noticed pathologists posted photomicrographs. What a great source of data to download!"

Aly, who is an assistant professor at New York's Columbia University, says, "I've long thought that Twitter is useful for keeping up with – and sharing – science. Andrew didn't believe me at first – but he finally caved!"

After discussing their idea, the two decided to begin by consulting an Institutional Review Board and obtaining informed consent before downloading the (anonymized) data. But, despite their eagerness to begin, their need for help went beyond ethical implications. "I had a good experience mentoring a high school student the prior year," says Schaumberg. "I figured that, if I mentored two students at once, we'd start and finish this project in the summer of 2018!"

"Naturally, projects take time, but the global scale of the effort was very enticing," explains Thomas Fuchs, Co-Director of the Hasso Plattner Institute for Digital Health at the Icahn School of Medicine at Mount Sinai in New York. "It is a pristine example of how AI can help to democratize knowledge and be helpful worldwide – so we decided to proceed with this project in my laboratory."

The first pathologist to consent was Mario Prieto Pozuelo – a pathologist at Hospital Universitario HM Sanchinarro, Spain, who not only provided his data, but also wrote a three-page introduction to fluorescence in situ hybridization (FISH) to explain his cases. "It was a simple thing," he says. "There were many good questions. I'm happy to teach." Schaumberg highlights their good luck in finding many approachable pathologists early in the project, citing both Pozuelo and Laura G. Pastrián – a pathologist at Spain's Hospital Universitario La Paz – whom he says helped build his confidence in asking questions until he began recognizing slides himself. "Path Twitter is a fun place to share educational cases like these," says Pastrián, highlighting one of social media's greatest strengths.

"Diversity is fundamental to establishing the most general data with which to train the most general AI."

An eye to AI

Schaumberg says, "Training an AI to predict whether or not an image was H&E was the low-hanging fruit we did first. Beach photos are not H&E (surprise!), and neither are chest X-rays." But even this basic stain presents a challenge for a computer.

Aurélien Morini, a fifth-year resident at Université Paris Est Créteil, explains, "In France and elsewhere, H&E may include saffron to highlight collagen. Phyloxin may be included instead of eosin – but these are all still essentially H&E."

Schaumberg adds, "Diff-quik, PAS, CISH, trichrome, and even some red-variant IHC stains may be easily confused with H&E, both to an untrained eye and to AI (see Figure 1). My mentees and I had a lot to learn!"

Next, the team took on harder tasks, such as training an AI to distinguish tissue types in the various subspecialties. Such tasks are simple for human pathologists, meaning an AI that struggles with them may not add much value. Distinguishing between benign and malignant tissue, on the other hand, might save significant time that pathologists could then devote to more complex problems. Unfortunately, that distinction varies from one tissue to the next – and the algorithm didn't have a lot of data. To learn the difference, the creators first had to rigidly define both extremes.

"All disease is on a continuum," says Pastrián. "There is no hard line between 'benign' and 'malignant' – and some things, such as infectious disease, are neither." Colleagues add that the distinction often determines whether or not a patient will undergo surgery – and what the patient's outlook is over the next six months or longer. Stephen Yip, a pathologist at BC Cancer in Canada, offers an example: "The acknowledged definition of 'malignant' in epithelial cancers is the ability to breach the basement membrane to invade into the adjacent tissue, lymphatics, and blood vessels. Extensive invasion can mean this is no longer treatable with surgical resection." He explains that, although cytological appearance is typically associated with malignancy, the infiltrative nature of some tumors (such as primary diffuse CNS glioma or chordoma) means they are considered malignant even with "benign" cytology.

In pathobot's case, "containment" largely defined malignancy, but a number of other factors help define what the AI can – and cannot – do. For instance, it is not designed to predict whether or not a patient should get surgery. "It can also be helpful that AI learns on a case-by-case basis in a data-driven manner," says Schaumberg. With enough cases that carry a consensus opinion (benign, malignant, infectious, and so on), the AI can generalize a definition of each concept. "Unfortunately, hard lines are a necessary evil for an AI to learn distinctions like 'benign versus malignant' – even though disease in general is on a continuum. Perhaps, with more data, the AI will need fewer hard lines and assumptions to accurately learn."

He goes on to explain how pathobot works. "Given a photomicrograph, the AI is basically trained to answer a multiple-choice quiz question about what the photomicrograph depicts: a) nontumor/infection, b) benign, or c) malignant disease. However, 'benign' was a grey area, especially for disease that may become malignant soon." Collaborator S. Joseph Sirintrapun, Director of Pathology Informatics and a pathologist at Memorial Sloan Kettering Cancer Center, says, "We agreed to call this grey area 'benign/low-grade malignant potential.'"

Gardner adds, "Some prior work of ours similarly classified all disease as one of three categories: non-neoplastic, benign, or malignant (4)." But did that consensus definition of disease work for pathobot?

Schaumberg says no. "The AI's disease prediction performance was horrible at first!"

Defining the details

To improve pathobot's performance, Schaumberg implored his pathologist collaborators to give him clues – and they stepped up. Morini says, "I reviewed all my cases shared with Andrew, and how they were annotated. A pathologist posts one to four images in a tweet to begin to describe a case. Some images show only benign tissue, whereas others show the malignancy. The photomicrographs in a tweet are not necessarily all benign – or all malignant."

Sanjay Mukhopadhyay, Director of Pulmonary Pathology at the Cleveland Clinic in Ohio, says, "We thought it would be fair for the AI to be given both the photomicrograph and the tissue type, because pathologists know this, too. Tissue type matters because infectious disease is more common in pulmonary pathology than hematological pathology, for example."

Folaranmi agrees. "Speaking of tissue types," he says, "pathological processes, like Langerhans cell histocytosis, may be a daunting task. For instance, in lung, Langerhans cell histocytosis is considered a smoking-related reactive/non-neoplastic disease. However, in other tissues, Langerhans cell histocytosis may be considered neoplastic instead. Context matters."

Once the AI (and its creators) had been fully trained, it was deployed as "pathobot" on Twitter – where pathologists liked the bot so much, they contributed their own data to help improve its performance. But how did pathobot transition from predicting disease to seeking out and connecting pathologists with similar cases? "Many AIs learn to predict in a way that also gives a similarity metric," explains Schaumberg. "To such an AI, it's as though some diseases are 'closer together' than others. So our AI that has learned to make accurate predictions gives us search capability 'for free.'"

Networking skills

"If you type a search query into a search engine, you are the only one typing. In contrast, pathobot uses context from discussion threads surrounding a case on social media, so many pathologists are typing, thinking, and searching together," says Schaumberg. "This is one way pathobot tries to leverage 'more brains' to search for similar cases. The notifications it sends when its search results link to their similar cases are another way to bring in more pathologist brains."

But the most important question is – does it work? Pathologists agree that it does.

Stayerman says, "In my experience, pathobot finds similar cases (see Figure 2). These tend to be a mix of recent cases and others from a few years ago. The older cases, and the older discussions for those cases, are otherwise difficult to find in Twitter history." Like Stayerman, many pathologists use social media to "check their work" – for example, by comparing their diagnostic impressions or differential diagnoses to those of colleagues. But when a case is unusual or there's no time to spare, pathobot serves the same purpose. "Searching for appropriate older cases to review can be a prohibitively time-consuming task when there is no time to spare. Pathobot can help find these cases, uncovering helpful colleague discussions from the past. Reviewing them is definitely another useful check for me!"

Mukhopadhyay says, "I have tested pathobot occasionally for over a year. For the cases I've tested, I am impressed that pathobot's histopathology search results are similar to my test cases and that they are quickly produced. Lately, I've found that pathobot's horizons have expanded, with pathologists who have not been a part of its development using it."

And Mukhopadhyay's cases have been useful to others as well – Sofopoulos Michail, a consultant histopathologist at St. Savvas Anticancer Hospital in Greece who has also conducted occasional pathobot tests, says, "I was glad to get access to pathobot for a challenging mediastinal mass. Pathobot identified several cases similar to mine, including a case from Sanjay Mukhopadhyay."

"The constant exchange of knowledge, thinking processes, diagnostic criteria, work-ups, and great images – all this will ultimately help us standardize good practices worldwide."

Folaranmi has also conducted pathobot tests since 2019. "I remember sharing a case of intravascular papillary endothelial hyperplasia and mentioning pathobot to trigger a search. Pathobot's social media case database was smaller in 2019; however, it managed to find an intravascular papillary endothelial hyperplasia on PubMed and correctly predicted the case as benign. I think there is educational value in the search results pathobot finds."

That was a bumper year for social media interactions – and for pathobot. Daliah A. Hafeez, a pathologist at Saudi Arabia's King Fahad Armed Forces Hospital, says, "There were rounded structures in a liver subcapsular collection case of mine, and it wasn't clear if these structures were helminth eggs, nematodes, or lentils (see Figure 3)."

At this time, in early 2019, pathobot's PubMed search did not yet exist, but Schaumberg had internal tools that could search PubMed. Hafeez says, "Pathobot found a similar case of lentil on social media (1, 5) and his PubMed searches found a similar case of food residue mimicking disease in a patient with a history of emergency surgery (6). We're all working together here. I found the searches and literature reference helpful."

Stayerman adds, "I've used pathobot's keywords and requires commands to focus search results on a specific entity, for instance papillary lung adenocarcinoma. This is helpful if I have a diagnosis in mind already, especially a rare entity."

Pastrián, who is internationally renowned for her expertise in seeds, has a specific rare entity in mind. "I'm waiting for pathobot to make a seed atlas of all the beautiful tomato seeds and lentils on social media!" A pipe dream? Perhaps not. Pathobot's ability to search for cases of a more vegetarian nature has already been tested with some success – though the algorithm still has difficulty identifying seed species, such as soy. Schaumberg would like to address that in a future iteration of pathobot. "I think fixing that would be 'soy' much fun!"

Data in, data out

It's clear that pathobot has found favor with diagnostic professionals on Twitter – but what of computational colleagues in the lab? Schaumberg recalls presenting pathobot in a recent lab meeting and getting his audience excited about the possibilities. "Pathobot sounded like a fun project," says Richard Chen, a PhD candidate at Brigham and Women's Hospital. "I wondered if I could query for similar cases in real-time during his presentation." But Chen lacked one key thing – authorization for pathobot searches. Immediately after the presentation ended, he requested it. ("And he didn't let me forget!" adds Schaumberg.)

"I queried with a whole-slide image region-of-interest in glioblastoma (no IDH mutation or 1p19q codeletion), and Pathobot retrieved cases of glioblastoma from Twitter and PubMed!" says Chen. "Some of these had similar molecular alterations. Impressive!"

"It was probably luck that pathobot handled all that negation correctly," Schaumberg admits. "I was just saying in the lab meeting that 'no,' 'not,' and 'absence' can be challenging. For pathobot, we chose Twitter specifically because tweets are limited to 280 characters – so people tend to keep their language simple."

Pathobot's creators are now starting to do more with published cases from PubMed – for instance, sharing PubMed-based pathology quizzes daily on Twitter and inviting users to post their diagnoses and receive feedback. Schaumberg hopes that, in the future, this kind of data-gathering will power a smarter and more well-rounded pathobot. "There are a lot of whole slide images at The Cancer Genome Atlas that we'd like pathobot to search as well," he adds. "This is still at a preliminary stage, but it's important as more hospitals consider whole-slide image-based digital pathology."

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IN PRACTICE

One Step Beyond: Artificial Intelligence for Image-Based Prognostication

Leveraging artificial intelligence for tumor detection and prognostication

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It can be disheartening to hear pathologist colleagues say, "With artificial intelligence, I'll be out of a job in 10 years." It is reminiscent of 1999, when doomsayers expected Y2K to unleash technology Armageddon. The reality, of course, is more nuanced, but there is no denying that AI-related innovations will have a transformative effect on our discipline. Though many of its perceived benefits focus on improving diagnostic services, there is also scope to harness these innovations to bridge the gap between pathology and oncology.

When digital pathology and whole slide image (WSI) analysis transitioned from the research space into the clinical environment, they received a lukewarm welcome. Reluctance to engage with this technology is traceable to a lack of familiarity or training; belief that digital diagnosis is inefficient; higher levels of confidence in light microscopy; and individuals' thresholds for embracing new technology (1–3). However, as scanners, algorithms, and perspectives have matured, WSI-based diagnosis has proven comparable to that with light microscopy (4–6) and numerous large centers across the globe now run partially or fully digitized pathology workflows (3, 7).

This forward motion is key to the current state of affairs in histopathology. Globally, the discipline is under growing pressure – our increasing, aging population will yield a 60 percent increase in diagnostic demand by 2029. The increasing complexity of patient-tailored investigations will further exacerbate this burden (8), and the diagnostic backlog in the wake of the COVID-19 pandemic will have a compounding effect. Ironically, this rise in service demand is expected to be paralleled by a 30 percent fall in active pathologists relative to 2010 staffing levels (9). This dismal scenario is exemplified by figures from the Royal College of Pathologists' workforce census that reveal that only three percent of departments are adequately staffed to meet diagnostic demand – a situation echoed in the US by analogous workforce shortages (10–12) that will only be worsened by an incipient retirement crisis and a shortfall in trainee recruitment (10). The impact of the status quo is not insignificant on National Health Service coffers, addressing the shortfall by using locum doctors and outsourcing services costs an estimated £27 million per year in the UK alone.

"The disappointing reality is that none of these technologies have transitioned into routine reporting practice."

AI steps in

AI in digital pathology offers a range of potential diagnostic solutions with clear merits – yet it has received a cold shoulder in some quarters, something of a disappointment for the "third revolution in pathology" (13). Despite early teething problems, many AI-based solutions have shown potential clinical utility, albeit in an academic setting. One key benefit is that AI could shorten pathologists' reporting time; algorithms capable of tumor detection, cell counting, and mitosis detection are now increasingly available (8). Others highlight areas of interest for review within WSIs (1), reducing the time needed for a pathologist to scan a case at low power. This is particularly useful in biopsies and resection specimens that are known to be time consuming to report (for example, nodal [micro]metastases) or where multifocality is important (for example, breast and prostate specimens) (1, 14).

Busy clinical pathology departments, such as those dealing with high-volume primary care skin excisions, could also make use of simple algorithms (for example, cancer present or absent) to screen and prioritize malignant cases for review (7). They could also standardize diagnostic performance to offset inter- and intra-pathologist diagnostic discordance (15) – in essence, providing a second opinion. The possibility of bypassing ancillary testing and its allied delays is also welcome, highlighted by algorithms that resolve immunohistochemically stained HER2-equivocal cases without the need for fluorescence in situ hybridization (16). Notionally, the aim is to adopt such solutions clinically to accelerate case turnaround, minimize ancillary testing analytical time, improve diagnostic accuracy, and reduce costs. However, the disappointing reality is that none of these technologies have transitioned into routine reporting practice; their use remains largely confined to the academic setting.

Offering prognostically meaningful information that could guide patient management would be a further boon. And within the research environment, we now have tools at our disposal that increasingly attempt to link tumor morphology to the underlying biology and subsequent clinical outcome. However, this is much more than a simple exercise in satisfying academic curiosity; algorithms have been developed to appreciate the spatial distribution of tumor-infiltrating lymphocytes (9) and to capture tumor-associated stromal features (17) or microvascular proliferation (18) – all of which have demonstrated prognostic significance. Indeed, we feel the greatest promise can be drawn from these tantalizing early results suggesting that AI may be able to identify prognostic features that elude visual inspection.

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IN PRACTICE

Beyond Digital

Understanding barriers in transforming pathology from digital to computational

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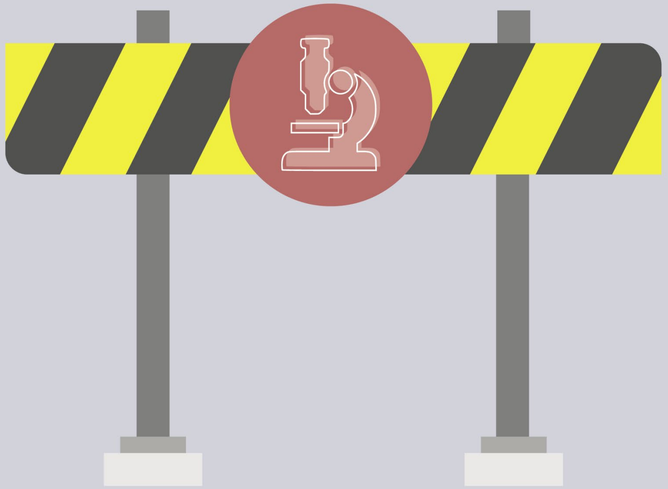

Pathology is involved in two-thirds of all diagnoses made in healthcare systems such as the UK's National Health Service – and an estimated 95 percent of clinical pathways rely on patients having access to efficient, timely, and cost-effective pathology services (1). However, the classical histopathology workflow from biopsy to a diagnostic report (Figure 1) takes up to 10 days on average in the US (2) and 14 days in the UK (3) – an excruciating wait for patients and their families.

The workload for diagnostic services will only continue to increase. On one hand, there is an increase in demand with the growing and aging population in the UK, and advancements in early detection and treatment pathways resulting in a predicted 28.4 million cancer cases in 2040, a nearly 50 percent rise from 2020 (4) – meaning that one in two people are expected to receive a cancer diagnosis in their lifetime (5). On the other hand, the number of practicing pathologists is declining. A 2018 workforce census from the Royal College of Pathologists showed that a quarter of all histopathologists are over 55, most of whom are expected to retire by 2023 (6). Furthermore, an all-time low number of trainee doctors are choosing to specialize in pathology with only 3 percent of NHS histopathology departments having enough staff to meet clinical demand (6).

To add to the problem, the COVID-19 pandemic has significantly disrupted healthcare systems with the shutdown of nonessential services and drastic changes in patient behavior. By March 2021, 4.7 million patients were waiting for treatment (7). An additional £2 billion per year is needed to recover this backlog over the next three years, requiring an estimated 11 percent increase in NHS activity – that is, an extra 4,000 consultants and 17,000 nurses per year (7). With pathology involved in 95 percent of clinical pathways and diagnostics, the pandemic has exacerbated the pressure on pathology departments.

"Ethical and regulatory considerations impact healthcare pathways and must be addressed to deliver the future of patient-centered medicine."

The rise of digital pathology

Telepathology and digital pathology emerged in the 2000s (8). The development and introduction of whole-slide imaging (WSI) enabled pathologists to "read" digital images on a computer screen instead of on a physical slide under a microscope (Figure 2).

The digitization of histology slides with remote image access offers several immediate benefits. It allows pathologists to report anytime, anywhere. This in turn reduces delays associated with the transportation of glass slides, improves laboratory workflow with reduced costs and increased workforce capacity, and provides pathologists with easier access to colleagues for second and expert opinions. Datasets of annotated digital images can also serve as valuable platforms for training junior pathologists and developing automated tools that increasingly support and streamline clinical decision-making. More recently, the COVID-19 pandemic has essentially demanded the adoption of digital pathology due to restricted access to pathology labs and a need for remote work. However, despite these benefits, the digitization of pathology has been slow, business cases have failed, and implementation projects have stalled (9, 10).

The cause of the stall

For the past 15 years, digital pathology has promised to change pathologist workflows. However, efforts to digitize pathology are yet to yield the promised increases in operational efficiency (10). This is primarily due to barriers in clinical adoption, infrastructure implementation, and operational excellence. These barriers are reflected in the underwhelming digital transformation of pathology laboratories, with only 31 percent of healthcare providers across the UK starting to invest in applying digital pathology technologies to steps in their clinical diagnosis workflows (11).

To deliver the promises of digital pathology, key stakeholders across the clinical workflow must work together to facilitate clinical adoption. Implementation and optimization of digital pathology is typically initiated and supported by laboratory managers and lead pathologists as a collaboration. Hospital laboratories invest in the hardware and software, as well as biomedical and IT staff to manage and deliver this digital infrastructure. Pathologists and clinicians define how the technology is integrated into clinical workflows and decision-making. Thus, digital pathology companies must play their part in providing first-class customer success programs and staff training schemes to encourage clinical buy-in and adoption.

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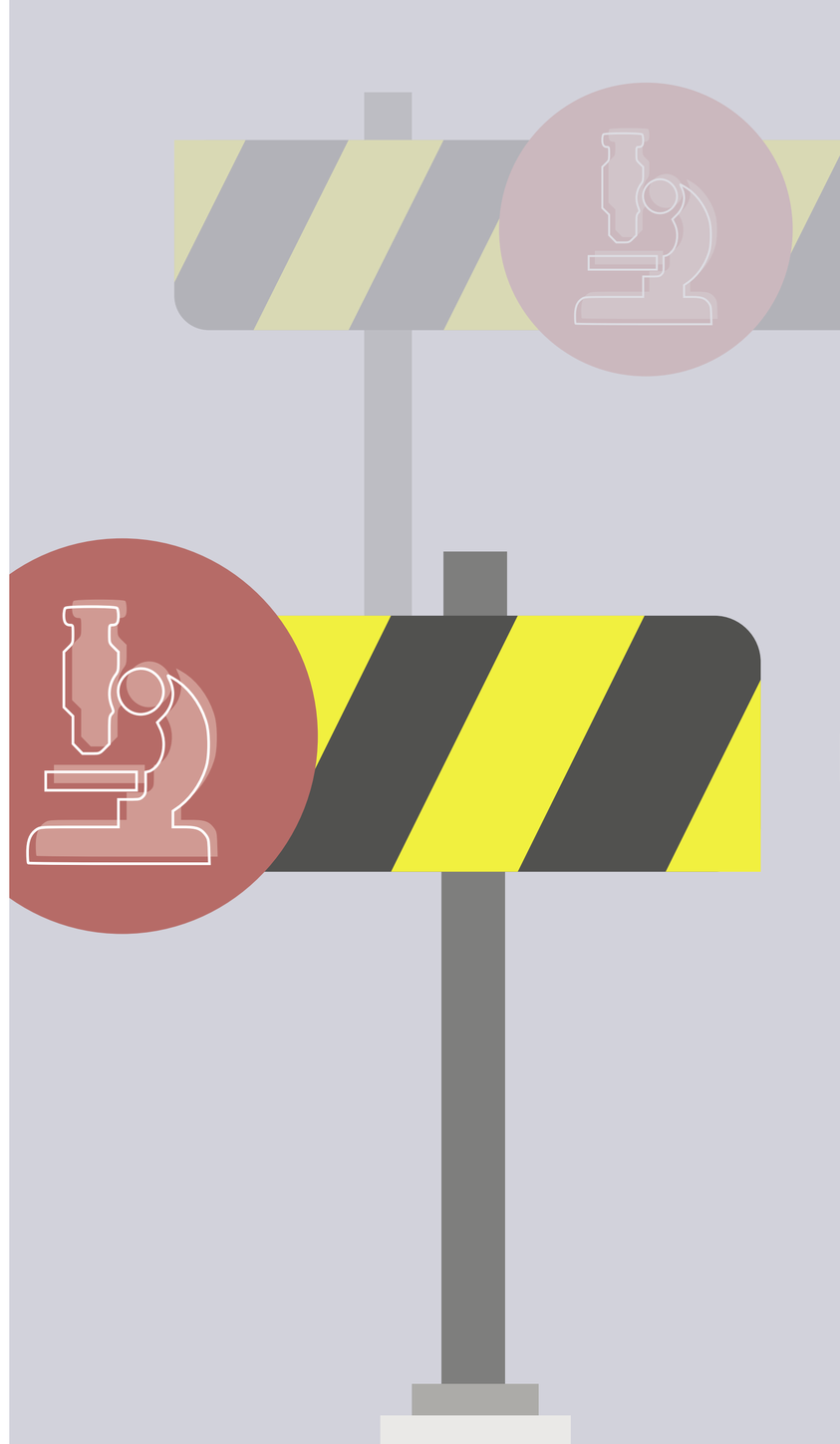

SITTING DOWN WITH

The Digital Pioneer

Sitting Down With… Rajendra Singh, Professor of Pathology and Dermatology, Director of Dermatopathology, and Associate Chair of Digital Pathology at Northwell Health, New York, USA

You're a pioneer in digital pathology – what led you to the field?

When I worked at the University of Pittsburgh Medical Center, we had residents, fellows, and visitors come from all over the world to train with us – and we had a lot of slides being digitized. I believe that, once you look at a digital slide, you realize it's going to change the way pathology is practiced and taught. I came to the US because I didn't have the resources to train myself, but digital pathology suddenly opened a lot of doors. Digital slides could be uploaded to the cloud so that anybody sitting in any country could log onto the platform and start teaching themselves pathology.

What inspired you to create PathPresenter?

I realized that I needed to make the resources we had at large academic institutions available to people anywhere in the world, but that was extremely difficult because the slides all came from different scanners that produced different file formats and therefore needed different viewers. To remedy this, we built a platform in which we could put the slides on the cloud, have the back-end software convert them into a single format, and then make them available on a single viewer. At first, it was just for our own use – so that we could use these digital slides for teaching – but, when other people saw the platform, they told us it was the sort of resource they had always needed. After that, institutions became interested and wanted to use the platform for their own internal teaching. That's when PathPresenter became a company and we hired people to build these platforms for interested institutions.

Last year, you hosted the first online pathology review for residents on PathPresenter. How did it go?

When COVID-19 hit, the entire medical education system had to go online – the question was, "How can we do it in a way that's easy to use and can bring together files from different scanners?" I reached out to a few people who are prominent on social media and, together, we built a conference in which we showed people how they can use these files for teaching – all for free. All the conference speakers volunteered and had the opportunity to pre-record their lectures if the timing didn't suit them. We also built a Q&A session that included even the pre-recorded lectures – when an attendee entered a question on the platform, the speaker received an email and could go online to answer the question. These tools weren't even heard of two years ago – and now we have an online community of renowned experts who are willing to put in the time to teach the entire world. More than 6,000 people registered for the conference (which is usually unheard of!) and we received a lot of good feedback that we'll be using to improve the platform.

Tell me about the new initiatives coming up on PathPresenter…

We are creating a section called "high yield" with the bread-and-butter cases that every trainee should know. We have teamed up with various societies and institutions whose members are going to build these high-use cases in which experts will point out features on the digital slides that helped them make a diagnosis. Because they're doing it on the cloud instead of on a multi-headed scope, it becomes an "infinite-headed scope!

How did you end up on the editorial board of the WHO Classification of Tumours, 5th edition?

I was presenting at a conference in Chicago, talking about how PathPresenter can be used for data sharing in education. Ian Cree, the current pathology leader at WHO and the person in charge of the 5th edition, was sitting in the audience. Afterwards, he approached me and said they were moving the Blue Books to an online digital format, but wanted to make sure they were in line with how pathology is taught. Of course, there is no way you can teach pathology without having access to the slides. When he saw how PathPresenter worked, he realized it had the same mission as the WHO – to facilitate the spread of information around the world and democratize availability of resources, especially to low- and middle-income countries. Because of that, he asked me if I'd like to be on the editorial board – and, of course, I accepted.

Do you have any time management tips for lab medicine professionals?

It has to be a passion. It's not about making money – do your job and money will come. If you have a passion, it becomes much easier because you're not worried about how much time you're putting in. Not everyone can put all of their time into building platforms like PathPresenter; I have been lucky enough to have institutions support me along the way. But there is no magic formula for time management – the more you want to do it, the more passionate you will be about your projects, and I believe then you will find the time to fit them around your day-to-day work. In the end, it is all about patient care – and if there is anything you can do to help our patients, the world will come together to help you achieve your goals.

OWKIN

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AI Diagnostic Screening for Microsatellite Instability, an Owkin Diagnostic

Q&A with Arnaud Fouillet, Owkin Product Manager, on making inroads with digital pathology AI models turned diagnostics

Why create an MSI pre-screening solution based on digital pathology?

Microsatellite instability (MSI) is a phenotype found in various cancer types and diagnosed for hereditary, prognostic, and therapeutic purposes. Recent guidelines recommend universal MSI screening for patients with colorectal cancer; and it is also becoming more commonplace with other types of cancers (stomach, endometrium). As you can imagine, this increase in testing directly impacts pathology labs and pathologists' workloads. At Owkin, we wanted to create a diagnostic solution that would alleviate the burden caused by increased MSI testing – and we're certain AI has a key role to play here.

How does it work?

At Owkin, we are dedicated to developing AI solutions for precision medicine and, over the years, have developed a great expertise in pathology slide analysis. Our solution enables dMMR/MSI pre-screening of colorectal cancer patients directly on digitized H&E slides thanks to our AI predictive model. It is automated, compatible with most WSI formats, integrated into digital pathology workflows, and respects data privacy. It only takes a few minutes to process the digitized slide and receive the result. With this new approach, pathology labs will be able to significantly decrease the burden of immunohistochemistry and/or PCR assay associated with MMR/MSI testing. The increasing demand that pathology labs are under is a risk for the time it requires to obtain results and may ultimately impact the availability of the test. With this in mind, we have developed a solution that permits a "preparation-free" workflow without sacrificing quality, thanks to highly reproducible results.

What can we expect from this technology in the future?

Our ambition at Owkin is to develop solutions for pathologists to increase their role in precision medicine while saving time. To reach this objective, we want to develop a complete toolbox that covers the automated prediction of multiple biomarkers and outcomes for various types of cancer. We have developed another predictive model for the risk of relapse in breast cancer. We are also working to extend MSI pre-screening to cancers other than colorectal, especially where dMMR/MSI prevalence is rare and routine testing is not done. Regulatory authorities are increasingly aware that AI technology can make a difference in precision medicine approaches; we expect to see more of these tools to support workflows and aid in outcome prediction in the near future.

When will it be available for use?

Currently, our models are used for research purposes only. We aim for CE marking mid-2022 and FDA clearance is expected in 2023—making these medical devices available soon for pathologists in routine clinical practice.

TO LEARN MORE ABOUT OUR MSI SOLUTION AND OWKIN DIAGNOSTICS CONNECT WITH US WWW.OWKIN.COM/DIAGNOSE