NOVEMBER 2021 # 80

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*Refer to instructions for use for more information.

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Agilent
Trusted Answers

Knowledge Is Power

But, to offer this gift to patients, we must provide both the information and the interpretation

Recently, I had the opportunity to participate in a clinical trial. The carrot dangling in front of me was a better understanding of my SARS-CoV-2 antibody profile and, therefore, my protection from COVID-19. I was intrigued; after all, knowledge is power – especially in a world still far from the end of a pandemic (and when the publicly available information on immunity is unreliable at best). Do antibodies decline over three months, six months, or one year? Do the remaining antibodies have neutralizing ability? What about cellular immunity? Should we be worried?

The process was simple – a blood sample couriered to the lab, a brief wait, and then a report that showed my IgG, IgM, and IgA responses to various components of the virus. One thing jumped out at me as soon as I read the report: a section that broke my results down into three simple yes-or-no questions that could be understood by any reader. Was there evidence that I had been either infected or vaccinated? Was there evidence of an immune response? And was there evidence that this immune response was protective? I didn't need to be an expert to interpret the results, nor did I need expert guidance (although this, too, was provided). I had the power to read and understand my own health information.

Immediately, the knowledge made a difference in my life. In a sense, I learned two things by participating in the study: my immune status with respect to COVID-19 and how important it is for patients to receive their test results quickly – and with appropriate guidance. Both aspects are key; although it's stressful to wait long days or weeks for health information, it's no less so to receive information without interpretation – and assistance from "Dr. Google" often causes more harm than good.

Many institutions are now including notes to patients in their pathology reports in an attempt to deter them from calling on Dr. Google (or Facebook, or TikTok, or Great-Aunt Martha…). Have you tried including patient education in your reports? If so, let us know – and tell us what difference it has made in your patient community. I know it made a significant difference to me!

Michael Schubert
Editor

In advanced ovarian cancer,

If you're not testing for HRD, you're not seeing the whole picture

1 in 2 women with HRD-positive tumors do not have a *BRCA1/2* mutation[1-4]

Homologous recombination repair deficiency (HRD) testing identifies tumor characteristics—beyond *BRCA1/2* mutation—that make it sensitive to PARP inhibition.[1,5]

Personalized medicine begins with personalized pathology. Discuss establishing a testing protocol for HRD in ovarian cancer with the multidisciplinary team at your institution.[6-8]

Learn more at **testforHRD.com**

BRCA, breast cancer susceptibility gene; PARP, poly ADP-ribose polymerase.

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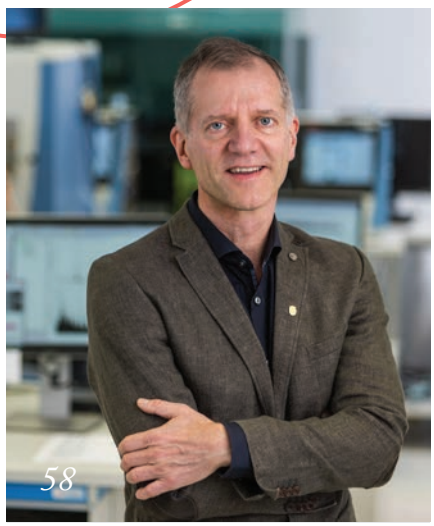
Contents



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Change of address info@thepathologist.com
Hayley Atiz, The Pathologist, Texere Publishing Limited, Booths Park 1, Chelford Road, Knutsford, Cheshire, WA16 8GS, UK

General enquiries
www.texerepublishing.com | info@thepathologist.com
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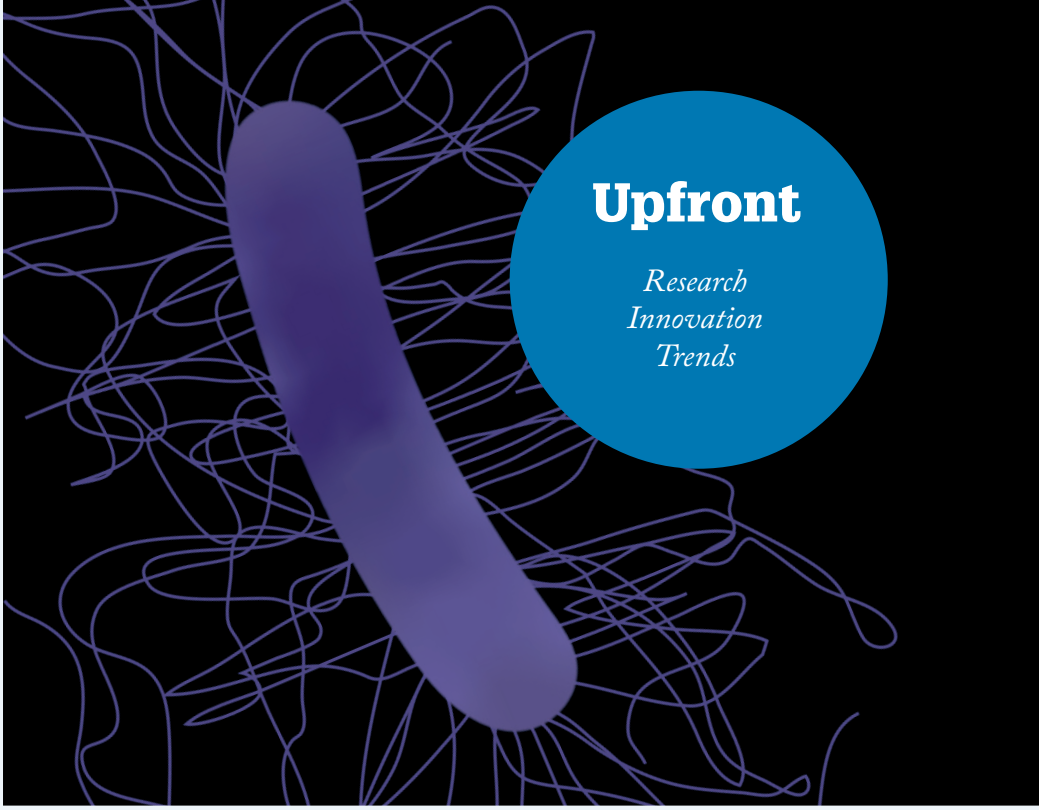


C. difficile, But Not Impossible

Surface-enhanced Raman spectroscopy could be the key to a fast and accurate clinical test for *C. difficile* infection in hospitals

Clostridioides difficile is notorious among hospital patients and staff for its ability to infect the bowel and cause (sometimes deadly) diarrhea. Because of its high toxigenicity and increasing antibiotic resistance, early diagnosis of *C. difficile* infection (CDI) is vital to stopping the spread of this disease and ensuring effective treatment. But current testing methods have a number of limitations; they cannot accurately determine infection severity, offer low sensitivity, and do not allow for quantification.

By combining the benefits of a lateral flow assay (LFA) with surface-enhanced Raman scattering (SERS), researchers from the University of Strathclyde and Newcastle University, UK, have overcome these limitations and offered hospital laboratories an ultra-sensitive, fast, cheap, and user-friendly test for CDI.

Their SERS-based LFA platform enables sensitive quantification (down to 0.01 pg/µL) of two key biomarkers, SlpA and ToxB, in 20 minutes. Importantly, this is the first time a duplex test for both biomarkers has been studied – and it could offer more accurate CDI diagnosis (and pathogenicity determination) without cross-reactivity from similar species. "Also, the use of the handheld Raman spectrometer means this measurement can be done at point-of-care and is highly portable, making it suitable for use in a wide range of situations," says Duncan Graham, Head of the Department of Pure and Applied Chemistry at the University of Strathclyde.

The Newcastle team had previously worked on a *C. difficile* assay with lateral flow, but the method (which relies on a visual assessment with the naked eye) wasn't sensitive enough for use in a clinical setting. "When we started collaborating with Neil Keegan from the Translational and Clinical Research Institute at the University of Newcastle, we recognized that the lateral flow assay could be merged with SERS detection to give the sensitivity required," says Graham.

The team's next step is to move onto clinical samples. "So far we've used simulated clinical samples (synthetic feces), but it's time for the real stuff now," adds Graham.

Reference

1. *WA Hassanain et al., Analyst, 146, 4495 (2021). DOI: 10.1039/D1AN00726B.*

TIMELINE

Virchow's Archive

The life and times of Rudolf Virchow

October 13, 1821
Born in Schievelbein, Kingdom of Prussia

1843
Graduated as a doctor of medicine from the University of Berlin's Friedrich Wilhelm Institute

1847
Defined a blood disease of reversed white and red blood cell balance and named it "leukämie"

RESEARCH ROUNDUP

The latest advances in pathology and laboratory medicine

Testing for TB

Next-generation sequencing of urine cfDNA has been found to be a valid biomarker of tuberculosis (TB) (1). The study found that TB cfDNA was significantly shorter than human genomic cfDNA, which could inform the development of improved assays for diagnosing TB from urine cfDNA.

Saliva Screening

Despite rising rates of human papillomavirus (HPV)-driven head and neck cancers, biomarkers are limited. However, high-risk HPV DNA has been successfully detected in 72 percent of HPV-driven oropharyngeal cancer patients' saliva and tumor p16 overexpression was observed in 89 percent (2). At a five-year follow-up, salivary HR-HPV-positive patients had a survival advantage over HR-HPV-negative patients.

Stress Test

A novel microfluidic assay for testing the effects of cyclic hypoxia on red blood cell (RBC) biomechanics has found that cyclic hypoxia alone can lead to mechanical degradation of the RBC membrane (3). RBCs affected by sickle cell disease are also less deformable and exhibit less fatigue resistance to cyclic hypoxia than normal RBCs.

Deep Learning Development

Using routine histopathology images, a new deep learning model, "DeepGrade," has shown independent prognostic value for risk stratification of breast cancer patients into the Nottingham histological grade 2 group (4). The method could provide a cost-effective alternative to molecular profiling.

Chain of Command

Patients with light chain-predominant multiple myeloma face a significantly higher mortality rate, which may be associated with renal damage caused by excess free immunoglobulin light chains (5). Researchers suggest early aggressive chemotherapy, plasmapheresis, and dialysis could help reduce renal damage, but further investigation is needed.

References

1. *A Oreskovic et al., Int J Infect Dis [Online ahead of print] (2021). PMID: 34562627.*
2. *C Ekanayake et al., J Mol Diagn, [Online ahead of print] (2021). PMID: 34325059.*
3. *Y Qiang et al., Lab Chip, 21, 3458 (2021). PMID: 3437862.*
4. *Y Wang et al., Ann Oncol, [Online ahead of print].*
5. *G Singh et al., Lab Med, [Online ahead of print] (2021). PMID: 34388245.*

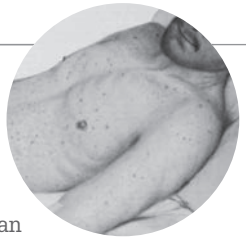
That's the SPIRIT

New guidelines aim to address variability in pathology evaluation in clinical trials

To address the variability in the way cellular and molecular pathology are reported in clinical trial protocols, an international group of cancer researchers has published new guidelines – named "SPIRIT-Path." Within the guidance, SPIRIT-Path recommends that "protocols should document the individuals, processes, and standards for all cellular and molecular pathology components of the trial, including all stages of the specimen pathway and any digital pathology methods, with specific consideration of the value of trial data and biological tissues for additional translational studies (1)."

Tim Kendall, Co-Chair of the National Cancer Research Institute's SPIRIT-Path working group, said, "The SPIRIT-Path extension will allow investigators to comprehensively address the cellular and molecular pathology aspects of trial protocols, ensuring adequate skills and resources are available at trial commencement, and fully leverage the value of biospecimens for translational research (2)."

See references online at: tp.txp.to/spirit



1848
Investigated an epidemic of typhus in Upper Silesia, inspiring his lifelong interest in social medicine

1855
Published his observation that *"omnis cellula e cellula"* ("every cell stems from another cell") – launching the field of cellular pathology

1859
Elucidated the mechanism of pulmonary thromboembolism

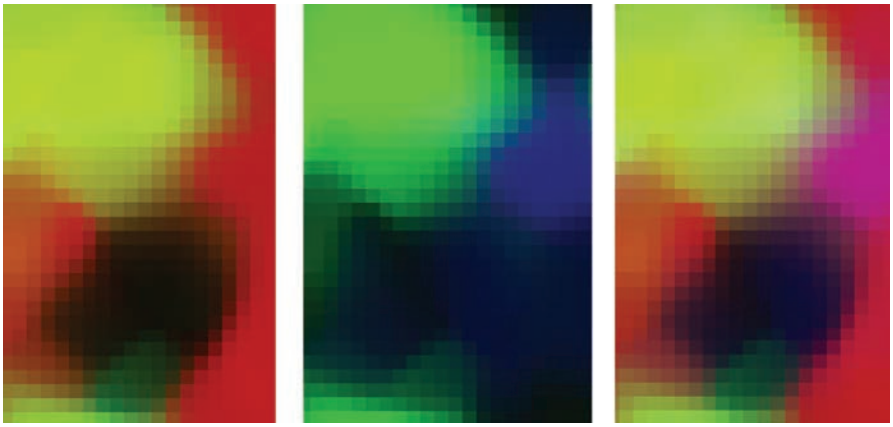
1874
Developed a standardized technique for performing autopsies

With a Little Help

Improving artificial intelligence for leukemia and lymphoma diagnostics

When it comes to artificial intelligence (AI) diagnostics, there are discrepancies between labs – with smaller standalone labs often yielding too little data to train highly accurate AI models. For leukemia and lymphoma diagnostics, multiparameter flow cytometry (MFC) is a vital tool in the pathologists' toolbox; however, protocols are subject to change depending on individual labs' diagnostic workflows and available cytometers. Could the two methods help each other out?

A group of researchers at the University of Bonn have combined transfer learning (a machine learning technique) with MFC to improve the robustness of AI in leukemia and lymphoma diagnostics (1). "The gold standard is diagnosis by hematologists, which can also take into account results of additional tests," said Peter Krawitz of the Institute for Genomic Statistics and Bioinformatics at the University Hospital Bonn (2).



Credit: Max Zhao.

"The point of using AI is not to replace physicians, but to make the best use of the information contained in the data."

The workflow takes AI models that are trained on a specific MFC panel and extends them to multiple MFC panels and data sizes. The team found that this extension improved AI performance and achieved high accuracy for multi-label classification of hematological malignancies across datasets. The workflow also enabled models to quickly adapt to changes in the data – making it accessible for a variety of routine diagnostic settings. Though the model's diagnosis is only a suggestion and requires physician verification, lead author Nanditha Mallesh noted that "AI takes full advantage of the data and increases the speed and objectivity of diagnoses (2)."

The researchers have made the data and software freely accessible – and their collaborators at res mechanica GmbH have created a web service to make AI more accessible to users who lack bioinformatics expertise. Hannes Lüling, founder and CEO of res mechanica GmbH, stated, "We want to enable the exchange of anonymized flow cytometry data between laboratories and in this way create the conditions for even higher quality in diagnostics."

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1. *N Mallesh et al., Patterns, 2, 100351 (2021).*
2. *University of Bonn (2021). Available at: https://bit.ly/3BLQOWw.*

Removing Race from the Equation

New recommendations aim to reduce racial health disparities in diagnosing kidney disease

To reduce racial health disparities, researchers have suggested a new approach for estimating kidney function that removes race from the equation (1). "Our research showed that if you use a blood cystatin C test instead of a blood creatinine test, you don't need to include race to get a similarly accurate estimate of kidney function," said Alan S. Go, co-senior author on the study (2).

The results have informed the National Kidney Foundation and the American Society of Nephrology Task Force's final report on diagnosing kidney disease without a race variable (3). Within the report, the group recommends use of the new eGFR 2021 CKD EPI creatinine equation, while increasing use of cystatin C combined with serum creatinine to confirm glomerular filtration rate or kidney function assessment.

References

1. *CY Hsu et al., N Engl J Med, [Online ahead of print] (2021). PMID: 34554660.*
2. *S Rochman, H Tremblay (2021). Available at: https://k-p.li/3iCOIRl.*
3. *C Delgado et al., Am J Kidney Dis, 78, 103 (2021). PMID: 33845065.*

IMAGE OF THE MONTH

Bone Marrow Model

"The upper part of the illustration (where the bone marrow has been omitted) shows the spongy bone meshwork composed of anastomosing bone trabeculae. Small spaces occupied by osteocytes are seen. In the lower part, the bone marrow occupies the spaces between the trabeculae. Numerous yellow adipose cells can be distinguished under low magnification."

By Bernard Kawa Kac

See the interactive 3D illustration at: tp.txp.to/3d-bone-marrow

Do you have a photo suitable for Image of the Month?
Send it to edit@thepathologist.com

QUOTE of the month

"A key attraction of laboratory medicine and pathology for me is figuring out how the human body and disease works, while also realizing that diseases don't read textbooks. To be successful in this field, you need a solid base of knowledge but [must] allow room for endless nuance."

Kelly Swails (@kellyswails)
Read the original tweet here: tp.txp.to/kelly.s/twt

Drillers Versus Scanners

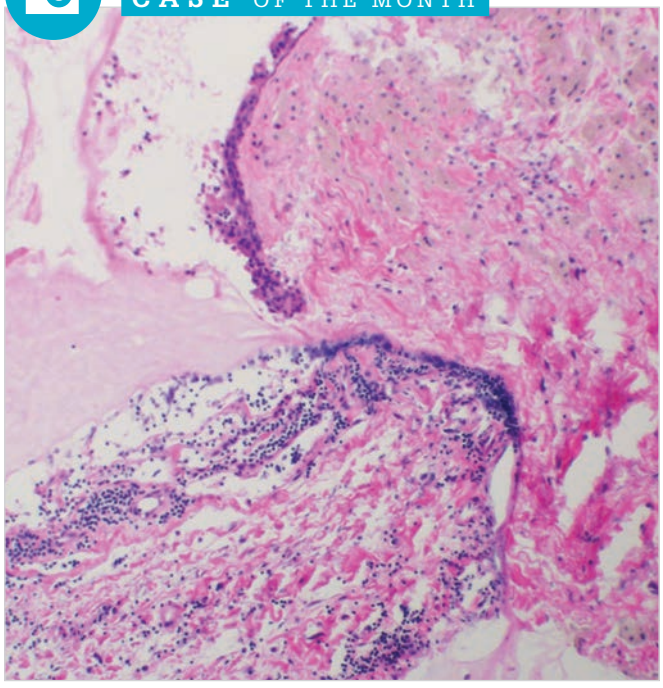
How do pathologists visually get the most information from digital breast pathology slides?

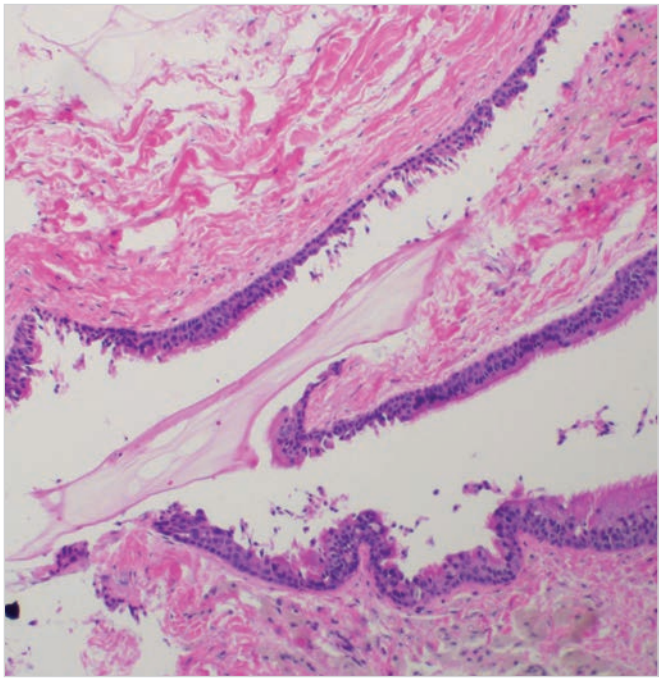
Diagnosing from medical images has become much easier in the digital age – and whole-slide images can offer gains in both processing and accuracy. But what is the most effective visual technique for evaluating slides in the digital realm – scanning the XY plane or "drilling" by zooming in and out of the Z plane? A group of researchers tracked eye movements to compare how pathologists and radiologists visually assess breast pathology slides – and established that, whereas pathologists gain their critical diagnostic information primarily from scanning, radiologists prefer drilling to interrogate critical features (1). They also found that pathologists' scanning rates correlate with higher diagnostic accuracy, but further work is needed to determine whether there is a causal relationship between scanning rate and accuracy. In the meantime, perhaps it's time to consider – how do you review your slides… and is there a better way?

Reference

1. *T Drew et al., J Vis, 21, 7 (2021). PMID: 34636845.*

CASE OF THE MONTH





A 41-year-old female presented with an 8.2x4.2 cm left anterior mediastinal mass incidentally detected via computed tomography. She reported some mild night sweats, but no fever or weight loss. Serum beta human chorionic gonadotropin was negative, making germ cell tumors less likely. Follow-up alpha-fetoprotein and anti-acetylcholine receptor antibody were also negative. Fine-needle aspiration revealed benign ciliated epithelioid cells. CT-guided biopsy revealed fragments of ciliated epithelium lining fibrous tissue and cystic contents as demonstrated in the histologic figures below.

What is the most likely diagnosis?

a) Branchial cleft cyst
b) Mature cystic teratoma
c) Thymoma
d) Metastatic cystic squamous cell carcinoma

Answer to last issue's Case of the Month…
e) *Trypanosoma cruzi*

This patient has megacolon of Chagas disease (CD), which is caused by the flagellate protozoan *T. cruzi*. Chronic infectious megacolon is found in approximately 20 percent of CD patients. The above case had a descriptive pathological diagnosis of fibrosis of the lamina propria, congested blood vessels, hyperganglionosis, neurotization of submucosal and myenteric plexus, and hypertrophy of the muscularis propria. Though this specimen did not show histological changes pathognomonic of CD, its diagnosis can be inferred from the clinicopathologic data and the serologic studies performed prior to surgery. Patients with CD may also develop megaesophagus and many have signs of chronic progressive Chagas cardiomyopathy. Chagas disease is endemic in parts of Brazil, most notably in the states along the Atlantic coast in the east and in the south and southwest regions of the country.

Submitted by Deilson Elgui de Oliveira, Associate Professor of Pathology at UNESP, Faculdade de Medicina de Botucatu, Brazil.

To register your guess, please go to http://tp.txp.to/1121/case-of-the-month
We will reveal the answer in next month's issue!

Case of the Month is curated by Anamarija M. Perry, University of Michigan, USA.

Watch This Space

The power of genetic analysis is undisputed – but relying on sequence information alone means losing critical information embedded in the tumor microenvironment. Here, we discuss spatial biology approaches with Carlo Bifulco, CMO of Providence Genomics and Director of Translational Molecular Pathology at the Earle A. Chiles Research Institute, Portland, Oregon, USA...

How did you get involved in spatial biology?

It began before immuno-oncology was widely recognized, when we learned, thanks to the pioneering work of INSERM's Jérôme Galon, that the quantification of T cells in the tumor microenvironment (TME) could predict clinical outcomes in colon cancer patients. That opened my eyes to the importance of the host-tumor interaction and I realized that the next logical step would involve multiplex immunohistochemistry/immunofluorescence biomarkers (mIHC/IF). Thereafter, I was fortunate to work on multiplexed approaches with Bernard Fox, who leads a team of immunologists at the Providence Cancer Institute. We were among the first to demonstrate the advantages of mIHC/IF for gaining insights into tumor biology and predicting patient outcomes.

How might spatial biology advance cancer pathology and immunology?

The host-tumor struggle plays out in the TME, but conventional analytic approaches such as tumor sequencing cannot provide a full representation of the TME – only spatial biology can do that. Indeed, spatial approaches are essential to understanding molecular interactions in the 3D space of the TME. Furthermore, spatial biology can support research from early biomarker discovery to late-stage translational research and therapy development. Companion diagnostics developed with the assistance of spatial biology will have more precise directionality than current biomarkers such as PD-L1 IHC. Also, I expect spatial approaches to guide the development of novel, rational therapy combinations in oncology. Importantly, spatial biology will provide much-needed clarity to immuno-oncology, where our current understanding of therapeutic mechanisms of action is still imperfect.

Spatial biology will also benefit from combination with other approaches. For example, mapping spatial biology data to single cell RNASeq data can support the early stages of therapy development by providing us with deep insights into the mechanisms that underlie patterns of host-tumor interactions in the TME. In brief, spatial approaches may enable us to unmask underappreciated aspects of TME biology, improving current therapeutic approaches and suggesting better immuno-oncology strategies.

What hinders broad adoption of spatial biology solutions?

The key issue is one of reproducibility. This needs to be addressed at every step in the process, from antigen retrieval/unmasking and tissue handling to the final pathological interpretation. This is essential to generate adequately reproducible data, without which we cannot translate discoveries into new therapies and diagnostics. Another key need is to develop a stack which is multilayered, not confined to a single layer – a reproducible, vertical solution.

Finally, the practicality of spatial biology needs to improve significantly; it is still very labor-intensive. And, because spatial biology generates very large datasets, it requires analytical methods that are both user-friendly and suitable for big data. In summary, spatial biology must become more reproducible and easier to perform if it is to be broadly adopted.

How do you envision the future of spatial biology?

I foresee a situation in which investigators can refer to a catalogue of biomarkers, choose the ones that best apply to a particular tissue or TME, and employ them via a simple protocol that generates reliable data. This ease of use will be maintained throughout the experimental pathway, from antigen retrieval and tissue staining to statistical analysis of the results.

What key messages regarding spatial biology would you like to convey?

To pathologists, I would say: watch this space! Pay attention to the rapidly evolving field of spatial biology and get involved if you can. It has potential beyond research and, I believe, will soon provide us with improved diagnostic tools that will lead to better clinical decisions. As pathologists, you will be the leaders of this change, so you should become familiar with spatial approaches as soon as you can. And remember – oncology will benefit from greater involvement with the pathologist community because interpreting spatial biology data requires morphological expertise. Without such expertise, patients will suffer worse outcomes; that's why it is essential for pathologists to more deeply engage with this field to the benefit of all.

In My View

Experts from across the world share a single strongly held opinion or key idea.

Big Data Or the Right Data?

Hidden information in digital H&E images can revolutionize pathology-oncology crosstalk

By Satabhisa Mukhopadhyay, Founder and Chief Scientist at 4D Path, and Tathagata Dasgupta, Founder and CKO/CTO at 4D Path, Newton, Massachusetts, USA

Applying artificial intelligence (AI) to digital pathology demonstrably streamlines workflows. Image quality improves, image acquisition and viewing are more efficient, teaching and research are augmented, and clinical sample testing is simplified. Nevertheless, significant challenges remain for deployment of AI solutions in digital pathology (1) – and the biggest of these is noise.

"Technical" noise stems from variability in slide and image preparation; sources include debris or contaminants, tissue tears or folds, retraction artifacts, hematoxylin and eosin (H&E) staining protocol variations, differences in staining intensity (e.g., due to tissue thickness or local image defocusing/aberration) and format variations between scanner platforms. "Biological" noise, by contrast, arises from tumor heterogeneity – and therefore harbors clinically useful information. In a perfect world, AI-based digital pathology tools would cancel out technical noise while capturing the diagnostic value hidden in biological noise. How close are we to this ideal?

Unfortunately, standard AI techniques cannot accommodate the pervasive variability of H&E histopathology images; the systematics and abstraction capabilities of current deep learning algorithms are inadequate. Furthermore, if we attempt to break down variability – for instance, from a cell or tissue perspective – we generate a huge number of patterns. This in itself causes significant problems, because we cannot collect enough structured or labeled data of sufficient quality to account for all such variation. Single-task-oriented AI algorithms with binary discrimination capabilities are already challenged by the demands of a multi-task-oriented diagnostic environment; data overload further complicates the situation.

Note, too, that deep learning algorithms use network architectures optimized for fast, heavy parallel computation of spatial and temporal correlations using layers of feed-forward or feedback loops. This means they are not necessarily optimized for pathologists' needs – the efficient interrogation of complexities associated with tumor biology – and consequently do not support rational decision-making. Moreover, their reliance on graphics processing unit (GPU) clusters and heavy-duty clinical system integration makes them costly.

"Standard AI techniques cannot accommodate the pervasive variability of H&E histopathology images."

Clearly, we need a new approach: an analytical framework that accommodates

biological noise by quantitatively addressing tumor oncogenic vulnerabilities from the perspective of an objective automated tool with either no or minimal human interaction – other than as quality management of source images.

Beyond the ability of minimizing all the technical noises at the first step, such a platform would need to have the capability of extracting the key tumor microenvironment interactions and the biologic signature of crucial oncogenic drivers from H&E biopsy or resection images as pan-cancer digital biomarkers. These biomarkers need to be explainable, continuous scales that are open to independent validation by direct or indirect orthogonal tests. They also need to be extracted rapidly (preferably in near real-time appropriate to the clinical tasks in hand) without demanding enormous computing power.

By their very nature, tumors are inherently biologically heterogenous entities contributing to the diagnostic challenges faced by pathologists as part of routine reporting. These include tumor grading, staging, and prognostication. Furthermore, evaluation of host tumor responses (e.g., quantifying tumor lymphocyte infiltrates) and certain key molecular subtypes, which have a bearing on both treatment selection and response (e.g., HER2, Ki67, PD-1/PD-L1), are vulnerable to this variability. As a result, any diagnostic solution that can address heterogeneity would offer invaluable support to such diagnostically challenging scenarios.

Tumor-infiltrating lymphocyte grade and certain treatment-initiating key molecular profiles (such as HER2, Ki67, or PD-1/PD-L1) are affected by biological variability. No doubt, such a tool would be especially valuable in these cases.

In summary, interrogating tumor biology to extract the right kind of hidden data returns information of great value to pathologists and oncologists. With no input beyond pre-treatment biopsies or resection whole-slide images, it delivers outputs that support rational diagnostic and therapeutic decisions. This next step forward in AI-based diagnostic support represents a true patient-centric democratization of digital pathology, avoiding ancillary testing and tissue requirements while still offering universal accessibility, faster turnaround times, better affordability and, crucially, greater diagnostic accuracy for patients.

"This next step forward in AI-based diagnostic support represents a true patient-centric democratization of digital pathology, avoiding ancillary testing and tissue requirements while still offering universal accessibility."

Reference

1. *HR Tizhoosh, L Pantanowitz, "Artificial intelligence and digital pathology: challenges and opportunities," J Pathol Inform, 9, 38 (2018). PMID: 30607305.*

On Becoming a Morphologist

No matter how high-tech our tools, morphology remains an irreplaceable part of our work

By Pranav Pramod Patwardhan, Resident Physician, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, USA

In an era where molecular genetics is rapidly advancing our understanding of disease, how relevant is "routine" hematoxylin and eosin (H&E) histomorphology in our training years?

Before the advent of immunohistochemistry (IHC), the study of human tissue depended largely on H&E staining and a few special stains in anatomic pathology. Now, IHC and molecular advances have completely changed the way pathology is practiced, improving our understanding of cancer and providing more precise, accurate information to the clinical care team. As our technologies evolve, does morphology still have a key role to play in modern pathology practice – and how much emphasis should pathology training place on learning histopathology as "morphologists?"

As a young trainee, I was, like many others, awestruck and amazed by the advent of ancillary techniques and their utility in surgical pathology. Indeed, they have helped us answer difficult questions, understand human disease, and open up newer approaches to disease management and drug design. In neuropathology, they have revolutionized the way we classify tumors; in hematopathology, they have helped us understand the heterogeneity, prognostication, and clinical treatments of lymphoma. No lymphoma would be signed out today without the use of IHC, flow cytometry, and other ancillary tools. In neuropathology, markers such as H3K27 are useful to ensure that pure morphological findings do not mislead us in considering a tumor "low-grade." A positive IDH1/2 immunostain is extremely useful in distinguishing dedifferentiated chondrosarcomas with osteosarcomatous differentiation from osteosarcomas with chondroblastic differentiation – a challenge when using pure H&E evaluation. In short, these tools are undoubtedly improving the practice of our discipline. Pathology trainees are exposed to an ever-increasing pool of knowledge and expected to understand and interpret these ancillary tests. It is easy for morphological training to take a backseat – so why should we continue to pay attention to it?

Even today, morphological evaluation helps us decide the further workup of any lesion or tumor. Categorizing cells into small, medium, and large sizes can assist with suspected lymphoma. Close observation of the amount and color of cytoplasm in tumor cells, their nuclei, nucleoli, and the pattern and cellularity of the lesion support the selection of immunostains for spindle cell lesions. The presence of lymphovascular invasion in the absence of lymph node metastasis on PET imaging hints at higher risk of future metastasis. Morphological examination is still a reliable way to differentiate atrophy, atypical hyperplasia, and prostatic adenocarcinoma grade 3 + 3 on a prostate biopsy – even when immunostains are unhelpful. In many cases, a simple morphological examination still gives us key diagnostic and prognostic information.

The scenario is likely to become even more complex in years to come, as newer treatment techniques, neoadjuvant chemotherapy, and immunotherapy change the way we treat cancer. Tumor cells change with neoadjuvant chemotherapy and radiation. Newer treatment modalities may change the information we gain from ancillary stains in the future. In these cases, morphology can step in. And it's not just about cell size and shape; morphology, in some scenarios, can yield insight into the "genotype" of various lesions. A colonic adenocarcinoma with lymphoid infiltrate raises the possibility of Lynch syndrome, whereas a type II papillary renal cell carcinoma with eosinophilic nucleoli raises the suspicion of hereditary leiomyomatosis with renal cell carcinoma. I recall an example from the WHO Classification of Soft Tissue Tumours stating that an epithelioid hemangioendothelioma consisting of well-formed vascular spaces with cells having eosinophilic cytoplasm suggests *YAP1-TFE3* fusion, rather than the common *WWTR1-CAMTA* fusion. This understanding of morphological patterns helps "triage" further workup in the right direction, potentially improving efficiency and reducing time and cost.

Newer tests and techniques are not readily accessible to pathologists in many parts of the world. And, with the tremendous strides our knowledge of tumor genetics makes every day, it is practically impossible for even well-resourced laboratories to stay fully up to date. Not only that, but pathological assessment of intraoperative frozen sections – which relies on H&E-based assessment – is of great value to the surgical team. In short, the heterogeneity with which we describe pathological lesions may increase in the years to come – and, when it does, our morphological knowledge can help provide the best possible guidance for testing, treatment, and outcome prediction. Nowhere is this truer than in resource-poor settings, but we can all benefit from a strong understanding of morphology in our work.

As excited as I am about the newest advances in molecular pathology, ancillary tools, and IHC stains available for use, I have tried to learn just as much about morphology. No matter how much information we have at our fingertips, we cannot replace the humble morphological assessment – a foundational part of our pathology training and practice.

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A Roadmap for the Future

How digital pathology puts the lab at the center of the patient journey

By E. Blair Holladay

As diagnostic care advances, new technologies evolve to give pathologists and medical laboratory scientists the ability to guide and administer high-quality care. Digital pathology is one such technology playing an increasingly critical role in patient care.

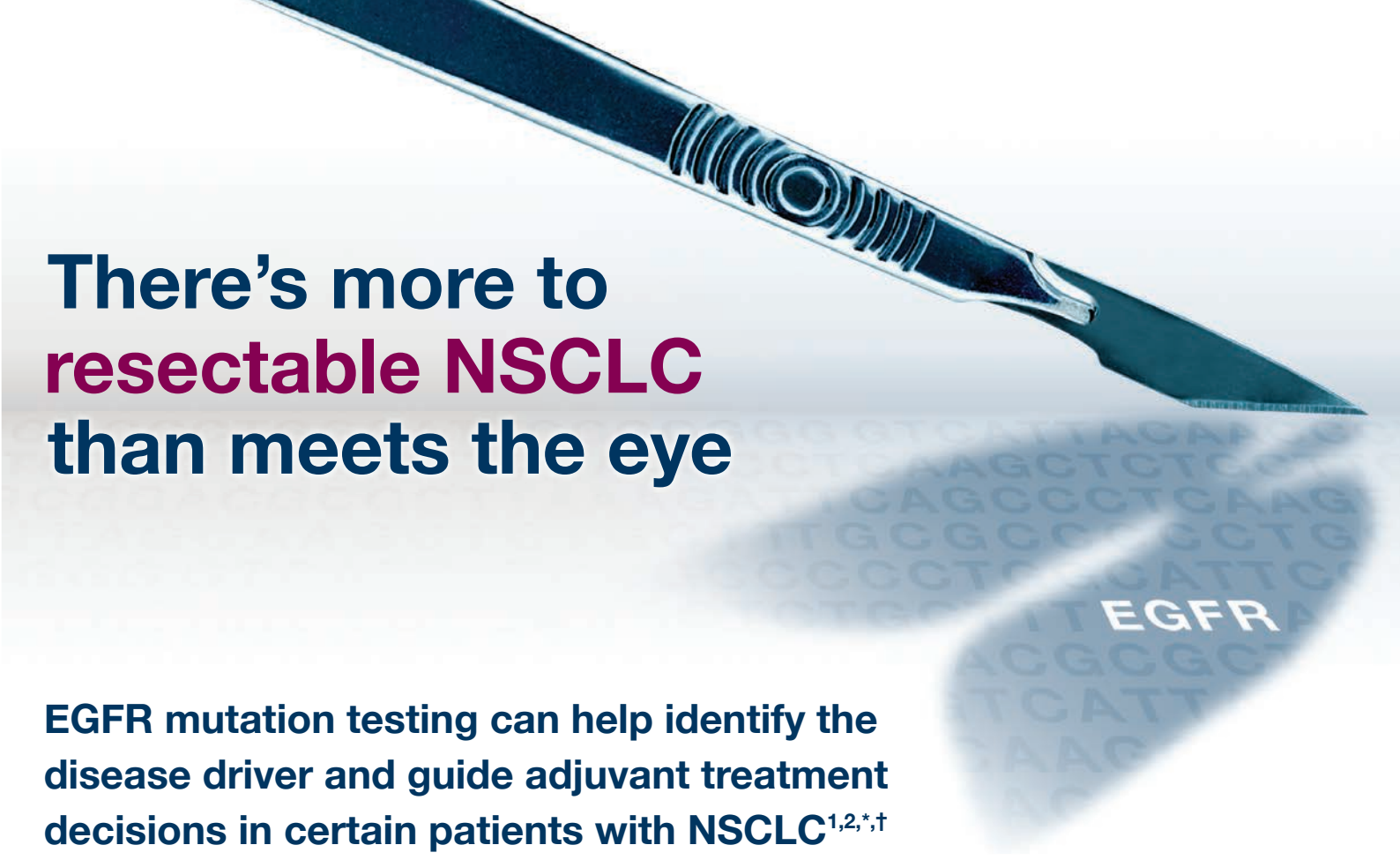
Not only has digital pathology provided the laboratory with another tool to more accurately diagnose and personalize care, but it has also opened up avenues to patient care that previously did not exist. The ASCP-led coalition Partners for Cancer Diagnosis and Treatment in Africa, for example, leverages digital pathology to help treat patients in sub-Saharan Africa. Employing these collaborative capabilities between pathologists in the United States and healthcare facilities in Africa allows more patients to receive high-quality care in a timely and efficient manner.

At its heart, digital pathology is a simple concept – share an image (a digital slide) for a pathologist to evaluate and interpret for diagnosis. When you look closer at the technology, however, it's easy to see that there is nothing simple about what digital pathology means for the field of laboratory science. It is a complex, continually evolving environment that changes pathology and laboratory medicine for the better every day. It is a pathway of innovation that allows for more precise, personalized management and underscores the patient in patient care. Digital pathology offers us innumerable possibilities for the laboratory to further position itself as the epicenter of a healthcare system – and of each patient's care journey.

ASCP recently had the honor of partnering with the Union for International Cancer Control on their World Cancer Leaders' Summit, which focused on "driving innovation to advance cancer control equitably." Thought leaders from around the world debated current innovations in cancer care and how best to implement new tools and technologies in settings with varying resource limits. Because the laboratory is the foundation of patient care, digital pathology is crucial to creating environments in which high-quality care can thrive, no matter where patients live. It drives the transformation of care delivery – for all patients – and, when used effectively, has the potential to improve outcomes.

As leaders in healthcare, pathologists and medical laboratory scientists are called to be the guiding force for patient care. A patient's journey starts in the lab, after all, and it is up to us to steer advancements that will directly impact and improve their experience. When we embrace advancements like digital pathology and allow them to expand our practice horizons, the forward motion we create saves lives and strengthens our position as leaders.

"A patient's journey starts in the lab, after all, and it is up to us to steer advancements that will directly impact and improve their experience."



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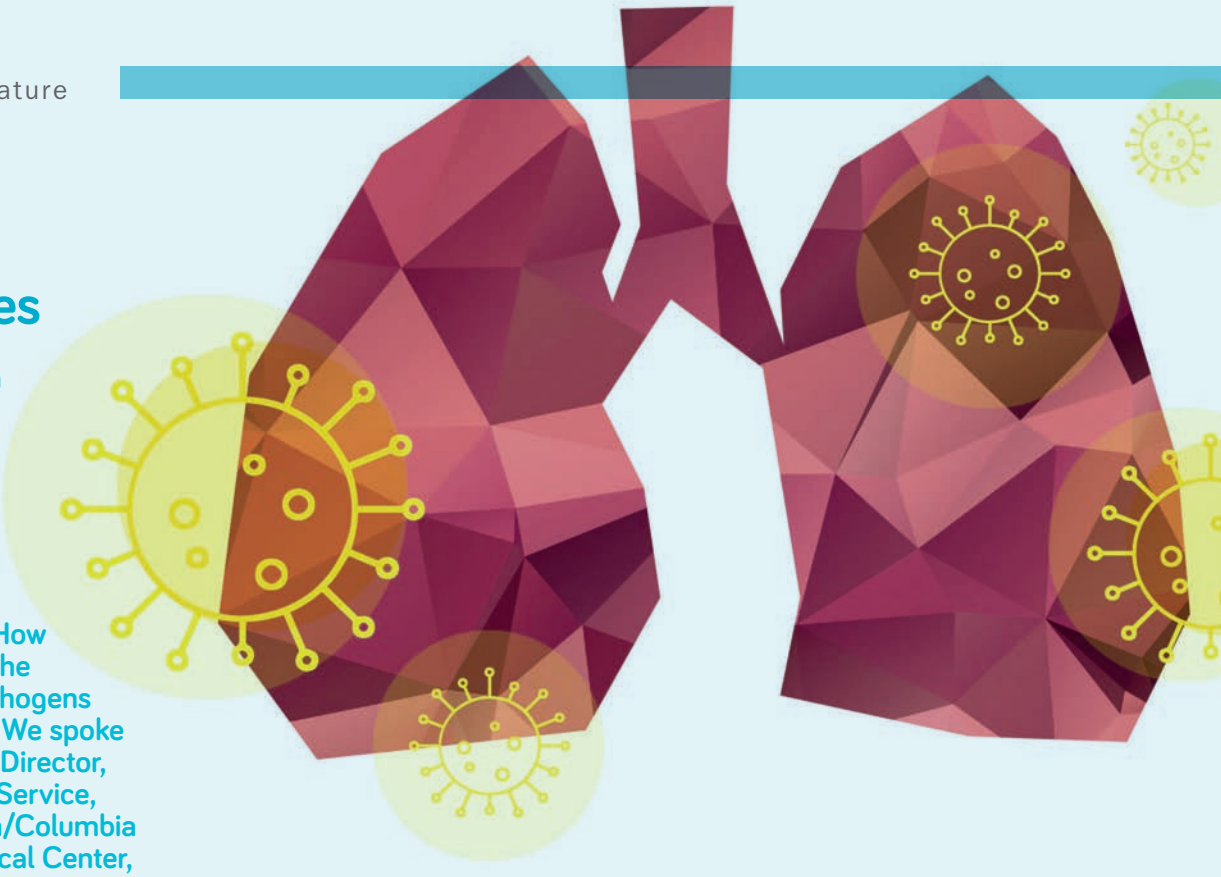


Testing Times

COVID-19 vaccination has been remarkably successful – but, as pandemic restrictions are lifted and social precautions relaxed, we should expect a resurgence in other respiratory diseases. How can we best manage the diagnosis of these pathogens in the coming winter? We spoke to Gregory Berry (Co-Director, Clinical Microbiology Service, NewYork-Presbyterian/Columbia University Irving Medical Center, New York, USA) to find out.

How has the COVID-19 pandemic affected your work?

In normal times, as a medical microbiologist and microbiology laboratory director, my employment encompasses all infectious disease clinical testing. The pandemic forced us to drop this broad remit and focus intensely on COVID-19 diagnostics. We had to be on top of every detail of the testing process, not least all aspects of inventory – from nasopharyngeal swabs and transport medias to assay consumables like pipette tips. Usually, the procurement of such items is trivial; with the advent of COVID-19 and the associated supply chain disruption, however, contingency planning for inventory shortfalls in these areas became a daily necessity.

Has the pandemic affected patterns of circulating respiratory pathogens?

Initially, severe restrictions in the supply of tests and related consumables demanded that we confine our activities to COVID-19 diagnostics. But, as consumable supplies normalized and multiplex assay options became available, we expanded our testing activities and made some interesting observations. Notably, we found that influenza and respiratory syncytial virus (RSV) had virtually disappeared; by contrast, human rhinovirus/enterovirus and adenoviruses – despite masking and social distancing – were still present in the population and were co-circulating with SARS-CoV-2. And the situation continues to evolve – we are now witnessing the reemergence of other respiratory viruses, such as RSV, parainfluenza, and common cold-type coronaviruses. I suspect that the end of social distancing and masking mandates is allowing these classic respiratory viruses to resume circulation.

Do you have any concerns for the forthcoming respiratory infection season?

Most concerning are the resurgences of influenza A, influenza B, and RSV. Pre-pandemic, these respiratory pathogens were significant causes of morbidity and mortality in certain patient populations; as they reemerge, they will cause the same health issues they did before their circulation was interrupted by COVID-19 lockdowns. Indeed, the reappearance of these pathogens is already apparent; data relating to national viral infection rates indicate recent outbreaks of RSV and parainfluenza in some parts of the country. I also expect influenza to reemerge and increase in frequency this winter. The forthcoming respiratory infection season could look similar to those we experienced prior to the pandemic, but only time will tell.

"It has been very interesting to watch the viral respiratory landscape change over the course of the pandemic."
– Greg Berry

What challenges did you encounter in respiratory diagnostics during the pandemic?

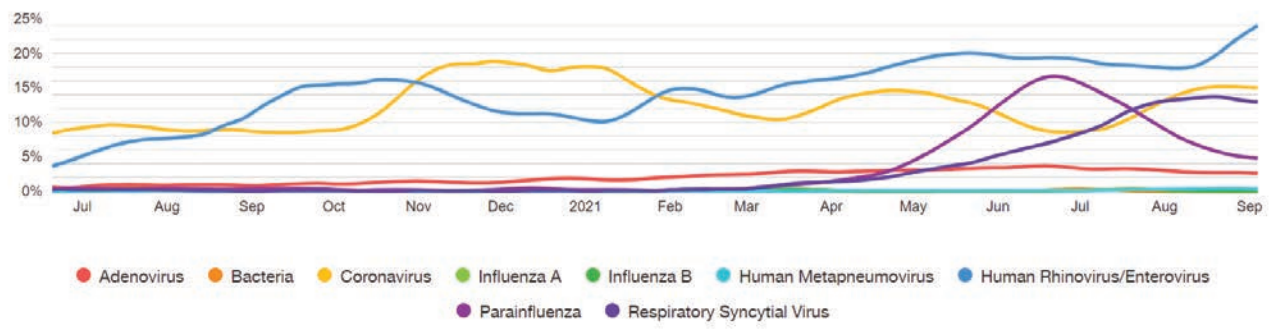
In addition to supply chain issues, we found that significant difficulties arose when we attempted to discriminate between COVID-19 and other common respiratory pathogens, such as flu and RSV. There is simply no way to distinguish between these infections based on the symptoms they cause. This is a problem because, if hospitals are to effectively manage patients who have respiratory symptoms but are COVID-19 negative, we must determine which of the other common respiratory pathogens is the causative agent. In our laboratory, we address this challenge with a suite of diagnostic tools comprising i) a large, automated testing platform offering a dedicated SARS-CoV-2 assay; ii) a four-plex assay system for influenza A, influenza B, RSV, and SARS-CoV-2; and iii) a multiplex respiratory pathogen panel – the BioFire RP2.1 Panel. Overall, our experience is that a multiplex pathogen test is the most valuable tool for assessment of symptomatic patients. By contrast, a dedicated COVID-19 assay is more useful when the goal is to identify asymptomatic SARS-CoV-2 infections that could spread to other people or result in poor patient outcomes; accordingly, we use the COVID-19 assay for pre-procedural testing and screening of asymptomatic patients.

What are the key features of an ideal diagnostic test for respiratory pathogens?

First, very high sensitivity and specificity, so that we can have high confidence in the test results. Second, speed; turnaround time should be as rapid as possible to allow clinical teams to act on diagnostic findings in real time. Finally, the ideal test should have broad coverage – that is, it should incorporate a range of analytes specific to the most common respiratory pathogens. Remember, COVID-19 looks very similar to diseases caused by other common respiratory pathogens, such as flu and RSV – we cannot separate these conditions on the basis of their symptoms. Therefore, an initial test that can rule in (or rule out) the most common causes of respiratory infections is useful, especially in hospitalized patients with upper respiratory tract symptoms.

Furthermore, by simultaneously testing for a range of common respiratory pathogens, we save time and resources and help clinical teams move forward with a rational treatment plan earlier than might otherwise be possible. The BioFire® Respiratory 2.1 (RP 2.1) Panel is a good example of this syndromic approach in that it covers many of the most common causes of respiratory infection (including COVID-19), helps laboratories optimize their testing strategies, and provides the clinical team with a rapid and accurate result. The BioFire panel will meet the needs of many laboratories while guiding rapid treatment decisions and thus will ultimately be of benefit to patients.

"Without testing, there is no way to tell COVID-19 from the other common respiratory pathogens."
– Greg Berry

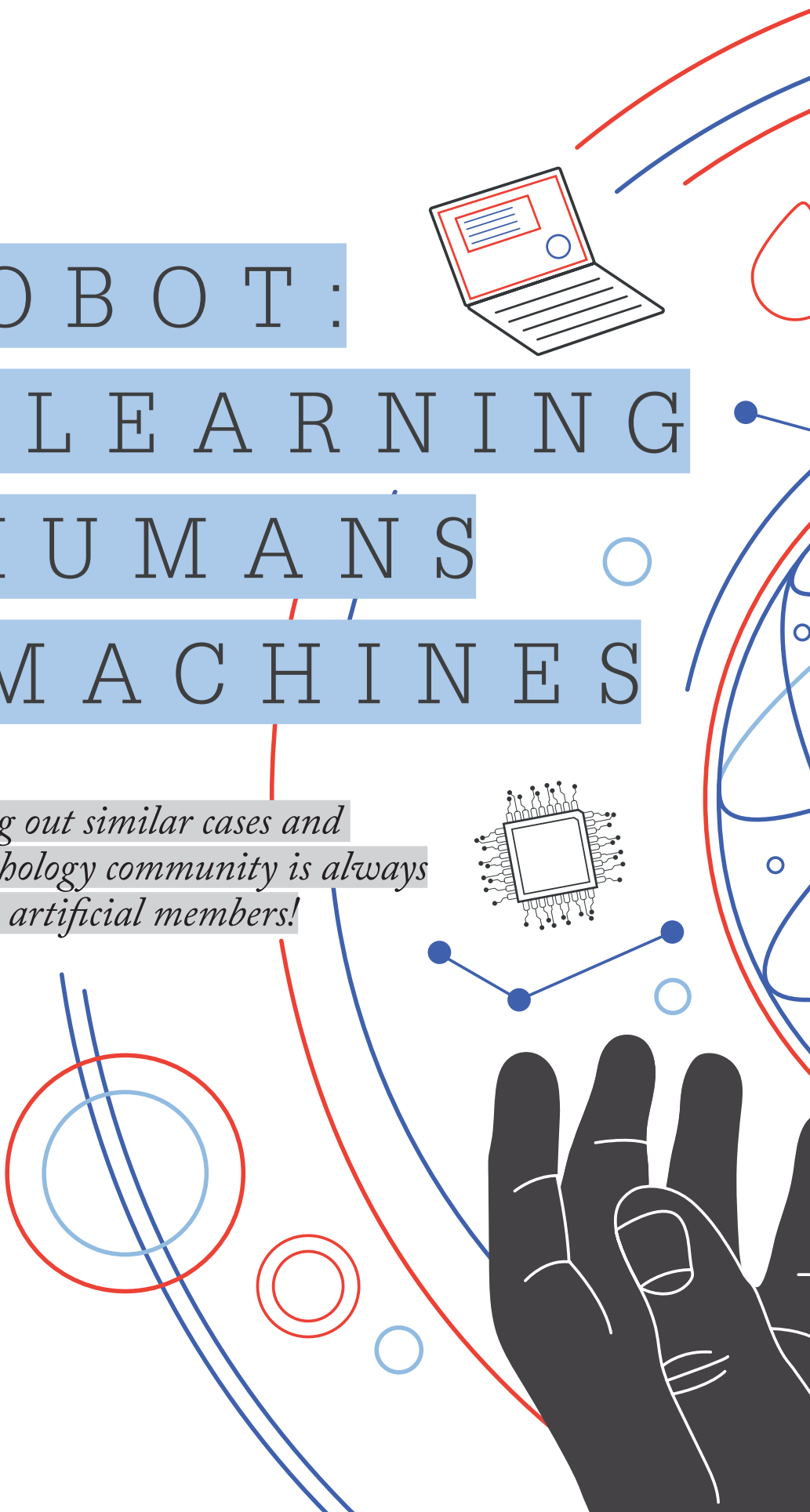


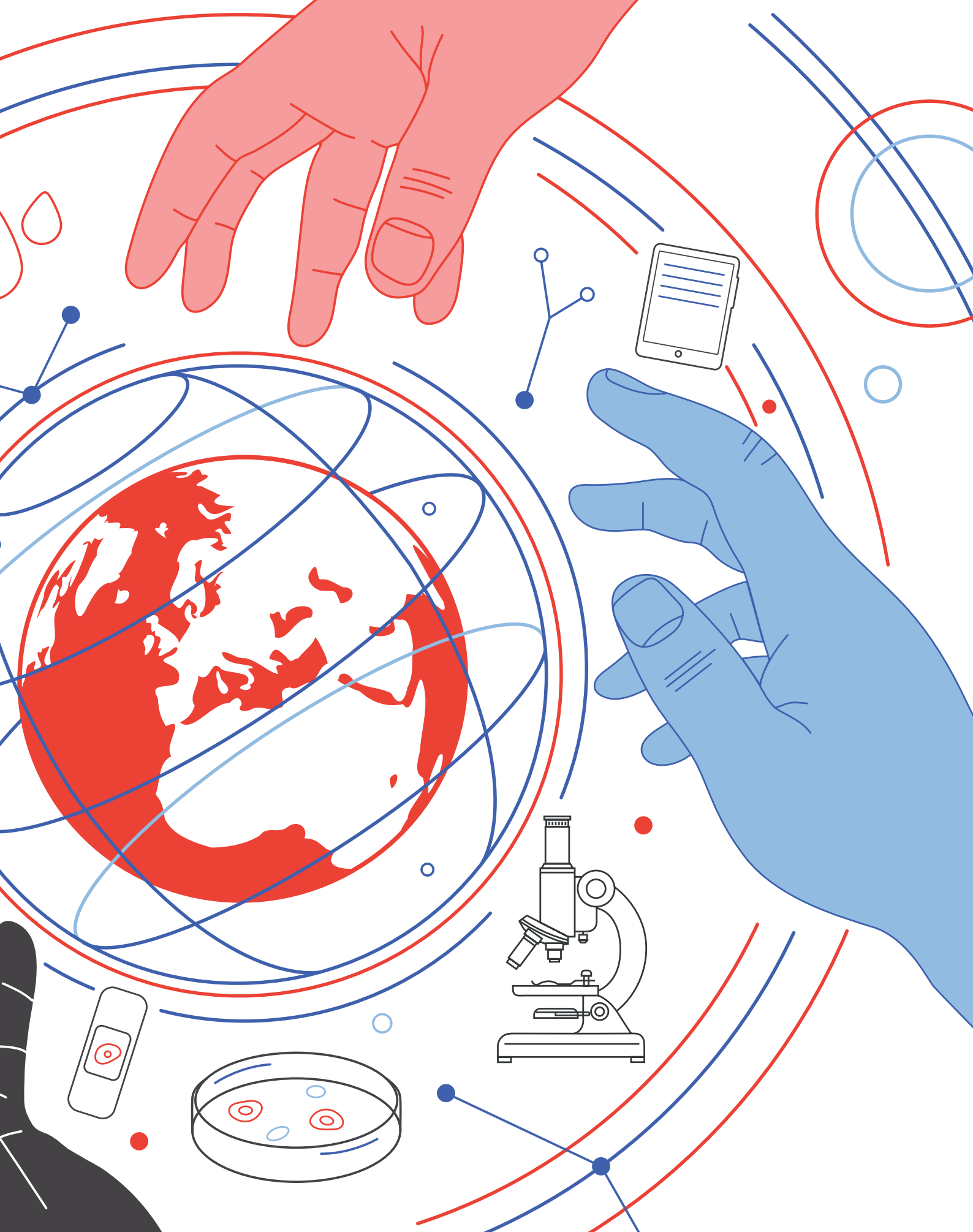
BioFire® Syndromic Trends: Respiratory Trends 2021. Credit: syndromictrends.com; accessed September 1, 2021.

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."

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.

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

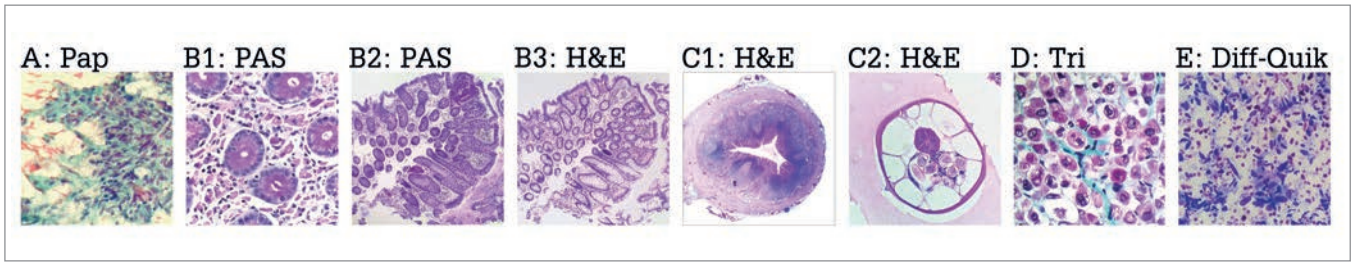


Figure 1. H&E and other select stains in the pathobot dataset. A) Papanicolaou stain. Credit: Ricardo S. Sotillo. B1) Periodic acid-Schiff (PAS) stain, glycogen in pink; B2) PAS stain, lower magnification; C1) H&E stain, human appendix, including parasite *Enterobius vermicularis*; C2) Higher magnification *E. vermicularis*; D) Gömöri trichrome, collagen in green; E) Diff-quik stain for cytology. Credit: Laura G. Pastrián. Adapted from (3).

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) non-tumor/infection, b) benign, or c) malignant disease. However, 'benign' was a grey area, especially for disease that may become malignant soon."

> "Social media is an increasingly popular platform for sharing and discussing deidentified cases."

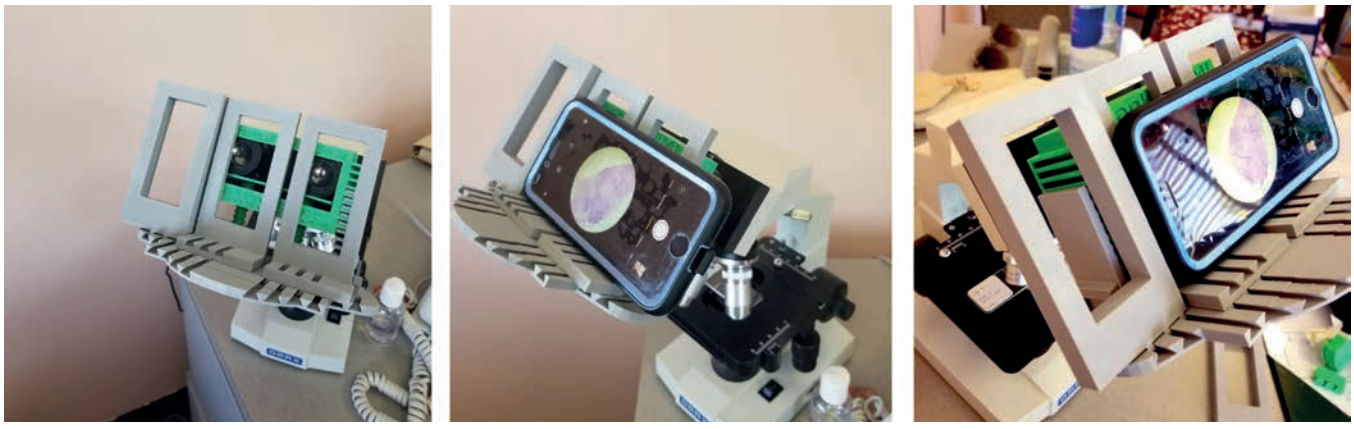


Figure 2. Pathobox mounts a smartphone to a microscope. Credit: S. Jeremy Minkowitz.

Figure 3. A pathobox with tape applied. Credit: Henrike Rees.

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. 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!"

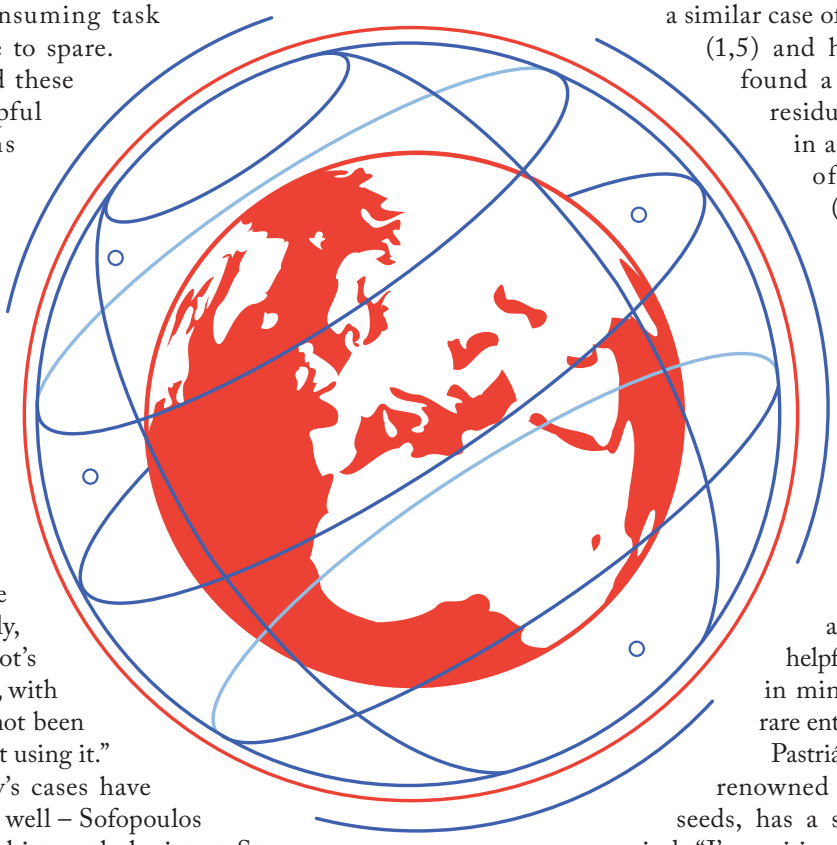
Mukhopadhyay says, "I have tested pathobot occasionally for over a year. For the cases I've tested, I am impressed that pathobot's histopathology search results are similar to my test cases and that they are quickly produced. Lately, I've found that pathobot's horizons have expanded, with pathologists 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."

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."

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!"

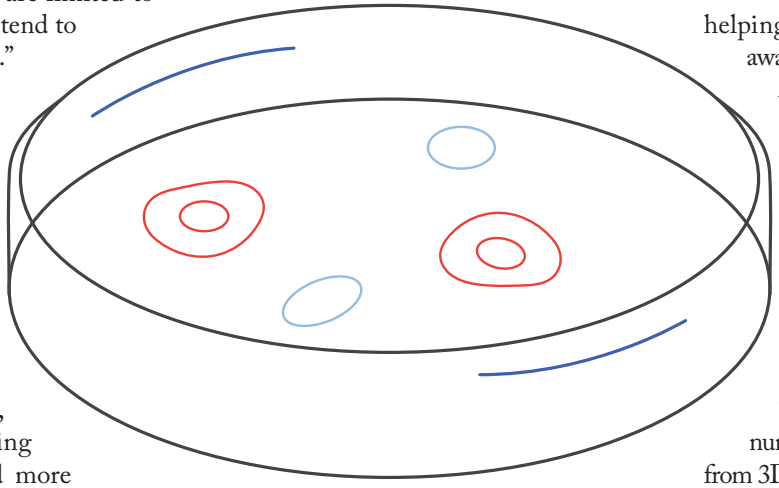
DATA IN, DATA OUT

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."



INTRODUCING PATHOBOX

Schaumberg also hopes to get as many students, residents, fellows, and pathologists as possible contributing to case discussions and helping each other, so he gives away 3D-printed "pathoboxes." A pathobox mounts a smartphone, camera, or iPad to a microscope eyepiece for photos or video conferencing (see Figure 2) – and the devices, which Schaumberg produces at home, have begun to draw in new colleagues. "They fit in well with a number of our efforts in the lab, from 3D-printing to computational pathology," says Faisal Mahmood, an assistant professor at Brigham and Women's Hospital. "There are exciting applications of such methods in low-resource settings and elsewhere."

And pathobox is slowly making its way from one pathologist to the next. S. Jeremy Minkowitz, a first-year resident at SUNY Downstate Pathology, recommends pathobox for sharing photos and videos with colleagues. "I used a pathobox from home as COVID-19 hit New York City. My father and I also used it at his private pathology practice. The pictures were pretty good – and

video conferencing worked with it too. Although whole-slide images have their place in pathology, pathobox can be a nice, cheap, fast alternative that assists with 'quick questions.'"

Minkowitz and Schaumberg collaborated to improve the device's design – but some problems remain insurmountable. "I left it in my car during the summer and the pathobox warped from the heat," confesses Minkowitz. "Wouldn't recommend leaving it on a car seat in the sun!"

Some pathoboxes, however, made their way to colder climates (see Figure 3). "My pathobox arrived in the middle of the pandemic in Saskatchewan," says Henrike Rees, a pathologist at Saskatchewan Health Authority in Canada. "I had started to work from home in mid-March of 2020, so teaching pathology residents remotely became a new challenge. The pathobox has helped me connect with my residents and teach them from my home office. Because it is a modular system, it can be easily adjusted for a variety of smartphones or tablets."

Second-year anatomical pathology resident Ariel Gershon agrees. "The pathobox is a great device. Here in Toronto, I use it to share images for informal consultation with friends or to save slides for viewing at home. When taking pictures by hand, I always moved slightly at the last moment, obscuring the picture. I had some trouble putting pathobox together initially, but Andrew kindly and quickly put together instructions on a YouTube video addressing my concerns (7)."

In April 2020, Schaumberg also tried shipping pathoboxes from the US to colleagues in Nigeria – but COVID-19 eliminated all shipping transport between the two countries, so the devices returned. Fortunately, the delay gave creators the opportunity to improve the design – and these updated pathoboxes were shipped in February 2021. The highly anticipated shipment arrived in March, but there was bad news. "Unfortunately, the pathobox did not fit my microscope. The eyepiece is too wide," says Dauda Suleiman, a pathologist at the Abubakar Tafawa Balewa University Teaching Hospital in Bauchi, Nigeria.

"It's a shame the pathobox design isn't truly universal yet. No amount of heat or acetone could reshape the pathobox on-site to accommodate the eyepiece. So there's room to improve the design, make things right, and keep testing as broadly as we can," admits Schaumberg. Unperturbed, Suleiman shipped the pathobox to a colleague, also in Nigeria – and, in May 2021, their luck improved.

"The pathobox was not hard to set up once I'd watched Andrew's video," says Nnamdi Orah, a pathologist at the College of Medicine, University of Lagos, Nigeria. "It needed a bit of tinkering to get the best position for my phone (see Figure 4). Once positioned, it worked very well. I expect the pathobox will be of great use to me in sharing pictures with my colleagues. Thank you very much!"

Figure 4. A pathobox in Nigeria. Credit: Nnamdi Orah.

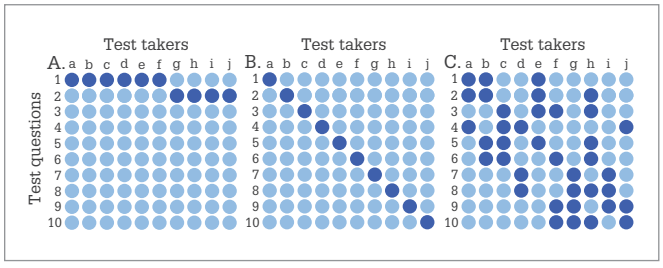


Figure 5. An example of hypothetical test takers and questions to illustrate a type of algorithmic diversity for an AI. A) Low diversity: most test takers get question 1 wrong (dark blue), so a majority vote of test takers still gets question 1 wrong. B) High diversity: all test takers get a different question wrong, making individual test takers 90 percent accurate and the majority vote 100% accurate. C) High diversity: test takers individually range from 40–70 percent accuracy, but the majority vote is still 100% accurate because more test takers get each question right than wrong – illustrating the value of test takers disagreeing in different and independent ways.

PATHOBOT AND DIVERSITY

"For me, diversity protects against bias, both at the human and algorithmic levels," says Schaumberg. "Diversity means we're aware that H&E isn't only H&E in every country – we know there may be saffron in the stain in France as Aurélien says, for instance. We have to handle the fact that H&E looks different across different institutions, countries, and photomicrographs; for instance, if the H&E appears more red (see Figure 6C) or pink (see Figure 6G) or brown (see Figure 6D) in enough cases, then the AI may be able to learn that the stain's color is less important than its location on the slide. With diversity, we also know that the same disease might get surgery at one institution, but not another – as Joseph pointed out to us for the differential diagnosis of atypical lobular hyperplasia (ALH) or lobular

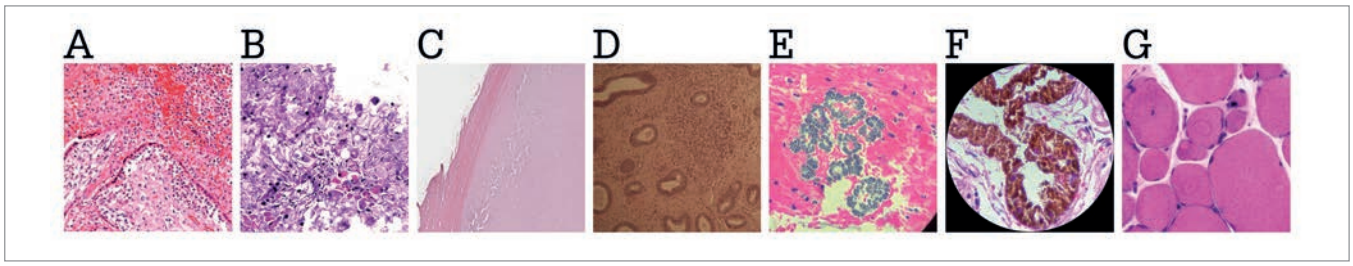


Figure 6. The pathobot dataset includes diverse H&E-stained slide microscopy images. A) Acute villitis due to septic *E. coli*. Credit: Srinivas Rao Annavarapu. B) Garlic. C) "Acellular" leiomyoma after ulipristal acetate treatment. D) Brownish appearance from dark lighting. Credit: Ricardo S. Sotillo. E) Sarcina in duodenum. Credit: Kathia Rosado-Orzco. F) Mature teratoma of ovary, pigmented epithelium. Credit: Betul Duygu Sener. G) Central core myopathy. Credit: Karra A. Jones. Available from (3).

carcinoma in situ (LCIS) – which is one reason we avoid predicting whether or not a patient needs surgery. Diversity forces us to reach consensus and do better." In his view, that involves defining disease in a way that works for all users – and then working on an AI that works toward that consensus. "Sometimes, we're defined more by our weaknesses than by our strengths," Schaumberg observes. "Diversity means that the group as a whole is less likely to have people who all share the same weaknesses."

But what does diversity mean to an AI? At an algorithmic level, a mechanical sort of diversity is built in. Pathobot, for instance, uses an approach known as random forest. "Part of our AI builds a committee of slightly randomized predictors, which can be thought of as a collection of individual 'test takers' that disagree with one another (see Figure 5). The overall AI's prediction is a majority vote of these varied test takers," explains Schaumberg. "We also use deep learning and ensembles to take majority votes for a mechanical sort of diversity that empirically works better (3). That said, these mechanical sorts of diversity won't prevent AI mistakes if the data aren't diverse enough, and there is a lot of great current work about AI methods to mitigate biases in non-diverse data. For us, though, we wanted to focus on collecting data from a diverse cohort of pathologists and patients to do the best we can. Diversity really comes from people, from data, and from inclusion."

And because patient cases come from all over the world, diversity is baked into the data AIs such as pathobot study. Real-world data make it more difficult for AI to perform well, but provide a realistic look at remarkable pathology cases across many tissues and diseases. In machine learning, one often wants to know how an AI might be expected to perform in general on data the AI hasn't seen before –sometimes called "generalization error." Diverse international datasets can provide a good measure of how an AI can perform some tasks in general. Of course, a single institution's whole-slide library would not have this level of diversity. Rather, the data might be biased toward institution-specific protocols or the average socioeconomic status of its patients. If the institution specializes in a specific disease, there may be further biases in the data. For instance, a cancer center might not have infectious disease represented in its data at all – yet infectious disease is common in developing countries, whereas cancer is underrepresented. Diversity is fundamental to establishing the most general data with which to train the most general AI.

> "Diversity protects against bias, both at the human and algorithmic levels."

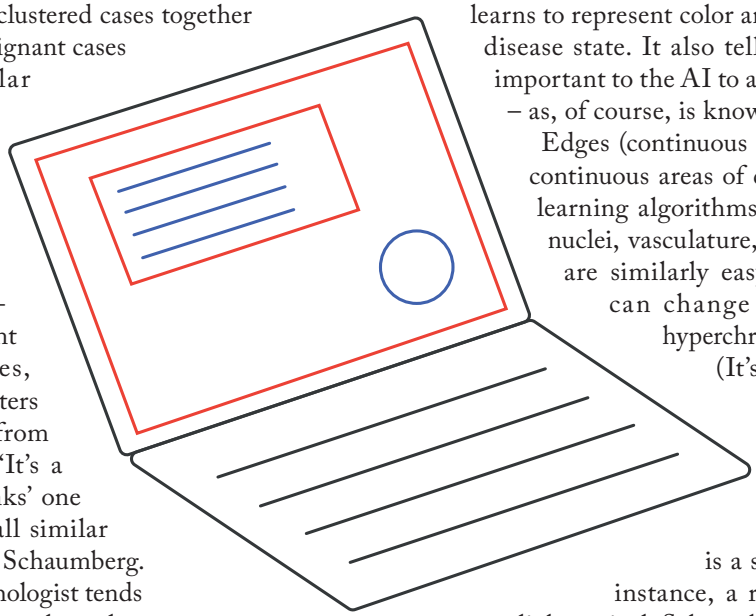
ANSWERS IN INTERPRETABILITY

"Interpretability in AI leads us to many interesting places!" says Schaumberg. "We revisited our definitions of nontumor/infection, benign/low-grade-malignant-potential, and malignant due to our AI's interpretability."

The AI had highlighted some hyperplastic cells as benign/low-grade-malignant-potential (8). "Some may argue hyperplastic cells are more closely 'nontumor,'" says Gardner. Schaumberg agrees – so pathobot's benign grey-area definition now explicitly includes pre-neoplastic disease.

"These conversations are a valuable consequence of interpretability," Schaumberg says. "We take better advantage of our diverse expertise this way."

Interpretability offers other benefits as well. For instance, Schaumberg and his colleagues observed that pathobot's deep learning approach clustered cases together by disease state – so malignant cases were considered similar to other malignant cases and nontumor cases more similar to other nontumor cases. That's a good thing – but, when they used features hand-engineered to represent color, texture, or edges, the team saw loose clusters of cases that were all from the same pathologist. "It's a bad sign if the AI 'thinks' one pathologist's cases are all similar to each other," explains Schaumberg. "Hypothetically, if a pathologist tends to share malignant cases, but also uses a specific smartphone camera with a specific microscope and saves photos with specific JPEG compression artifacts… an AI may incorrectly learn that that camera, microscope, or JPEG artifact predicts malignancy." Although these predictions of malignancy may be accurate, they will be accurate for the wrong reasons – meaning that the AI might also predict malignancy where none exists. Fortunately, the issue proved insignificant for pathobot. "In the end, we only saw a trace amount of potentially pathological behavior in the AI, so we were able to convince ourselves that the AI's learning made sense."

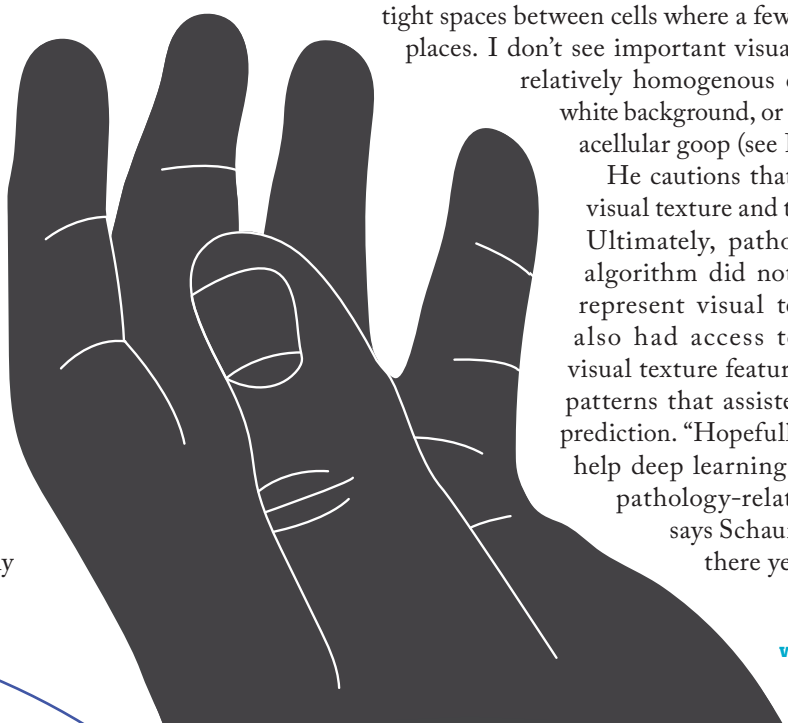


AI has a reputation as a "black box" because many users don't understand its inner workings. Could interpretability "open the box" for pathologists? Schaumberg says, "Interpretability lets us see things that we haven't seen before – such as what the AI 'thinks' are the core signatures of disease." What has interpretability revealed about pathobot so far? "Loosely speaking, it tells us that the deep learning part of the AI learns to represent color and edges to accurately predict disease state. It also tells us that visual textures are important to the AI to accurately predict disease state – as, of course, is knowing the tissue type."

Edges (continuous areas of bright pixels next to continuous areas of dark pixels) are easy for deep learning algorithms; they can arise from glands, nuclei, vasculature, and other structures. Colors are similarly easy to discern, although they can change for reasons ranging from hyperchromatic nuclei to understaining. (It's important to keep in mind that over- and understaining can reduce AI accuracy.)

Visual textures, in contrast, present a challenge. These occur where there is a specific pattern of pixels – for instance, a ring of dark pixels around a lighter pixel. Schaumberg says, "I've seen important visual textures around chromatin, dirty necrotic debris, in the tight spaces between cells where a few cells meet, and other places. I don't see important visual texture so much in relatively homogenous cytoplasm, or in flat white background, or in vast swathes of pink acellular goop (see Figure 6C)."

He cautions that blur greatly reduces visual texture and therefore AI accuracy. Ultimately, pathobot's deep learning algorithm did not effectively learn to represent visual textures, but the AI also had access to hand-engineered visual texture features called local binary patterns that assisted with disease state prediction. "Hopefully in the future we can help deep learning represent important pathology-related visual textures," says Schaumberg. "But we're not there yet."



WHY PATHOBOT TWEETS

"Activities that seem trivial or playful to us, such as sharing interesting cases on social networks, can have interesting spinoffs, such as the creation of algorithms that predict the nature of a tumor or the presence of a somatic mutation, or tools such as pathobot that allow us to find similar cases or differential diagnoses," says Morini. "When people are motivated and share their skills, the result is an enriching experience for everyone."

> "Social media is an increasingly popular platform for sharing and discussing deidentified cases."

Stayerman adds, "If someone had told me before I joined Twitter in 2018 that there was a vibrant worldwide community of pathologists eager to share their expertise, discuss cases, and respond to calls in a matter of seconds… I would have thought it was pure science fiction!" But for her, the Pathobot community stands out in the AI field because it grounds itself in a deep appreciation of pathologists' ability to make a diagnosis – whether for a simple case with just a microscope, eyes, and brainpower or a more complex diagnosis involving ancillary studies. "I think pathobot paves the way for an easy connection between pathologists and the ever-growing data available in the pathology Twitter community."

For most pathologists, asking for a "quick" expert opinion means physically visiting the offices of nearby colleagues with pertinent subspecialty expertise – or, if none are available, potentially mailing glass slides to more distant experts. However, pathologists in developing countries may not have the same opportunities – and they may have to make diagnoses without the benefits of ancillary studies or collaboration. Stayerman's favorite thing about Twitter? "It allows every pathologist in every corner of the globe to be exposed to new entities. We also encourage active discussion by sharing up-to-date information and expert consensus on established entities as brief, enjoyable tweets. The constant exchange of knowledge, thinking processes, diagnostic criteria, work-ups, and great images – all this will ultimately help us standardize good practices worldwide." In fact, she and other members of the #PathTwitter community have begun using the hashtag #PathTwitterFellowship – both because it describes explicitly what such tweets are about and because it highlights Twitter's ability to contribute to pathologist education. "This platform serves dual purposes: acquiring the greatest repository of diverse pathology images and aiding the global standardization of good practices that will ultimately improve patient care," says Stayerman.

Not a pathologist himself, Schaumberg has found himself impressed by Twitter's pathology community. "There is so much to learn, and I'm grateful to the many colleagues who have taken the time to help me! After getting some generic familiarity with various stains and tissues, I still don't have the expertise to really appreciate some of the challenging cases pathologists share. I'll never have that expertise, but sometimes there's a certain attention to detail that I find really striking." Discussion of a particularly tricky case prompts him to add, "AI will never be as good as a pathologist, certainly within my lifetime, and probably many more. For me, it's staggering that, from so much visual information, pathologists have the power to find a few cells that decisively change the diagnosis. That's why we use AI to connect pathologists – because a pathologist's power to investigate and accurately diagnose a vast universe of possible diseases isn't well-approximated by an AI that excels at some number of narrow benchmarks in isolation for controlled scientific study."

So how can the pathology community maintain pathobot's – and social media's – momentum? "Whether you're a pathologist with cases to share or a data scientist interested in analysis, get in touch," says Schaumberg. "I fund many of these efforts privately, with additional support from Mariam Aly and family. When I graduated in the summer of 2020, my grandmother gave me a monetary gift, so I decided to treat it like a microgrant for constructive purposes. This led to our 3D-printed pathobox giveaways, allowing us to help pathologists mount their smartphones to their microscopes for all kinds of telepathology – from photomicrographs to video conferences. Thanks, Grandma!"

His next goal? World domination – after a fashion. "Let's mount a smartphone on every microscope and help each other out!"

If you'd like to get involved with future pathobot efforts, find out more at pathobotology.org.

See the extended version of this feature and references online at: tp.txp.to/pathobot

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tribun HEALTH

FEELING THE SQUEEZE?

Can digital solutions "bring to light more than the eye can see?"

By Lorine Marcoux

Modern laboratories must manage higher caseloads in less time with fewer pathologists. This problem, however, is a tremendous opportunity for laboratories to adopt digital pathology – and benefit from its many advantages. Consider TRIBUN's industry-leading digital pathology platform, CaloPix 5. Optimized with input from working pathologists, this AI-based software offers features such as case assessment and annotation; slide analysis and navigation tracking; slide alignment and synchronization for comparison of different stains; dynamic, infinite-capacity work lists; and patient folders specifically designed for efficient image management. Importantly, these features are compatible with a broad range of image analysis.

CaloPix 5: the heart of your digital pathology workflow

- intuitive, pathologist-centric interface
- web browser-based application: "anytime/ anywhere" working
- remote telehealth-based collaboration capability: rapid and deep zoom viewing; simplifies requests for remote second opinions
- complete, seamless solution: image acquisition to analysis
- analysis automation via quantitative, AI-based algorithms
- versatile: compatible with many scanner and image formats (light background, fluorescence, Z-stack)

"Since our inception, CYPATH has been leading the way in pathology. Today, we demonstrate our continued commitment to providing the most advanced, accurate, and data-driven solutions for our clients," says Philippe Chalabreysse, President at CYPATH. "We selected TRIBUN after rigorous assessment to ensure we lean on the right partner."

Furthermore, CaloPix 5 accommodates key requirements of precision medicine, including assessment of the molecular signatures for breast cancer (MoSi4Bca: Ki-67/ER/PR, HER2 scores, mitosis) and analysis of colon lesion biopsies. Forthcoming developments include integration of external CE-IVD-certified algorithms, and incorporation of proprietary algorithms for predicting therapeutic responses in non-small cell lung cancer and cervical cancer. Finally, advanced automation enables fewer pathologists to address a higher number of cases. "TRIBUN's deep expertise in the end-to-end pathology workflow is what our organization needs to ensure successful implementation of digital pathology in our group," says Laurent Huguenin, Head of IT at CYPATH. "IT will play a critical role and we trust their expertise."

CaloPix 5 enables pathology laboratories to benefit from unprecedented flexibility (web-based application with broad compatibility), superior clinical confidence (AI-based analysis and automation tools), and enhanced productivity with automated workflows that accelerate and simplify the entire process – enabling higher output with fewer resources.

Lorine Marcoux is Marketing Executive at Tribun Health, Paris, France.

https://www.tribun.health/

DELL Technologies

SCALE UP, SCALE OUT

Securely store and readily access your whole-slide images with Dell EMC PowerScale

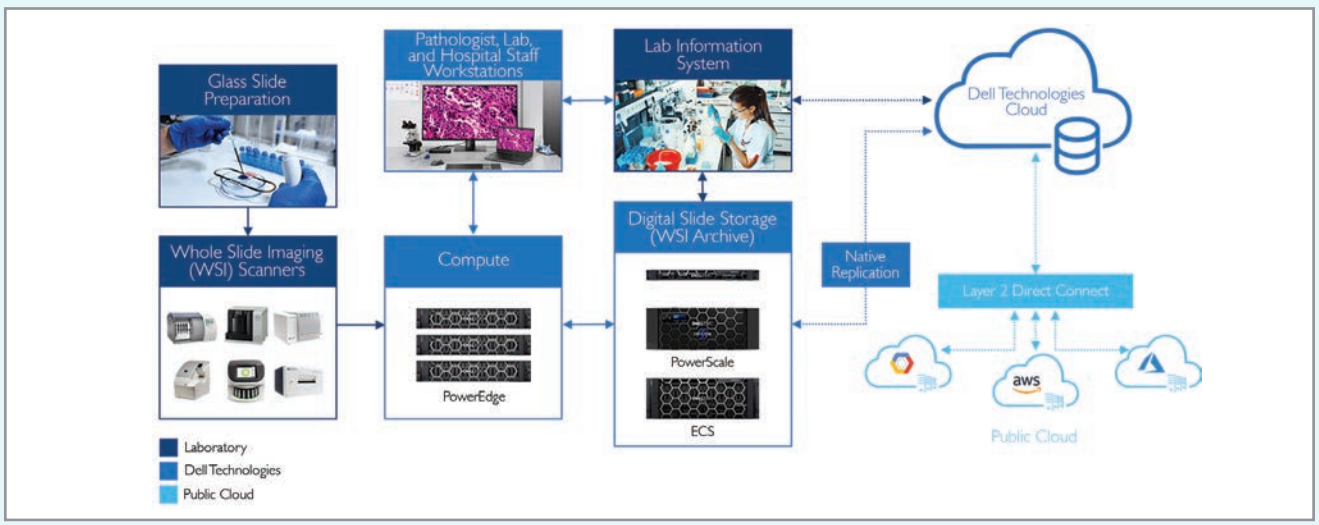
Dell EMC PowerScale is healthcare's leading scale-out network-attached storage platform – trusted by organizations across the globe for its reliability and performance in managing the most challenging healthcare data storage use cases. What makes the technology stand out from the rest? PowerScale is based on a unique, industry-leading architecture and operating system, OneFS. In a fully digitized department, pathologists are generating nearly a petabyte of data annually – but the OneFS architecture makes PowerScale easy to manage while ensuring that required levels of performance, scalability, reliability, and security are always achieved.

In a recent (unpublished) survey conducted for Dell by The Pathologist, approximately 80 percent of respondents cited storage of whole-slide images as a major concern when adopting digital pathology. However, OneFS-powered clusters allow IT departments to eliminate storage silos, consolidate unstructured data, and store and analyze petabytes of file data. And, with up to 252 nodes in a cluster and clusters comprised of all-flash, hybrid or archive nodes, digital pathology departments can scale both capacity and performance to meet the most demanding medical imaging storage needs – all without any additional IT burden.

"Dell EMC PowerScale provides the scalability, performance, security, and simplified management to accelerate our digital pathology transformation. By modernizing with Dell Technologies, we increased the ease and speed of accessing digitized pathology images, which helps improve patient outcomes and quality of research," says Nikolas Stathonikos, Principal Investigator of AI Development and Implementation at UMC Utrecht, Netherlands.

With digital pathology's potential to support research and help accelerate time to diagnosis, Dell Technologies has continued to work toward transforming lives by forming strategic partnerships with its customers – helping them to deliver better patient care. Based on its proven track record in the industry, healthcare organizations around the globe have put their trust in Dell Technologies and PowerScale to securely store patient data and make it available when needed.

"Now, we can enact better ways of doing things – not just do the same things better," says Graham Evans Chief Information and Technology Officer and Senior Information Risk Owner at North Tees and Hartlepool NHS Foundation Trust. "With Dell EMC PowerScale, we're ready for what's next – today, tomorrow, and for years to come."



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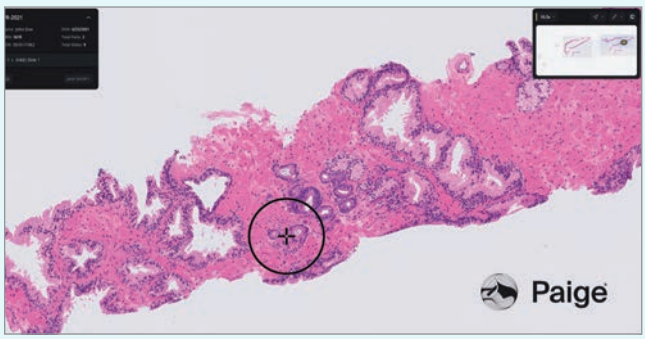
ALL ON THE SAME PAGE

FDA marketing authorization of Paige Prostate software brings heightened confidence and peace of mind to pathologists



Pathology must modernize to meet the twin challenges of rising workload and falling numbers of pathologists – but how can laboratories with limited personnel manage the projected 60 percent increase in cancer cases? One answer is to boost workflow capacity and efficiency by adopting artificial intelligence (AI)-based technologies, which will also improve the quality of diagnosis by generating detailed information to support personalized treatment recommendations.

Paige's computational technology – created by pathologists for pathologists – meets these real-world needs. Its flagship product, Paige Prostate, is the first AI-based pathology product to receive de novo approval from the FDA, allowing in vitro diagnostic use via FullFocus™ – an FDA-cleared, CE-marked viewing software compatible with most existing digital pathology solutions. In a clinical study submitted to the FDA, pathologists using Paige Prostate exhibited a 7 percent sensitivity increase in correctly diagnosing cancer, a 70 percent reduction in false negative diagnoses, and a 24 percent reduction in false positive diagnoses. This improvement was independent of pathologists' diagnostic subspecialization or years of experience, and whether the analysis was done remotely or on-site. Proven to improve diagnostic accuracy, Paige Prostate can help pathologists reduce detection errors and boost workflow efficiency.

In Europe, Paige's AI-based capabilities include two CE-marked tools: i) Paige Prostate, which detects foci of prostate cancer, assesses primary and secondary Gleason patterns, and measures tumor percentage and linear extent; and ii) Paige Breast, which assists with detection of premalignant and malignant breast neoplasms.

Ultimately, Paige's clinical-grade, AI-enabled computational technologies constitute a complete and fully FDA-cleared solution that enables pathologists to work more efficiently – pairing AI-based digital diagnostics with a broadly compatible imaging platform. With Paige Prostate, pathologists can review cases with heightened confidence and peace of mind. With FullFocus, pathologists can collaborate and review cases remotely, prioritize cases efficiently, and make diagnoses with increased speed and precision. By identifying easily overlooked diagnostic signals, Paige's technologies improve clinical confidence and accelerate the pathology workflow. Unsurprising, then, that Paige's software is associated with high levels of user satisfaction. The low-cost, easy-to-adopt software tools increase workflow capacity and accuracy – optimizing diagnosis and analysis in prostate and breast cancer case review.

Better Together: Paige Prostate and FullFocus Advantages

- easy adoption: no IT hardware required; intuitive AI interface throughout the workflow
- immediate availability of AI results
- compatible with most laboratory information systems and scanner platforms
- permit simultaneous comparison of multiple slides
- secure, remote access permits location-independent case review, diagnosis, sign-out, and report submission

www.paige.ai

deepbio

DEEP DIVE INTO HIGH-LEVEL DIAGNOSTICS

AI-mediated analysis of prostate biopsies enables faster and better diagnoses

Healthcare systems are struggling with a pathologist shortfall. In the US, the number of active pathologists dropped by 18 percent from 2007 to 2017; in South Korea, 65 pathology residency slots were available in 2020 but only 7 graduates enrolled. At the same time, laboratories must manage the ever-growing oncology workload associated with rising cancer rates and increasing calls for early detection – potentially leading to situations that do not make careful diagnoses possible. Deep Bio believes these challenges can be overcome with the power of artificial intelligence (AI) – providing objective and quantified slide analyses and supporting pathologists to make better informed decisions faster and more consistently.

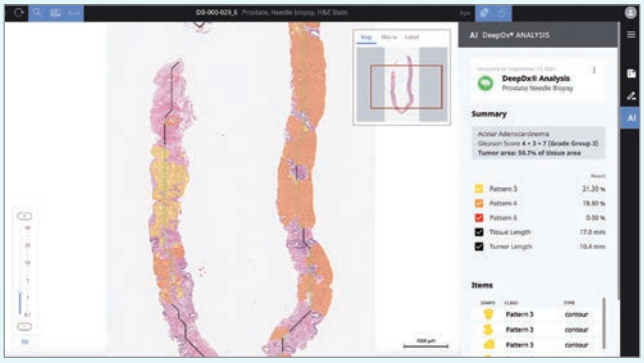
Deep Bio's first tool, DeepDx® Prostate, analyzes and assesses H&E-stained prostate biopsy slides to detect cancer – analyzing multi-gigapixel whole-slide images in under 30 seconds. At the same time, it provides clinically meaningful information regarding cancer localization and severity, including percentages of each Gleason score and pattern and total tumor and tissue length. This vastly reduces time and effort on the pathologists' part – improving workflow efficiency and accuracy.

The software assists pathologists by highlighting Gleason patterns 3, 4, and 5, where present, with different colored overlays. The gland-level segmentation of these overlays permits pixel-level accuracy of key metrics such as total tumor-to-tissue ratios and Gleason pattern-to-tumor ratios. DeepDx® Prostate has also been validated in a clinical study published in *Cancers*, yielding high concordance compared with reference standard generated by three board-certified pathologists, with a quadratic-weighted Cohen's kappa coefficient of 0.907; 99 percent sensitivity; and 94 percent specificity. It demonstrates that the software can provide specialist-level support to pathologists.

DeepDx® Prostate for quality control and research and development empowers pathologists to make more accurate and consistent decisions with faster turnarounds, enabling improved workflows. "This tool is very helpful for quality assurance, enabling pathologists to re-assess areas that they did not annotate originally, but which the AI algorithm indicated as areas of interest," says Hillel Kahane, Founder of StarPath, New York, USA, and a user of DeepDx® Prostate.

Moreover, Deep Bio is dedicated to developing innovative solutions in the digital healthcare sector and has active collaborations with renowned universities and laboratories around the world. At the 2021 annual meeting of the American Urological Association, researchers from the Stanford University School of Medicine presented two posters featuring analyses by DeepDx® Prostate – providing external validation of the algorithm and utility of the software in measuring concordance in tumor detection between preoperative MRI and prostatectomy histopathology. Results demonstrated high performance of DeepDx® Prostate in diagnosing and grading cancer on prostatectomy specimens. Recently approved by the University of Utah's Institutional Review Board, the company plans to conduct a prospective study to validate the performance of DeepDx® Prostate with ARUP Laboratories, a leading reference laboratory in the US.

**DeepDx® Prostate is for Research Use Only.*



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In Practice

Technologies and techniques
Quality and compliance
Workflow

Beyond Digital

Understanding barriers in transforming pathology from digital to computational

By Aishwarya Khanduja and Charlene Tang

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.

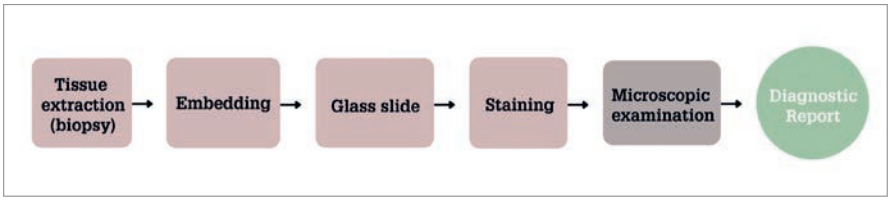


Figure 1: The classical histopathology workflow.

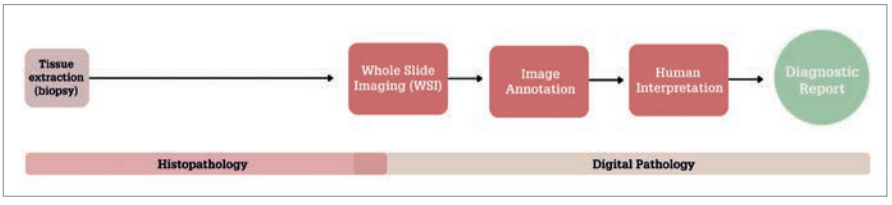


Figure 2. The digital pathology workflow.

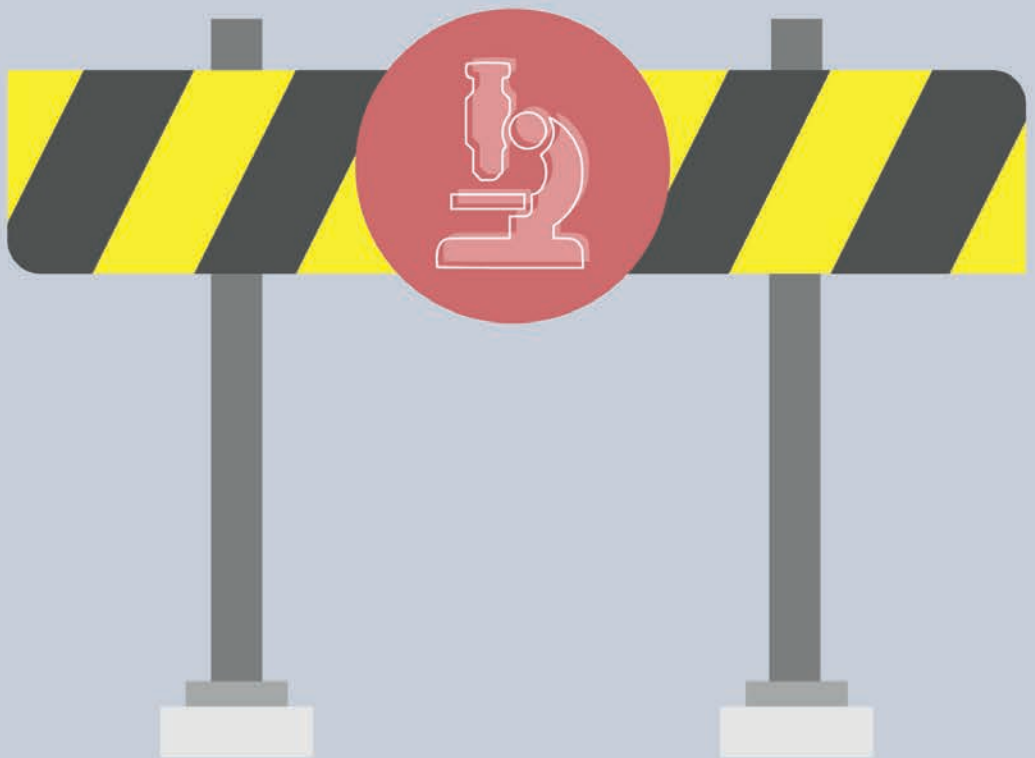
The workload for diagnostic services will only continue to increase. On one hand, there is an increase in demand with the growing and aging population in the UK, and advancements in early detection and treatment pathways resulting in a predicted 28.4 million cancer cases in 2040, a nearly 50 percent 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.

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,



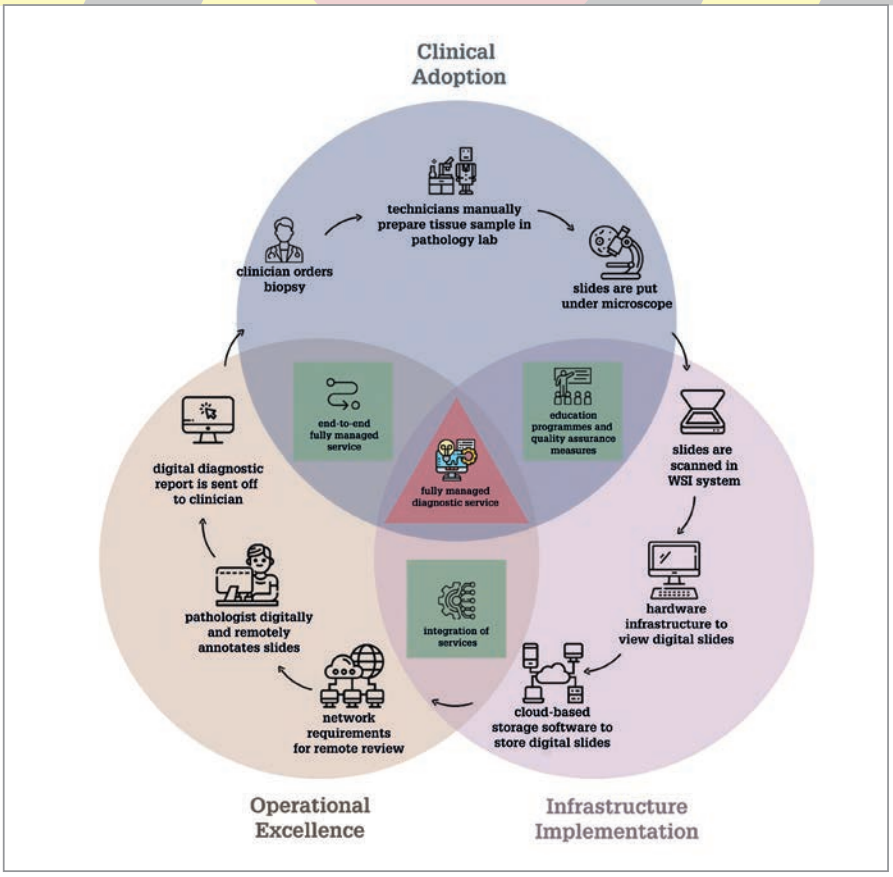


Figure 3. The key barriers in the implementation of digital pathology technologies (in circles) and their resolutions (in overlaps).

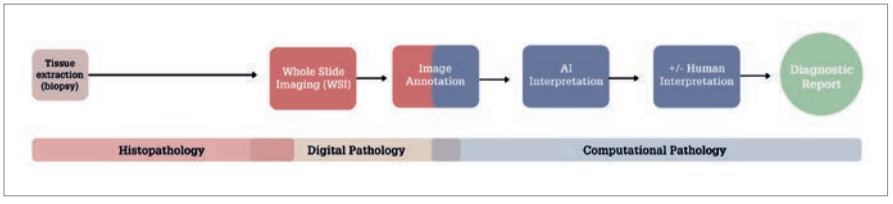


Figure 4. The computational pathology workflow.

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.

Moreover, the implementation of digital pathology in a hospital or laboratory first requires the setup and integration of back-end infrastructure such as scanning equipment, image viewer software, and network capacity to store images. Commercial solutions in digital pathology currently typically center on software for workflow management and operations for pathology laboratories in hospitals. However, such solutions do not account for variations between scanner hardware and image annotation techniques, hindering technology acceptance by laboratory staff and contributing to interobserver variability between consultant pathologists. To overcome this barrier, companies must ensure that their solutions integrate with on-site infrastructure, as well as provide training programs and quality assurance schemes for reporting pathologists and laboratory staff.

A recent evaluation of traditional analogue and digital pathology

workflows concluded that the logistical savings from digital pathology would not be enough for a financial business case (10). The researchers compared the impact of traditional analogue versus digital pathology on the efficiency of five laboratory workflows, concluding that digital pathology saved over 19 hours on an average day across all laboratory workflows. Critically, however, remote reporting on digital images instead of glass slides saved the pathologist *only* one hour per day.

Altogether, the uptake of digital pathology has stalled because the digitization of glass slides alone does not resolve the pressures of an increasing workload on a diminishing workforce of pathologists. Instead, digital pathology solutions add to hospital overheads in operating and capital expenditures, weakening their own business case. Notably, if the integration of digital pathology infrastructure stalls diagnostic workflows, this inevitably results in an increasingly volatile workload and pressure for reporting pathologists. This backlog may be outsourced to company laboratories who offer a centralized resource of pathologists in a hub-and-spoke manner. Moving forward, to supply and scale pathology services in response to increasing demands, we need a fully managed diagnostic service that integrates digital pathology infrastructure with the automation of both laboratory and pathologist workflows (Figure 3).

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

The computational promise

To relieve the pressure on pathologists, we need to streamline clinical decision-making. Repetitive pattern recognition tasks in pathology, such as cell counting or object classification, are ideally suited to number-crunching computers. This would allow us to reserve our human expert pathologists for more nuanced tasks and cases. However, this baseline computation depends on data that are captured and generated through digital pathology infrastructure. Just as the Internet provides a foundation on which to improve the efficiency of communication, digital pathology is the foundation on which we can build computer-automated tools to support and streamline clinical decisions.

This emerging field of "computational pathology" leverages artificial intelligence (AI) technology for diagnostic pathology by extracting information from digital images with a "big data" approach – using mathematical models to make diagnostic inferences and presenting clinically actionable recommendations for pathologists and clinicians (Figure 4).

Over the past six years, two defining computational pathology models have emerged in academic research and are increasingly being deployed in the clinic:

- *Semi-automated review:* providing routine and repetitive tasks, such as cell counting and cell classification, to help categorize and triage samples for review by a human expert pathologist.
- *Fully automated review:* providing grade scoring, outcome prediction, and survival analysis to provide second opinions for pathologists and perhaps soon even diagnostic reports for clinicians.

Research across academia and industry demonstrates how AI tools can be developed for clinical decision support across different pathologies and disease types. For example, Grand Challenges in Pathology encourage multidisciplinary teams to build and optimize AI tools to tackle fundamental steps in routine pathology reporting that currently depend on human experts. The AI tools developed to tackle areas of unmet need will increasingly move from an initial validation environment through real-world evaluation to regulatory approval and national clinical development.

One such Grand Challenge seeks to streamline prostate cancer biopsy grading. Gleason scoring is a strong predictor of patient prognosis, but is challenging and time-consuming due to tumor heterogeneity. This leads to significant variability between the conclusions reached by expert pathologists. Notably, in September 2021, the FDA approved the first AI tool to increase the rate of prostate cancer detection on digital slides by identifying and highlighting areas of interest for pathologists (12). The tool is now also being evaluated by the UK's National Health Service through a national implementation pilot.

Similarly, the Cytosponge diagnostic test is being evaluated and rolled out by the NHS to drive the earlier detection of esophageal cancer. Here, pathologists review digital images of over three million esophageal cells, a

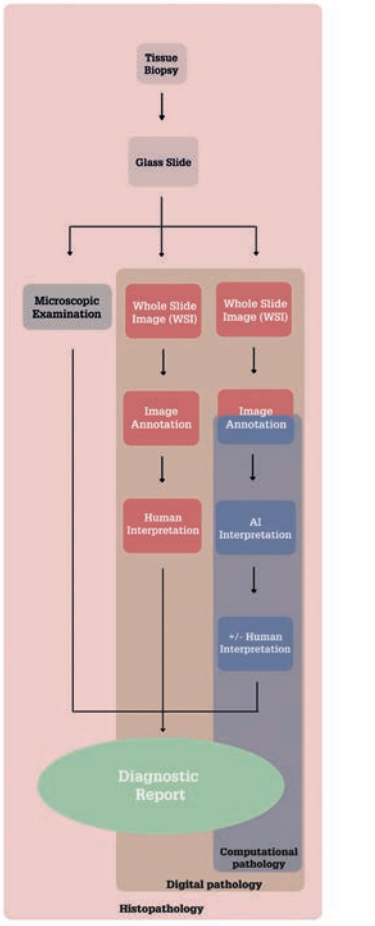


Figure 5. Histopathology and digital pathology as building blocks of computational pathology.

resource-intensive and repetitive process. Research demonstrated that, for diagnostic testing of cell samples for early esophageal cancer, a semi-automated review can reduce pathologist workload by 57 percent while maintaining the diagnostic performance of human expert pathologists (13). This will enable the test to scale to a national level without placing unsustainable pressure on our pathologist workforce.

Notably, fully automated models for computational pathology are still being validated in research. Thus, such tools are unlikely to materialize anytime soon – likely not until perceived barriers in regulation, ethics, human-AI interaction, and technology implementation are addressed. These primarily revolve around issues of trust, public acceptance, transparency, and explainability. To put it into perspective, we are more likely to see self-driving cars globally accepted and in use before fully automated pathological review.

Issues and considerations surrounding patient-AI interaction models are being explored and debated by think tanks around the world. For example, to what extent should semi- and fully automated models be used – to provide a second opinion for pathologists or an independent test score for clinicians? Clearly, such ethical and regulatory considerations impact healthcare pathways and must be addressed to deliver the future of patient-centered medicine.

Computational pathology offers to relieve pressures on reporting pathologists by increasing throughput without compromising accuracy. Digital pathology's impact on the workload overwhelming a diminishing workforce of pathologists may be limited – but computational pathology can help.

The key

Although computational pathology is the answer to relieving the pressure on pathologists, the key is in digital pathology infrastructure – the backbone that enables computational pathology (Figure 5). By ensuring a fully managed digital pathology service from biopsy to laboratory processing to reporting – and by solving the infrastructural, adoption, and operational challenges in the digital pathology workflow – the burden on pathologists can be reduced.

However, we must not forget that the challenge in computational pathology is the full adoption of AI tools by clinical teams. To address this, stakeholders in industry must collaborate with clinicians, academics, and policy partners to address implementation gaps in digital pathology. Such interdisciplinary projects will be crucial to establishing best practices, implementation frameworks, and change management for the system-level adoption of digital and computational pathology. There is a need to standardize processes and infrastructure for data sharing, image annotation, and image analysis techniques to ensure interoperability. Pathologists and clinicians must support policymakers and regulatory bodies in critically evaluating and defining governance guidelines and regulatory protocols for data protection. All stakeholders must work together to ensure that digital and computational pathology can have a sustainable positive impact on pathologist workflows and patient-centered care.

So how can you – as a pathologist, a clinician, or a patient – tackle the problems in digital pathology and unlock the promise of computational pathology?

- Get involved with local initiatives at academic institutions, small-to-medium enterprises, or bigger corporations that focus on providing solutions for digital and computational pathology.
- Reach out to local health-focused think tanks and policy advocates.
- Be open to change and growth in new computational technologies that support clinical decision-making.

Aishwarya Khanduja is a Research Fellow at Cyted. She conducted her research with the support of Charlene Tang, Luiza Moore, Alec Hirst, and Marcel Gehrung at Cyted. Charlene Tang is Business Development Manager, Market Access at Cyted, Cambridge, UK.

See references online at: tp.txp.to/beyond-dig

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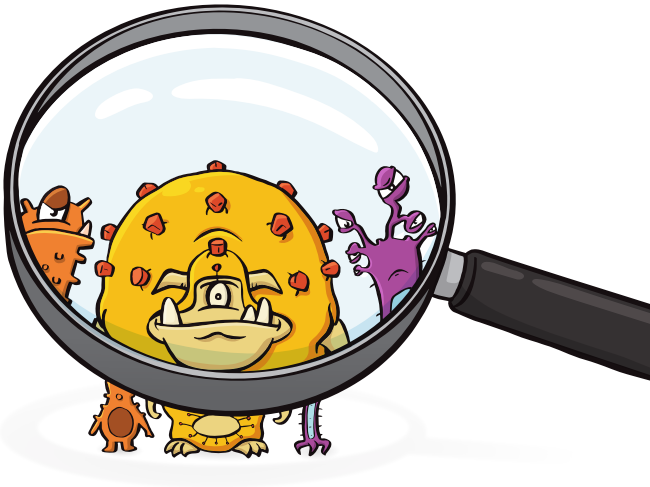

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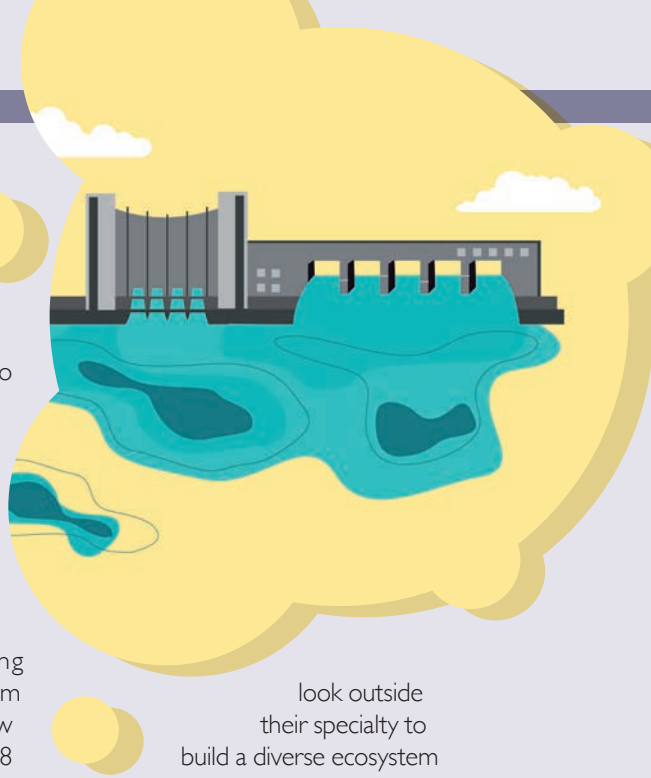


Beyond the Dam and the Floodwaters

Digital pathology's watershed moment

By Colin White

It's no secret that change is hard. And, as someone whose job involves introducing novel technology for scientific and medical endeavors, I know just how hard it can be.

Over the decades, I've studied the work of experts including well-known authors Clayton Christensen (The Innovator's Dilemma), Geoffrey Moore (Crossing the Chasm), and Chip and Dan Heath (Switch) in an effort to better understand factors that prevent and propel change at individual, organizational, and societal levels, and to learn about frameworks to ease and advance change. These authors' work tackles how difficult it is to effect change and acknowledges that change involving innovation is much harder to realize.

Their perspective rings especially true when I consider the state of digital pathology – a topic that tends to evoke strong reactions from pathologists and the lab community.

The dam and the floodwaters

Even a cursory online search for "digital pathology" unearths numerous articles depicting the forces preventing or propelling adoption and use. Authors frequently reference the metaphor of a "dam" of entrenched beliefs and practices under pressure from a "floodwater" of pro-digital market forces. These are a complex interplay of global forces including rising rates of cancer worldwide, escalating diagnostic workloads, aging and dwindling pathology workforces, and increasing patient expectations regarding access to health information.

I envision the dam as anchored by two large pillars – value-based concerns (such as time to return on technology investment) and operational concerns (such as turnaround time or reliability) – that are buttressed by change-related concerns (such as familiarity and comfort with existing technology or skepticism about the performance of new technology). In the last 12 to 18 months, I've started to see cracks in the proverbial dam walls, inviting a watershed moment for our industry. These fissures are the result of persistent pressure from the floodwaters, which has only intensified during the COVID-19 pandemic. As Liron Pantanowitz observed in the Journal of Pathology Informatics, the pandemic has been a technology stress test, allowing us to collect real-world data and gain a better understanding of digital pathology's promise.

Now, it's time to advance our conversation beyond the dam and floodwaters and explore two important downstream topics: building a solid digital foundation and watching for emerging swells to feed the floodwaters.

Fortifying the IT backbone

Conventional wisdom suggests that healthcare organizations transitioning to the digital realm should first focus on clinical considerations – but real-world experience indicates otherwise.

Successful institutions start by fortifying their IT backbone to support an end-to-end digital pathology workflow: scanning, storage, distribution, viewing, and sharing. Furthermore, they prioritize work related to ecosystem, standardization, and scope.

- *Ecosystem:* Effective digital adoption requires the pathology community to look outside their specialty to build a diverse ecosystem unified by a shared purpose. This ecosystem should include stakeholders with functional expertise in enterprise technology, security and privacy, data management, and data science. The Digital Pathology Association is one of the organizations leading this work. Although it's not easy to coalesce a cohesive ecosystem, the benefits associated with doing so are many. Ecosystem leaders will be well-positioned to jointly create and support validated workflows and efficient implementations, as well as document outcomes and benefits at department and enterprise levels.
- *Standardization:* Noted UK pathologist Darren Treanor has commented that "standardization and interoperability are vital for the successful adoption of digital technologies in healthcare." I agree. I'm fortunate to work for Leica Biosystems, a company partnering with other industry leaders to champion the creation of global data standards, including the Digital Imaging and Communications in Medicine (DICOM) standard for digital pathology. DICOM is a decades-old global standard in medical imaging that translates well to pathology and supports the integration of digital pathology

into routine practice. This work, along with efforts by Integrating the Healthcare Enterprise and updated guidance from the US Food and Drug Administration, increase pathologists' confidence and trust while setting the stage for a sustainable approach to digital pathology.

- *Scope:* A vital component of an effective digital strategy involves sizing the amount of change to a specific organization's culture and needs. Attempting to transition an entire department in one monumental shift is unlikely to succeed. Models to consider include the Heath brothers' approach to "shrinking the change" or Moore's approach to "landing a beachhead." Whichever model best suits your organization, I suggest finding opportunities for phased improvements to common pain points, measuring those small wins, documenting the process and outcomes, and sharing the findings broadly. I take inspiration from the work of the digital pathology team at Leeds Teaching Hospitals NHS UK Trust, which has published a virtual playbook in the Leeds Guide to Digital Pathology.

A new era of patient engagement

The World Health Organization identifies digital health technologies as a means of strengthening health systems and supporting patients to live healthier lives. I wholeheartedly agree, which is why I call out this topic as an important emerging swell that will add to the floodwaters compelling digital adoption.

Digital pathology has the potential to support the delivery of equitable healthcare to all patients. Once we're engaged in the digital realm, we will have a greater ability to tap into broad networks, move information around, and enhance patient care.

Related to this is the ability to involve patients more deeply in managing their health. Though early days for such efforts, thought-provoking work by Eric Topol (The Creative Destruction of Medicine; The Patient Will See You Now) and Bob Wachter (The Digital Doctor) invites us to consider how engagement with patients can shift to bring about better healthcare and – more importantly – better health. We can look to other specialties when crafting responsible policies around data transparency and patient access to health data to yield meaningful patient advocacy and engagement.

Recently I had the pleasure of speaking with Frank Gannon of the Baylor School of Medicine on the podcast Digital Pathology Today – and the topic of patient engagement was raised. Gannon aptly remarked, "What's really exciting about this is for the treating physician to be able to show a patient, 'This is what the cancer looks like,' or, 'This is what your infection looks like,' so patients are better able to understand and become more involved in their treatment." Cancer would no longer be an unseen mystery, but something easily visualized so patients knew what was going on inside their bodies. In addition, Gannon commented, "Better-informed patients able to help in their decision-making is something we all look forward to."

Toward the horizon

Gannon's words echo my personal sentiments. I consider it my great privilege to collaborate with pathologists to bring novel technologies to the mainstream. Certainly, it is my life's work to bring to reality Leica Biosystems' patient-centered mission of "Advancing Cancer Diagnostics. Improving Lives."

As hard as change can be, I believe the payoffs of a transition to digital pathology will be well worth the effort. I equally believe that, working as an ecosystem, we can make it easier. The potential of better patient care awaits.

Colin White is Senior Vice President and General Manager of Advanced Staining & Imaging at Leica Biosystems, Melbourne, Victoria, Australia.

Digital Pathology at Baylor College of Medicine

A crucial early step in Baylor's adoption of digital pathology was establishing an IT backbone structured to address the institution's needs for infrastructure to generate, move around, annotate, report on, and share images.

"Information technology was where we decided to start, which may seem a little atypical for pathologists," said Francis H. Gannon, who co-leads Baylor's clinical pathology practice, Community Pathology Associates. "However, the analogy that I use is that it's equivalent to building a stadium. It's a captivating proposition to build a new stadium but, if you don't have the roads and the plumbing, it's just a big, expensive building sitting there."

Working with Leica Biosystems, Baylor Pathology identified and addressed foundational IT considerations including selecting a project technology leader; partnering with the enterprise and laboratory IT teams; determining networking, storage, and security needs; comparing requirements to tools, budgets and timelines; and prioritizing specifications for short and long term.

Gannon elaborated, "Simply put, we transformed the way we think about and implement IT connections, transference, and bandwidth. Doing so allowed us to move forward to the point that, by 2022, Baylor Pathology will be a fully digital anatomic pathology service, including hematology."

Francis H. Gannon currently serves as the Vice Chair of Operations for the Pathology and Immunology department at Baylor College of Medicine, Houston, Texas, USA.

Profession

Your career
Your business
Your life

But You're So Good with Patients!

Dispelling medical professionals' misconceptions about pathology

By Colton Biehl and Kamran Mirza

"Oh no!" they cry.

"But you're so good with patients!" they exclaim.

"What's the point of doing things once they're dead?" they joke.

"Don't bother teaching that student; they want to go into pathology," they say.

These phrases are familiar reactions to medical students who show an interest in pathology. For many reasons – some due to a lack of advocating for themselves, some because other physicians don't fully understand our role – pathologists are probably the most misunderstood physicians in medicine. Even when you search "pathology" online, most hits are for "speech pathology," which doesn't help matters (no offense to speech pathologists). This often leaves pathologists and aspiring pathologists feeling like broken records as they clarify misconceptions surrounding their field of work and explain their central role in patient care.

Brilliant, hardworking students should not be deterred from pathology by archaic ideas that don't truly represent the field. A student's choice not to apply for pathology should be based on their interest in another field – not on the inaccurate stereotypes that have become too commonplace even among medical professionals. And students who do choose pathology should be encouraged to pursue their passion – not denigrated for it. Our goal is to raise pathology's profile so that medical students are inspired and encouraged by their faculty and peers when they express an interest in the field.

Pathologists don't like to socialize

This misconception is like claiming that a monk attends long meditation retreats because they do not enjoy the company of others. The analogy seems appropriate because both miss a large portion of the truth and tend to look at a situation through a rather negatively tinted lens. Medical students, physicians, and others commonly don these lenses when they find out that someone wants to be a pathologist. Those lenses miss the depth and richness of the field. The myopia hides the possibility that perhaps an aspiring pathologist cares so deeply about their future patients – and about medicine itself – that they want to study the root cause of disease processes at the cellular level.

Although it is important for medical students to understand whether they want to work directly or indirectly with their patients, we can assure you that those who choose diagnostic fields such as pathology or radiology care no less about patient contact. Though neither author is a monk, we can still imagine that their deep meditation practice and experiences attained while on retreat exponentially enhance their relationships with others after the retreat ends. The study of disease at the cellular level also significantly changes a pathologist's view of medicine and their patients for the better. We contend that far more pathologists are drawn to the specialty by the magnetic pull of demystifying human ailments – examining cells, stains, and microscopic images of various disease processes – than by an opportunity to avoid patient contact. The intellectual and academic variety of pathology is its most exciting attribute.

Pathologists prefer working with dead people; they want to do autopsies rather than treat the living

In medical school, Colton Biehl had the opportunity to be a part of an anatomy fellowship program in which he and a partner were assigned their own cadaver to dissect throughout the summer and use to teach other medical professionals anatomy. Their professor explained to them that these were their first patients. These patients donated their bodies to science so that students could better understand

Colton scrubbed into a surgery.

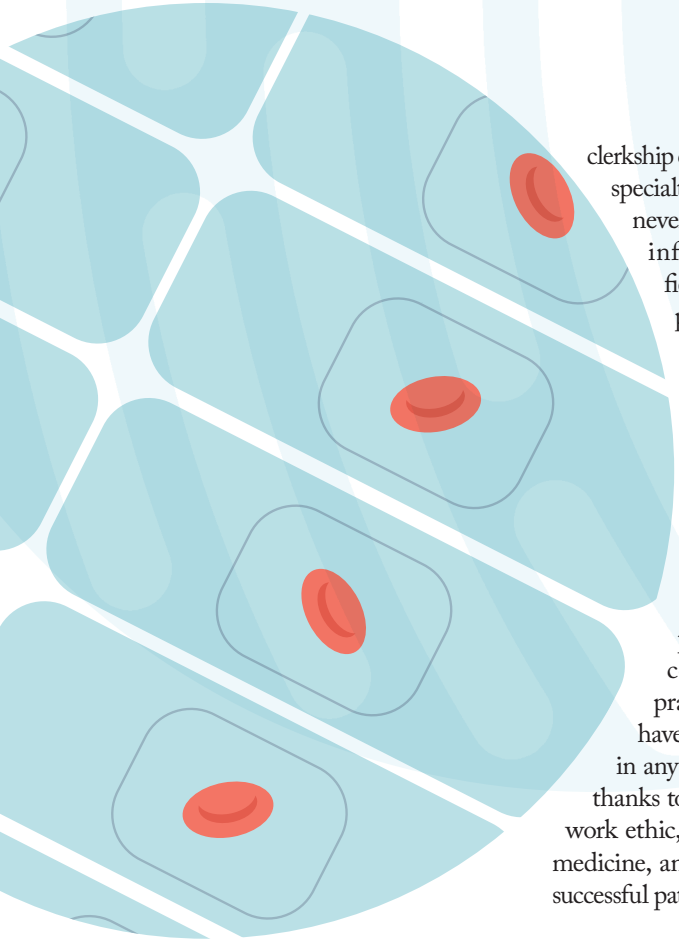
the intricacies of the human body and, one day, apply that knowledge to save another person's life. These patients were shown the utmost respect and appreciation; at the end of the course, the medical school held a ceremony to honor all of these patients after the course was over and they were always shown the utmost respect and appreciation. Hundreds of students became more intelligent, more knowledgeable, and more compassionate people because of the experience of working with the dead.

Multiple preceptors have responded to Colton's interest in pathology with two comments: "Really?" and "Oh, so you prefer working with dead people?" It is understandable to an extent that the word pathology often fires up the neural circuitry of morgues, autopsies, and the movie Concussion (thank you, Hollywood). After all, it is true that forensic pathologists are the doctors who conduct autopsies and determine the cause of death. It is also true that forensic pathologists do an extremely important job that provides emotional gratification and peace of mind to many families on a regular basis. It is not, however, true to say that all pathologists perform autopsies every day. Although autopsies are likely part of the training process in most pathology residency programs, they do not encompass the entirety of a pathologist's training and specialization. It would be like saying to a medical student, "Oh, so you only want to study biochemistry?" Both responses indicate a lack of understanding of the training process. Medical students take biochemistry courses – but they also learn many other things. Pathologists are often trained to perform autopsies – but the field's opportunities and specialties go far beyond death investigation alone.

Pathologists lack the social skills to be successful clinicians

Somehow, the idea persists that people only decide to spend their life pursuing pathology after realizing their clinical skills are inadequate and they just don't have the social skills to compete in other fields. At that point, we just throw our hands up, buy ergonomic chairs, and accept the hand the universe has dealt us – pathology.

Or, in an alternate and more realistic universe, a medical student has a revelation on a quiet sunny afternoon during their dedicated Step 1 study period. That student thinks to themselves, "The past four hours I spent reading and studying Pathoma were really enjoyable. Understanding disease processes at the molecular and cellular level arms me with the information I need to help resolve these disease processes." Colton, for instance, distinctly remembers going on a



long walk with his wife and talking about his newfound love – pathology. Luckily, she wasn't jealous of his new love affair and has supported Colton in his journey to becoming a pathologist ever since.

Perhaps pathology's negative image comes from its assumed association with autopsies and cold, dark microscope rooms – but any trip to a pathology department will present a different image. Medical students will have the opportunity to interact with pathologists who are much warmer and friendlier than stereotypes would suggest. Spending time in the pathology department could replace words like "cold" and "detached" with ones like "approachable," "knowledgeable," "encouraging," or "inspiring."

Or perhaps the issue is that, during preclinical years, medical students are exposed to pathologists as teachers and not as clinicians. The latter only happens if students choose pathology electives in their third or fourth years of training. The lack of a universal clerkship cements negative notions of the specialty and most medical students never get the chance to make an informed decision about this field. Undertaking an elective in pathology would show medical students that, although much of a pathologist's day-to-day work may be physically removed from the patient, the decisions and diagnoses that the pathologist comes to after concentrated effort has the most direct and personal impact on that patient's life and treatment course. Undoubtedly, many practicing pathologists would have made outstanding clinicians in any number of other specialties – thanks to the same attention to detail, work ethic, love of learning, respect for medicine, and focus that has made them successful pathologists.

Pathologists don't care about their patients (or other people)

Ouch! This misconception is wrong on so many levels. The most successful counterargument to it is the fact that pathology, by definition, is the study of diseases and disease processes. Why would someone commit their life to understanding disease if they didn't care about the people it affects? What excites us about pathology is that it equips us with the fundamental understanding of why a disease occurs; thus, if an adequate treatment does not yet exist, perhaps we can help develop one. Perhaps a medical student's life was drastically affected in early childhood by losing a loved one to cancer and they hope to help contribute to the body of knowledge and research effective therapies. The words written (or typed) by a pathologist carry an immense burden of responsibility – diagnosis, prognosis, and correct treatment all lie in the balance. Without this first step, there can be no healing.

Pathology's draw is that it addresses the question of "why?" Pathologists – whether aspiring or practicing – want to get to the root causes of issues. We enjoy thinking about complex problems in life and science. For those interested in medical research, evolutionary biology, cell biology, the origin of life, or genetics, pathology seems like the ultimate answer to all of life's curiosities. The entire field aims to answer the "whys" of a patient's disease and provide their medical team with the appropriate information to resolve the issue.

We often think about medicine at various levels or planes. Imagine a microscope with various objective lens sets to examine a specimen – say 4x, 10x, 40x, and 100x. Different diagnoses will require different objectives to provide the right level of magnification for accurate diagnosis. Some disease processes can be diagnosed clinically at the "zoomed out" 4x objective level and don't require lab work or imaging. Others require a much more magnified 100x look at the patient's blood or tissue to see what is happening at the cellular level. Think of the various medical specialties as 4x or 10x levels of patient interaction. You're analyzing the macroscopic manifestations of a disease process that is occurring at the cellular level. Pathology analyzes the microscopic level and sees what is happening below the field of view of the naked eye. Tissue diagnosis is the gold standard.

(Of course, this is not to disparage any other field of medicine; the 100x view is not superior to the 4x view, but is better suited to certain diagnoses.)

We pathologists prefer to interact with our patients on the 100x level. We see patients every day in the laboratory – their cells, their tissue – and we apply all of our effort, training, and mindful concentration to each slide in hopes of providing an accurate answer that can guide their treatment. We don't care less about our patients; we care so deeply about them that we are willing to spend as much time as it takes at the 100x level to make the proper

Kamran Mirza.

diagnosis. Before medical students decide which specialty best suits them, they first should establish on which level or plane they desire to interact with their patients. We, personally, prefer the 100x plane.

Only introverted physicians can find fulfillment in pathology

It is important for medical students to understand themselves and to factor that knowledge into their residency decision equation. Not all pathologists are introverts – and the notion that pathologists hide in ivory towers with their microscopes should be discarded. Much of a pathologist's day is actually spent interacting with other members of the medical professional team – and though we may not spend our entire day interacting with patients, the illusion that we don't interact at all is simply not true. We believe that any medical student can look at the bigger picture, see the vital role of the pathologist, and consider joining the profession an honor equal to joining surgery or medicine.

Imagine the time an author spends in solitude and deep thought to produce a book that can forever change someone's life. Similarly, a pathologist's concentrated effort in the quiet of a laboratory corner can provide an accurate diagnosis to a patient that forever changes the course of their life. We don't think of novelists as "cold" or "uncaring" – so why apply those labels to pathologists?

Colton Biehl is a fourth-year medical student at Nova Southeastern University Dr. Kiran C. Patel College of Osteopathic Medicine, Fort Lauderdale, Florida, USA.

Kamran Mirza is Associate Professor and Vice Chair of Education in the Department of Pathology and Laboratory Medicine, Loyola University Chicago Stritch School of Medicine, Maywood, Illinois, USA.

Dear Pandemic...

Fighting the good fight against the COVID-19 infodemic

Olivia Gaskill interviews Lindsey Leininger

How did "Those Nerdy Girls" and the Dear Pandemic campaign begin?

It started off when our founding editor-in-chief, Malia Jones, an epidemiologist at the University of Wisconsin, wrote an email to her friends and family back in March 2020 to tell them that COVID-19 was the real deal and that, as a pandemic, it was going to be a problem for a while. The email went viral on social media and ended up getting published in USA Today; Malia was even invited to speak on Dr. Phil. After that, she was flooded with questions from everyone. "What's a pandemic?" "What do I need to do differently?" "What's life going to be like?"

Her colleague, Alison Buttenheim (also an epidemiologist, behavioral scientist, and public health scientist), was also getting a lot of questions. So they decided to answer them more efficiently (together) on Facebook – and that's how Dear Pandemic was born. They reached out to their personal networks, including me, Jennifer Beam Dowd (our nerdy girl across the pond at Oxford University), and a few other epidemiologists and clinicians to ask if we could help answer some of the questions. Initially, we thought it would be for our friends and family and personal networks, but it just kept growing.

We've now posted over 2,000 evidence-based posts on staying safe and sane during the pandemic. We have over 100,000 followers on our English-language Facebook page and another 49,000 on our Spanish page. We have satellite presence on Twitter and Instagram, we've done hundreds of interviews with traditional media, and we've given talks to many different audiences – from middle school classrooms to the World Bank.

Has the campaign's aim changed since its launch?

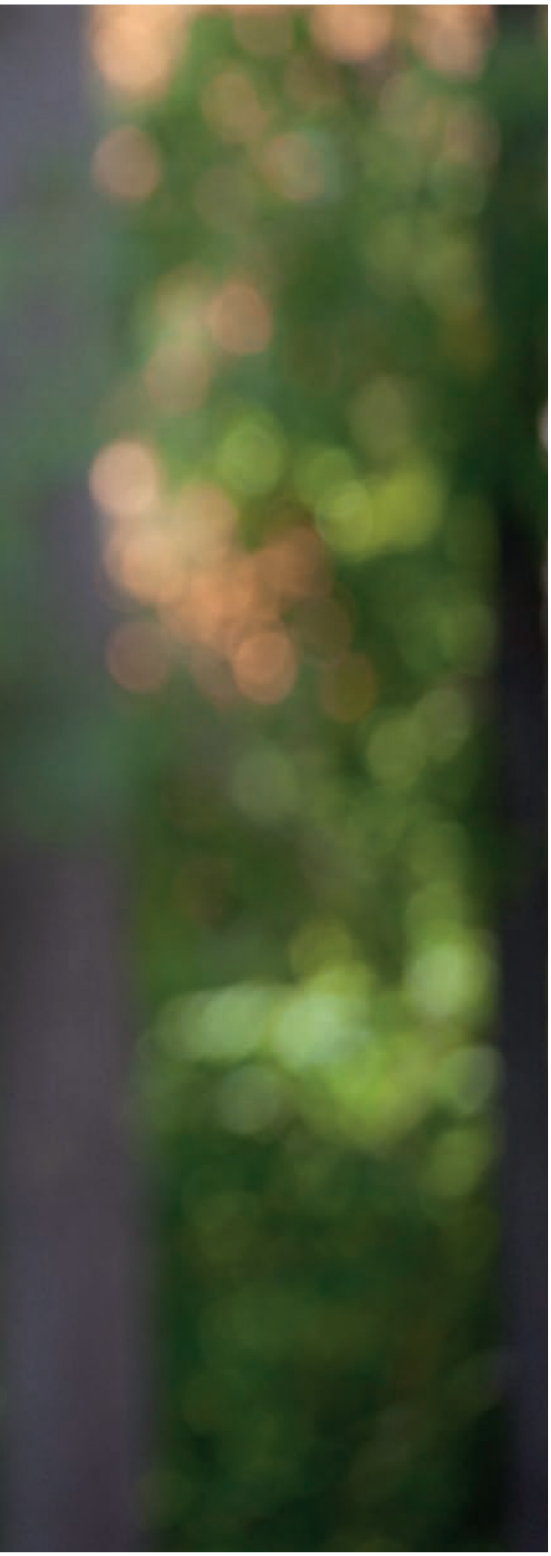
Dear Pandemic is based on a decades-old advice column, "Dear Abby," where people would write in with their problems and "Abby" would answer with her advice. We still very much play this social listening role, and we are also more intentional about a few things. We try to be timely and we care about being trustworthy, so we focus on using credible citations and references. We also try to be comprehensive, because we've learned that people are overwhelmed with information; many of our community members look to us as a one-stop shop. They don't want to see all the headlines; they just want one consistent place they can go for their COVID-19 news. This timeliness, trustworthiness, and comprehensiveness is something we've evolved into from our initial question-and-answer format. We still take questions, but now we get more than we can answer, so we try to respond to those that pop up the most, cover a broad range of issues in the pandemic, and are timely and relevant.

"We need to equip the public with their own critical thinking tools."

Talk me through that process...

We have a formal question box in which we've received over 4,000 questions so far; we also receive questions on our Facebook page and in the community. We have an editorial calendar where we each take a spot every week. We've tried to have a broad coalition of scientists writing, so our Nerdy Girl team ranges

Lindsey Leininger.



from immunologists to mental health practitioners as a reflection of all the different types of questions we receive. My background is in health policy, analytics, and economics – I don't understand lab science, so I'm grateful to the scientists on our team who give me the "bottom line" for those types of questions.

When it comes to writing, we are scientists, so the rigor and citing of sources comes naturally – the learning curve has been more about writing in a clear, accessible style. Our community doesn't want to track down all the references we cite; there are pathologists and lab scientists in the community who will seek them out, but I've learned that the lay public just appreciate that the citation is there in the first place. It gives us a credibility boost and generates trust from our community and, even though they may not love science as much as we do, we can give them the "tl;dr" (too long; didn't read).

Why has health misinformation been so prominent during the COVID-19 pandemic?

I don't have a conclusive answer to this, but tech and social media platforms have become a major force in society – and regulations have not kept pace. More and more people are gathering their information from these platforms, rather than from the countervailing forces of traditional media and press conferences. Furthermore, the landscape of traditional information channels has been blown up to the point where information-seeking has become highly fragmented. I can go to my social media pages, someone else can go to theirs, and never the twain shall meet. With this fragmentation, misinformation can proliferate – and has proliferated.

Going forward, we must get better at fighting back. I'm hopeful that the World Health Organization (WHO) is throwing its shoulder into a scientific discipline called "infodemiology" – characterizing and battling health misinformation on the internet. Our existing communication infrastructure has been a disaster; the COVID-19 pandemic has been running parallel to this "infodemic," and the Centers for Disease Control and Prevention (CDC) in particular needs to learn from this and improve its response to future epidemics.

The democratization of medical knowledge is a force for good and, as scientists, we all have a role to play in fighting misinformation. We can do this by teaching scientific literacy, data literacy, and media literacy – giving people the tools of science; teaching them that science is a method, not a fixed set of facts; and showing them how to think like a scientist. We need to equip the public with their own critical thinking tools.

Are there any differences in how you relay information on each social media platform?

As a first-time public-facing communicator, one thing I've learned (that may be obvious to my communication scholar friends, but wasn't obvious to me) is that every

platform is different. The campaign started on Facebook and it was many months before we had a website. On Facebook, people want to be in the community – they respond and react in a raw, emotional way. The conversation can go sideways quickly, but it can also be beautiful. Often, we watch our community members step up and fight misinformation themselves. However, we soon learned that we needed a website, because journalists and fellow scientists and clinicians will not cite a Facebook post as a trustworthy source. On the website, we don't get that instant user feedback, but publishing a blog post on the website means that professionals will feel comfortable citing it.

Our Instagram audience is entirely different to Facebook – on the latter, they're a lot like us. We're middle-aged, female, mom scientists, but our Instagram audience is younger and has different cultural and political lenses on the world. We have to cater to a younger audience who are much more socially aware. Also, Instagram is a visual format, so we don't get as many written comments, but we can create a more visual brand.

Have you faced any challenges as an all-woman team?

Actually, I think we have benefited from it. Our brand was given to us. It was unintentional – we just happened to all be female. Early on, community members would say, "I'm going to listen to those nerdy girls," and the name stuck, so we made it more intentional because we found that our audience liked having a public-facing team of female scientists. We know that male experts have had more media time and more opportunities to be public-facing. For our community (most of whom are women) to see female scientists in the public eye and the media has given them some hope.

It has also been very empowering. Some of the notes that we get (we keep them because they're personally meaningful) are along the lines of, "Thank you, Nerdy Girls, you're showing my daughter that women can be scientists," and "Thank you, Nerdy Girls, I am a female scientist and have experienced a lot of sexism. I'm so delighted to see you doing this work in the public eye." When we receive these types of emails, we realize that this is why we do it.

We mostly run Dear Pandemic on a volunteer basis. We are working moms in a pandemic – at one point we counted 30 kids between us, even before we onboarded new writers. There are two key pillars that engender trust in science communication: source credibility and relatability. Our credibility comes from being scientists, but the fact that we are working moms has made us more relatable to our community in a way that sparks and maintains trust – which, in today's world, is sacred.

What's the most frustrating myth you've heard about COVID-19?

When it comes to misinformation, the 5G network myth is a head-scratcher; it kind of blew my mind. But the two that have made me the maddest are "COVID-19 is just the flu" and "We don't need to wear masks." I've spent the past 18 months debugging a bunch of those comments. They're like a Hydra – cut off one head and two more spring up in its place. There is all kinds of misinformation out there that rears its ugly head, but COVID-19 killed eight times more people in a year in the US alone than the worst flu season in a decade. There's always a flavor of the week, but those two myths just won't die.

The other one that has made me viscerally angry as a mother is the myth that the COVID-19 vaccine impacts fertility. It's a sucker punch because, if you want to incite vaccine hesitancy, you go straight for that. It was like the MMR vaccine/autism myth all over again – nasty, intentional, and coordinated. I have now had dozens of conversations with worried young women in my life and in my personal networks about this piece of misinformation, but it's much easier

"There are two key pillars that engender trust in science communication: source credibility and relatability."

to poison a well than it is to clean it up.

We need journalism training for scientists to teach them how to tell a story and provide an anecdote or give an example in a way the lay public can understand, so that we can stop journalists running away with results and spreading misinformation. Going forward, I want to train other people to be public-facing scientists rather than be one myself, so I've been thinking a lot about how to train the "nerdy girl" nation. I'm just one person and it's not about me; it's about arming every school nurse, pathologist, clinician, or school librarian – all of the "nerdy girls-next-door" across the country. Our most powerful force against misinformation is equipping and empowering them to use their voices in public spaces.

What's the key to getting through to people who believe health misinformation?

There is a science of science communication and there are some empirically backed tips on how to talk about conspiracy theories and misinformation. Typically, it's to show empathy – don't come at somebody with shame or ridicule; connect authentically, affirm critical thinking, and invoke conspiracy theory "exiters" as trusted messengers. However, you also have to know when to walk away. If you're batting .250 with these conversations, you're a superstar. It's slow, hard work and it takes multiple conversations that often don't end up working.

We all have a part to play. For example, lab scientists are patient-facing in a way they don't understand; they live in a community, they have friends, family, kids, and though they may not see patients all day long, they're embedded in a community where their voice matters and they have the credibility to be a trusted source. That's powerful because we've learned that the truly effective way to fight misinformation is via offline communication. It's the personal connection that brings people back. I want lab scientists to feel empowered in the role they play as community members – they're a potent resource against misinformation.

Once the pandemic is past, what will be next for Dear Pandemic?

Medical myths and misleading health headlines preceded the pandemic and they will be around long after. We will continue to help people understand health news and we are planning to create a nonprofit to make sure that good health information is accessible on all kinds of different platforms – meeting people where they are. As a society, our wiring has been scrambled; we're going to be so anxious and tuned in to infectious diseases that there's going to be a significant appetite for keeping up with emerging threats. Personally, my next step is to ensure we get better at fighting the infodemics that inevitably emerge when health emergencies pop up.

It has been a challenging time, but I would feel remiss if I didn't say that there has been joy and meaning and purpose in this work that we've been doing – the joy of being in a community with fellow female scientists has been a real bright spot in the dark and we've been fueled by our purpose of explaining scary headlines. It has been an honor and a privilege to be a standard-bearer for women in science. The work is serious and heavy, but there are some rewards that I will take with me for the rest of my life.

To find out more about the Dear Pandemic campaign, visit: tp.txp.to/dearpand

Lindsey Leininger is a public health scientist and Clinical Professor of Business Administration, Tuck School of Business, Dartmouth College, Hanover, New Hampshire, USA.

Supporting Laboratories Through the IVDR Transition

With new regulations coming into effect for in vitro diagnostics, how can laboratories prepare?

The new EU legislation for in vitro diagnostic (IVD) medical devices, In Vitro Diagnostic Regulation (IVDR) (EU) 2017/746, is currently scheduled to go into effect in May of 2022 after a five-year transition period. The new regulations aim to improve the quality, safety, and reliability of IVDs in countries requiring CE-IVD compliant products. These products will be reassessed according to level of risk; the majority will require review and approval by a notified body. Manufacturers and suppliers of IVDs will be obligated to provide analytical performance data, scientific validity, peer-reviewed literature, and clinical performance data to show that their products meet these new, more stringent standards for clinical evidence.

Thermo Fisher Scientific has made significant investments to ensure that its CE-IVD products will meet the new requirements. In this article, Nicola Normanno (Director of Cell Biology and Biotherapy Unit, Istituto Nazionale Tumori-IRCCS-Fondazione G. Pascale, Naples, Italy, and President of the International Quality Network for Pathology) and Garret Hampton (President of Clinical Next-Generation Sequencing and Oncology, Thermo Fisher Scientific) discuss the steps the company has taken to prepare for the IVDR transition – and what clinical laboratories must do to ensure they are ready.

GH: How ready are EU clinical laboratories for the new regulations?

NN: Unfortunately, most labs are not prepared for IVDR. They are counting on having IVDR-ready solutions available from their partners and don't realize that many test companies have been slow to start the necessary validation to achieve compliance. Additionally, many labs involved in clinical practice believe they can continue to use the panels available based on their current regulatory labeling and don't realize they will be required to provide additional validation.

Although the date for IVDR implementation is widely known, there has not been enough communication to help labs prepare. As a result, most labs are unclear on the implications and what they should be doing to get ready for the new regulations. This gap in preparedness is going to create a huge problem in the European diagnostics world in the next few months.

GH: How will the new IVDR requirements impact patient care?

NN: Generally speaking, the introduction of additional guidelines to reduce variation and increase oversight of in vitro diagnostics is a good thing for patient care. Manufacturers and developers must provide clinical and analytical validation of new tests and external bodies verify that companies' claims are accurate.

Currently, there is little oversight in this market, so the new regulations will improve our ability to provide high-quality biomarker tests. However, we need to be sure labs can focus their attention on achieving compliance to avoid a gap in accessing this testing once IVDR goes into effect.

GH: What is the role of the International Quality Network for Pathology in supporting clinical labs in complying with new IVDR requirements?

NN: IQN Path will play an essential role in the implementation and maintenance of IVD regulations in the next few years. Every member of IQN Path is involved in external quality assessment (EQA) or quality market testing. We do not certify labs; when there is a new biomarker, our group looks at the technology to help harmonize the approach from different EQA providers.

EQA will play an important role supporting post-market surveillance of in vitro test performance to make sure the technology isn't failing after IVDR compliance is secured. In some cases, this post-market surveillance has identified areas that need additional focus or innovation before the product is fully compliant in real-world settings.

IQN Path will also help guide academic labs that want to continue to use laboratory-developed tests or commercially available solutions designated as "research use only" in clinical research. In these cases, labs will need to provide additional information on clinical and analytical

validation. EQA will be increasingly important to identify gaps in the process or performance of these tests.

GH: How do you see new IVDR requirements impacting EQA programs in the EU?

NN: To accelerate validation of devices and tests, academic labs and companies developing these technologies will need to collaborate closely. Companies and manufacturers will need to provide additional clinical and analytical validation, which will be difficult without ready access to patient samples and data from lab partners. As new devices are jointly validated by academia and industry, other clinical labs can trust this data knowing it came from their peers at the bench, not just device makers looking to secure approval.

NN: As a manufacturer and distributor of medical devices, how is Thermo Fisher preparing its NGS solutions to meet the new IVDR requirements?

GH: Thermo Fisher is committed to assisting our customers through this transition by assuring them that our CE-IVD products are prepared to meet IVDR compliance. As president of clinical NGS and oncology, I have been focused on ensuring our NGS instruments will meet the new requirements. We began our preparation for the IVDR transition several years ago with the design and development of our Genexus platform; it was developed under IVDR design controls and, for existing customers, a future field service update will update the sequencer to full compliance and eliminate the need for the purchase of another IVD-labeled instrument.

For our NGS platforms and assays, Thermo Fisher has invested heavily in our manufacturing facilities to ensure that these products are manufactured and tested with the quality and documentation requirements needed to be compliant to the new regulations in the future.

NN: Can you expand on the clinical evidence that a manufacturer like Thermo Fisher must demonstrate to support the intended use of your NGS instruments?

GH: The new regulations require manufacturers and suppliers to ensure that their products meet more stringent standards for clinical evidence. As such, we've made significant investments to demonstrate the clinical utility of our NGS solutions.

There are two primary pillars to our approach in demonstrating this clinical evidence for our oncology applications. The first is developing solutions that can detect and report relevant biomarkers, such as EGFR mutations and ALK fusions, that are widely used in the clinical field and supported by medical guidelines. The second pillar will leverage our pharmaceutical partnerships to demonstrate the assays' clinical utility as companion diagnostics (CDx) to support targeted therapy selection. Thermo Fisher also embarked on a multimillion-dollar program to collect clinical-grade samples for testing and development to support the clinical validation needed for IVDR.

NN: Which NGS products are you preparing to meet the new requirements?

GH: Our primary NGS platform that will be fully IVD compliant is the Ion Torrent Genexus Integrated Sequencer. This is a first-in-class, highly automated, fully integrated NGS sequencer capable of generating results in as little as 24 hours.

To complement the Genexus sequencer, we will also have a fully compliant automated platform, the Ion Torrent Genexus Purification System, to facilitate the extraction and quantification of nucleic acids directly from clinical samples. The Genexus Purification System links directly to the Genexus sequencer, allowing full sample-to-result processing with only two touchpoints and less than 20 minutes of hands-on time.

To support clinical oncology applications, we will also launch a CE-IVD labelled 50-gene solid tumor diagnostic test to run on the Genexus System, Oncomine Dx Express Test, which will dramatically improve oncology patient care by providing complete actionable precision medicine results in as little as 24 hours. We also plan to ensure that the 46-gene solid tumor Oncomine Dx Target Test will be compliant under IVDR.

For reproductive health applications, we are planning to release the Ion Reporter Aneuploidy Dx as a fully IVD-compliant workflow for preimplantation genetic testing for aneuploidy (PGT-A) on the Ion GeneStudio System. The Ion Reporter offers rapid, simple workflows to support aneuploidy detection using as little as a single cell's DNA as input.

Thermo Fisher is committed to delivering additional clinically validated assays that will operate on the Genexus System in the future. These assays include comprehensive genomic profiling, hemato-oncology, and reproductive health applications.

Would you welcome the proposed extension of the transition period?

NN: I think that an extension of the transition period is definitely needed. However, I feel that we need clear and defined plans from government bodies, companies, and laboratories to ensure that the new system will be in place at the end of the transition. Even in the initial transition period, we only began discussing the new IVDR a few months before the deadline.

GH: It would not change our plans; we will carry on with our work at full speed.

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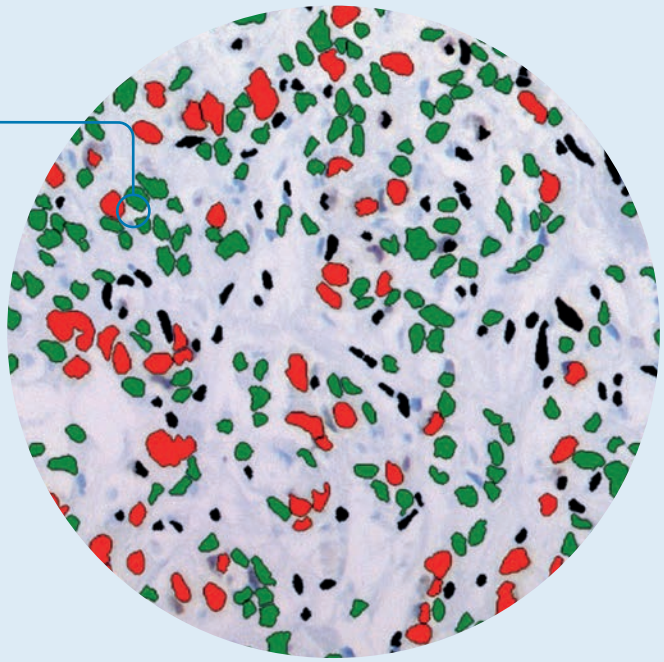

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The Proteomics Ethicist

Sitting Down With… Matthias Mann, Professor of Proteomics and Signal Transduction, Max Planck Institute of Biochemistry, Munich; and Director at the NNF Protein Research Center, Copenhagen

What drives you forwards?

I'm immersed in developing proteomic technologies – and understanding how these precision tools can impact the study of cancer and other diseases. However, we are also very concerned with the ethics around the applied use of proteomics. Technology is advancing at pace, and it is imperative that we stop to consider the ethical implications of our efforts, and how, importantly, this is put into practice.

Throughout my career I have mostly been driven by technology. For instance, as a PhD student I was intrigued by how mass spectrometry (MS) works and how this could be applied to studying biology, which was not as commonplace then as it is today. Some 30 years on, the technology has advanced considerably and we are able to interrogate more and more complex systems. This forward motion shows no sign of abating and still captures my attention just as much now as it did when I was a PhD student.

How did you get to where you are today?

I had a chance encounter with a visiting professor – John B. Fenn – from Yale whilst studying for my master's degree at the Max Planck Institute in Goettingen. He encouraged me to move with him to undertake a PhD. He is the inventor of the electrospray ionization technique for the analysis of biological macromolecules and was awarded the Nobel Prize in Chemistry in 2002 – making this choice in my career a particularly fortuitous one!

I realized that, though physics and chemistry were well-served by this kind of technology, John had demonstrated applications that stretched into biology – a very underserved discipline.

Molecular biologists at the time were starting to unravel complex biological processes that required understanding and characterizing specific proteins. They would painstakingly purify the proteins using gels, only to struggle with analysis because they only had access to techniques that required a lot of source material. And, unfortunately, gels were not compatible with MS. We figured out how to make these proteins available for MS, devised the nano-electrospray technique to increase sensitivity, and created peptide sequence tags to allow protein identification. With the human genome sequencing project underway, we were able to identify various proteins for the first time, including telomerase and key proteins in the immune system.

How has modern computing impacted upon your work?

Computing power has ramped up significantly over the years. I'm somewhat unusual in that I come from a physics and mathematical background, which has stood me in good stead when it comes to harnessing such advances. I could write new algorithms and programs to handle complex MS data. I would say my perspective – very much shaped by my multidisciplinary background – has helped me see biological problems in a different way and given me the ability to drive the technology forward.

Tell me about your interaction maps?

We work with and derive interaction maps that highlight the connections between various biological systems. It's basically network analysis – akin to the social network mapping used by Google and the likes. One such map is the protein interaction map, where protein–protein interactions can be mapped to help elucidate their function.

We became involved in a project to map a whole organism – the "holy grail" of interaction mapping! A network describing a cell is already in place and we have since been involved with repeating this work for a significantly more complex yeast cell. This work illustrates the progress the field has made in the last 20 years. Modern advances have allowed us to analyze these interactions using a fraction of the material required previously – and at much greater speeds and resolution. The impact of this progress is seen in human biology, where a newly identified protein can be dropped into a map to shed light on its possible function and utility. The next step is to explore these maps in a dynamic process, during some cellular activity or response over a specific timeline.

What are the implications for COVID-19 research?

The multiple waves of COVID-19 certainly spurred us to see what our technology could add to the research landscape. In a fruitful collaboration, we used SARS-CoV-2-infected cell cultures to look at what was happening in the infected cell, including post-translational modifications. We discovered that the virus uses cellular proteins to modify its own, which was not known at the time. We also looked at the interaction map to determine which proteins were interacting with which. These findings led to the postulation that some drugs could be repurposed for fighting COVID-19. We are also investigating patient body fluids and post-mortem tissues to aid disease prognosis and tissue-specific mechanisms.

What is the future for proteomics?

Proteomics has developed greatly over the last 20 years or so, with many good research groups in the field – and that has been coupled with the emergence of enhanced computer power and commercial collaborations. However, we still have a long way to go! That said, we now have higher sensitivity, we can mine a wider range of data, and, critically, we need less sample. Modern techniques have real clinical utility because a small blood sample can be analyzed as a diagnostic for diseases. Such an approach can also be prognostic; for instance, where a breast or prostate cancer has not yet manifested but the patient is predisposed to such changes. These techniques may determine the potential severity of the disease and inform better treatment strategies. But such a direction calls into focus the ethical positioning of such tests because we do not want to overdiagnose. Specificity and sensitivity are critical to make the use of such tests ethical, especially when screening a large number of people.

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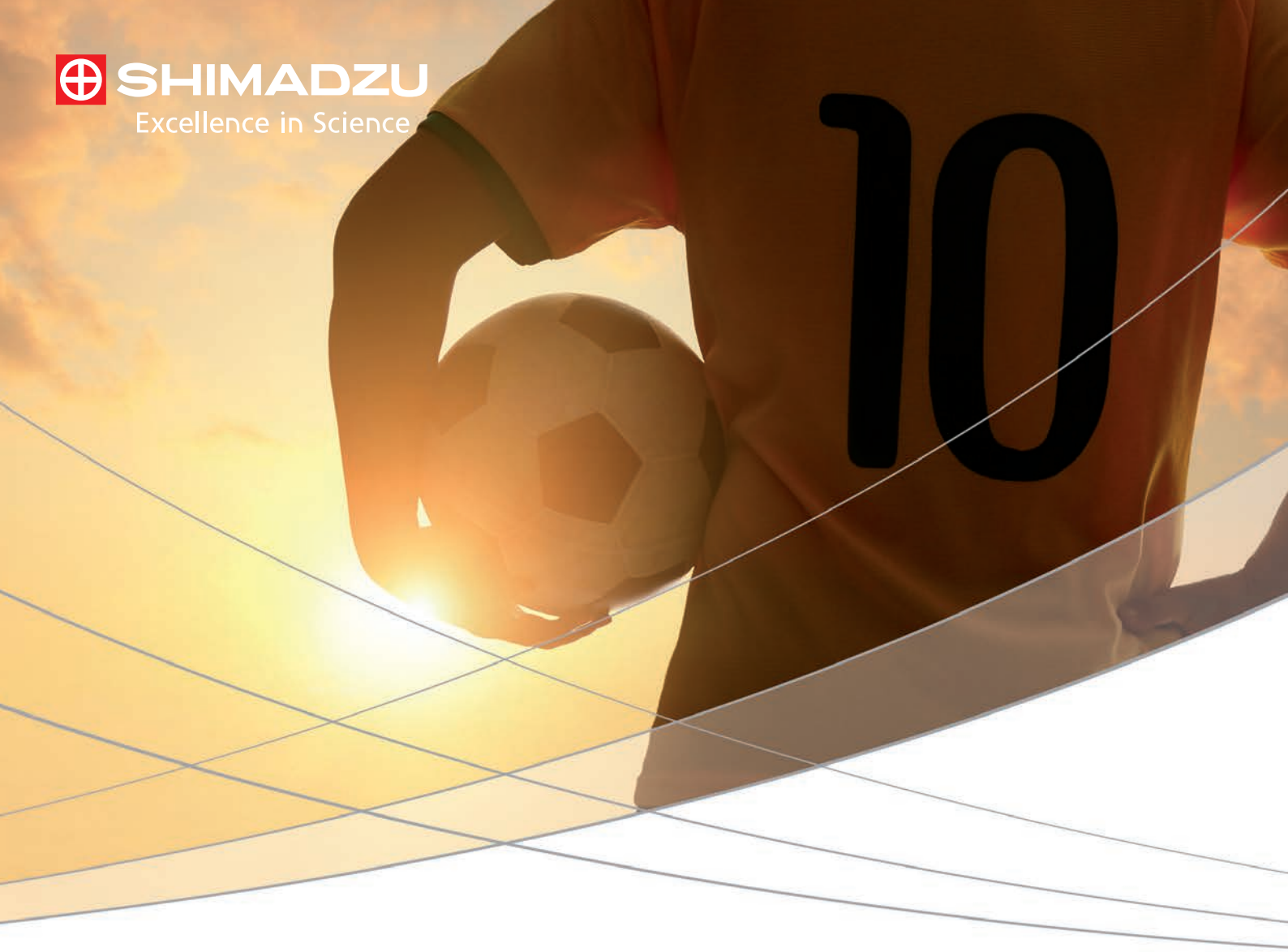

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