JANUARY / FEBRUARY 2023 # 88

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The first comprehensive study on the global pathologist workforce tells us one thing is certain: that demand vastly outweighs supply. How do we fix it?

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Antimicrobial resistance is among the top ten global health threats facing humanity, killing at least 1.27 million people worldwide. In the U.S., more than 3 million infections occur each year, resulting in 48,000 deaths. Antibiotic-resistant organisms, many of which are pan-resistant, are spreading rapidly. While progress is being made, development of new antibiotics is insufficient in addressing the spread of antibiotic-resistant organisms. Hardy Diagnostics is committed to making it easy for you to screen for these dangerous pathogens by developing novel chromogenic media for the detection of MSRA, ESBL, CRE and *Candida auris*. Vivid color change on a bright white agar background allows you to identify if one or more of these deadly pathogens is harming your patients.

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New Year, New Faces, New Directions

Where will 2023 take you?

Over the last few months, some of you may have seen my name appear in your inbox under the banner: "Willing to change for you." And I'd like to extend the same offer to those of you who predominantly connect with The Pathologist through the print (or PDF) magazine by asking a question:

What would you like to change about The Pathologist?

After 88 issues (including this one), we don't want to make the mistake of resting on our laurels – especially as the field evolves and as your needs change. Perhaps you want more on certain topics or less on others. Maybe you'd value more learning opportunities in the form of quizzes or gamification (Ivan Damjanov recently wrote a great short article on this niche – with games!). Perhaps your answer is simply, "Nothing!" – in which case, thank you.

Whatever your needs (or wants), we will strive to satisfy them in 2023 and beyond.

My inbox is always open (rich.whitworth@texerepublishing.com) – or you could get in touch the old fashioned way: Texere, Booths Park 1, Chelford Road, Knutsford, Cheshire, WA16 8GS, UK. (I'll freely admit that receiving some actual mail would make my day – possibly year.)

While we're on the subject of change, you will see some new faces pop up in The Pathologist team in the coming months. For one thing, we have to bid a fond farewell to former Deputy Editor Liv Gaskill – but for all the right reasons. I'm delighted to announce that Liv is now leading ID Transmission (www.IDTransmission.com) – our new hub for all things infectious disease. That said, I have a feeling that Editor Liv will still have content to share with the pathology and laboratory medicine community, so I guess it's not really goodbye.

ID Transmission represents an exciting evolution of a humble but well received newsletter (any original subscribers to The COVID-19 Curator?!) – and I cannot wait to see where Liv takes her fast-growing community in 2023.

But where do you want 2023 – and The Pathologist – to take you?

Rich Whitworth
Content Director

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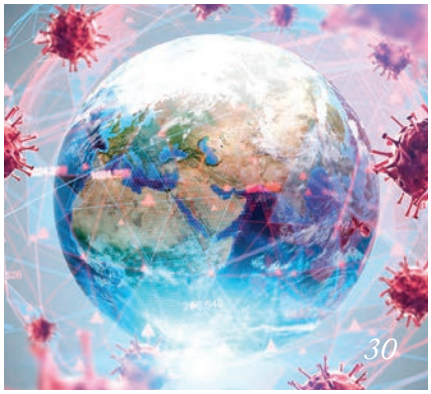

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Identifying disparities in pathologist supply is the first step to addressing them

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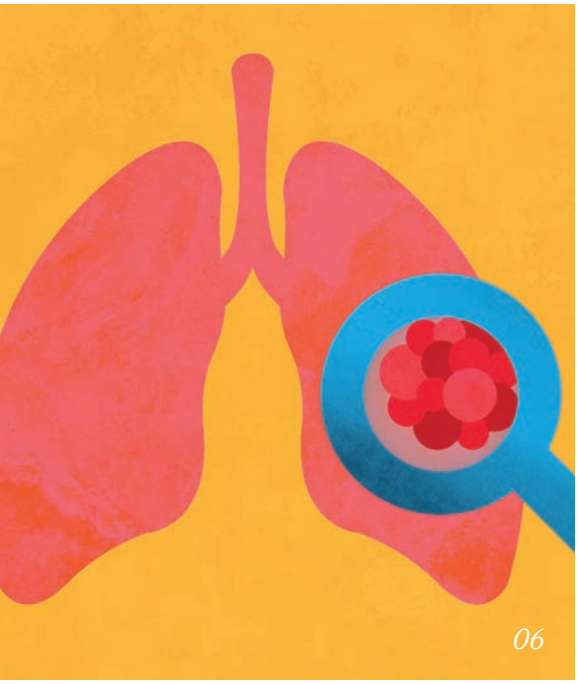
Feature



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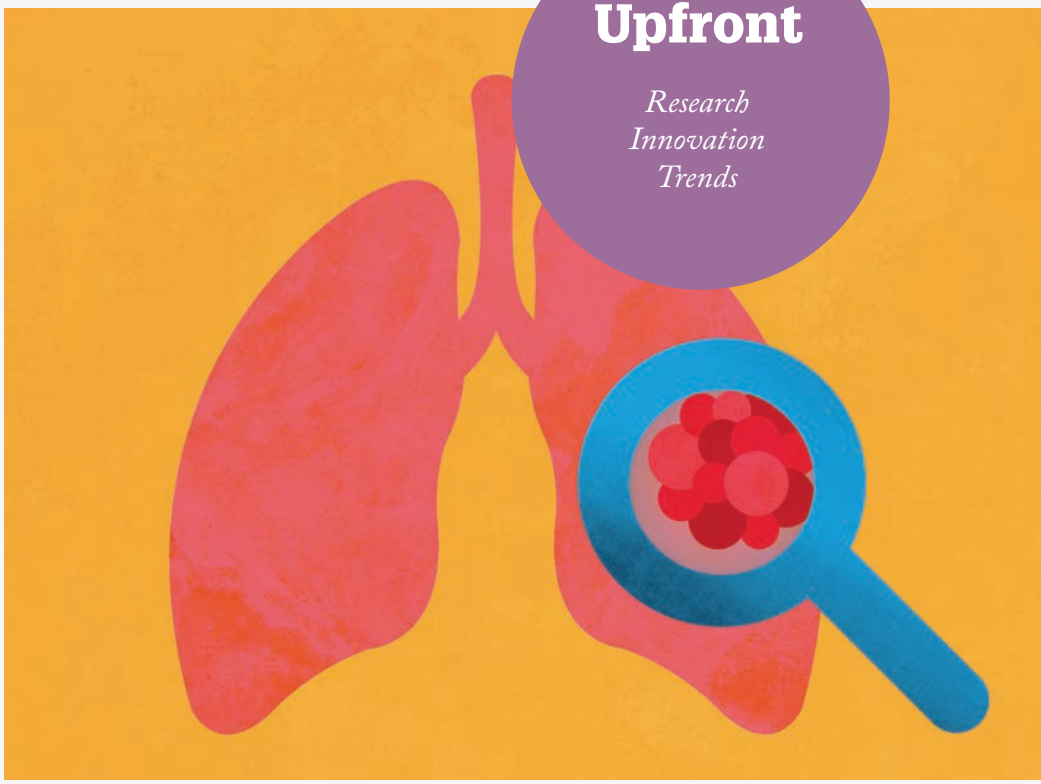
Upfront

Research
Innovation
Trends



Proteogenomic Prognosis

How proteins, RNA, and smoking status can predict lung cancer outcomes

Lung cancer remains the leading cause of death in cancer patients worldwide (1). Could advanced analytical investigations change the status quo? A recent study subjected 87 lung adenocarcinoma (LUAD) tumors to a plethora of techniques, including whole-genome sequencing, transcriptome sequencing, mass spectrometry-led proteomics and phosphoproteomics, and reverse-phase protein arrays (2). The multi-pronged approach led to the discovery of three distinct forms of LUAD – a transition-high subtype linked to non-smokers, a transversion-high subtype linked with current smokers, and a structurally altered subtype linked to former smokers and characterized by *TP53* alterations and genome-wide structural alterations.

The researchers also identified that protein expression and groups of RNA within sample tumors were linked to cell immunity and concentration of cancer cells within tissue. The team was then able to identify and validate the expression signatures of RNA and proteins and establish their association with patient survival.

When the tumor subtypes were compared by outcome, the team saw that expression and histological subtypes were strongly associated with metastasis-free survival (MFS). Meanwhile, somatic genome signature subtypes were not linked with overall or MFS. The paper suggests that the biological factors of LUAD recorded in the proteomic approach hold a determining effect on MFS.

Finally, the authors of the paper highlighted how a detailed understanding of the different molecular subtypes of LUAD could lead to therapy pathways designed to halt the development in pre-cancerous and early-stage LUAD tumors.

References

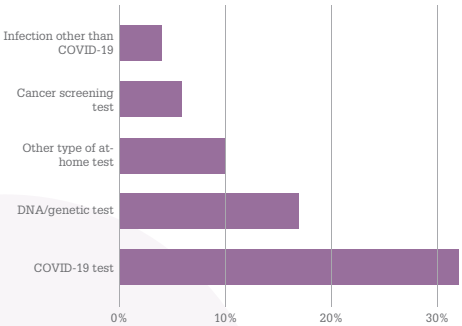
1. *American Cancer Society (2023). Available at: http://bit.ly/3QMt8Kj.*
2. *AR Soltis et al., Cell Rep, 3, 100819 (2022). PMID: 36384096.*

INFOGRAPHIC

Do Try This at Home: The Numbers on At-Home Testing

Home is where the heart is, but could at-home testing be at the heart of future diagnostics? Take a look at the numbers on patient responses to taking diagnostic tests at home.

Purchases of at-home tests by type in adults aged 50–80



Reasons given by patients uninterested in at-home tests

- ✖ Can get tests from a HCP
- ✖ Not relevant to the patient's health concerns
- ✖ Never considered at-home testing
- ✖ Lack of trust in results
- ✖ Not worth the cost

WHAT'S IN THE NEWS?

Take a brisk jog through some of hematopathology's most interesting research stories from this year's American Society of Hematology Meeting and Exposition

Good for the environment

Mass cytometry imaging of more than 300 primary diffuse large B-cell lymphoma (DLBCL) tumors has led researchers to map more of the condition's tumor biology and microenvironment. The DLBCL cellular landscape is now known to include two sets of 34 protein markers, as well as 57 markers identifying major cell lineages (CD3, CD20, PDPN, CD68), immune function (IDO, PD1, granzyme B,) and tumor phenotypes (IRF4, BCL6, p53) (1).

If you're LaPI and you know it…

The Laboratory Prognostic Index (LaPI), first announced at the 2021 ASH Annual Meeting, has shown that it can predict DLBCL outcomes by analyzing three blood parameters that are frequently assessed in most labs: lactate dehydrogenase, hemoglobin, and beta-2 microglobulin. The LaPI score is capable of the same prognostic quality as other methods and can even identify patients with severe prognoses to guide targeted treatment (2).

Not on a WHIM

Warts, hypogammaglobulinemia, infections, and myelokathexis (WHIM) syndrome is an immunodeficiency usually caused by *CXCR4* mutations. Because WHIM presents with a wide range of clinical symptoms, it can be difficult to diagnose. Recently, *CXCR4* sequencing has been used to confirm diagnosis in patients suspected of WHIM syndrome – but pathologists and patients still want an accessible, noninvasive biomarker. To this end, a team has identified a unique CD19+CD10+CD38+IgM–IgD–CD21–CD27– B-cell in WHIM patients that could be a potential candidate (3).

Bone marrow biomarkers

Isolated extracellular vesicle miRNA from the bone marrow of AML patients may have potential as a biomarker. In downregulated miRNA sequences, hsa-mir-181b and hsa-mir-143 correlated with unfavorable risk and worse overall survival. For upregulated miRNAs, hsa-mir-188 and hsa-mir-501 were correlated with unfavorable risk, but not associated with survival (7).

See references online at: tp.txp.to/0223/hematopathology

A New Castleman Disease Subtype

Researchers believe that idiopathic plasmacytic lymphadenopathy warrants its own disease subgroup

Idiopathic plasmacytic lymphadenopathy (IPL) is a rare benign inflammatory disease. Idiopathic multicentric Castleman disease (iMCD) is a unique subtype that is unrelated to the unicentric and the HHV-8-associated forms. Historically, iMCD has been classified into two groups: iMCD-TAFRO (thrombocytopenia, anasarca, fever, reticulin fibrosis, and organomegaly) and iMCD-NOS (not otherwise specified).

Some believe IPL belongs to the iMCD-NOS group due to their similarities, but a recent paper suggests that IPL makes up a separate disease subunit in iMCD. 34 specimens were classified under the IPL group and eight as the non-IPL group – with the former characterized by greater plasmacytosis and hyperplastic germinal centers. The vascularity of the non-IPL group was higher than that of the IPL group, which was also seen to respond better to the anti-IL-6 receptor antibody, whereas the non-IPL specimens needed more intensive medical treatment.

Reference

1. *A Nishikori et al., Int J Mol Sci, 23, 10301 (2022). PMID: 36142213.*

Of patients aged 50–82 who shared at-home test results with primary care providers…

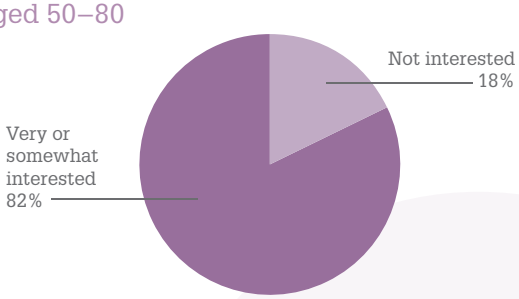
92 percent believe in discussing results with their doctor

55 percent shared infection test results

90 percent shared cancer test results with their primary care provider

9 percent of adults shared DNA/genetic results with their care provider

Future interest in at-home tests in adults aged 50–80

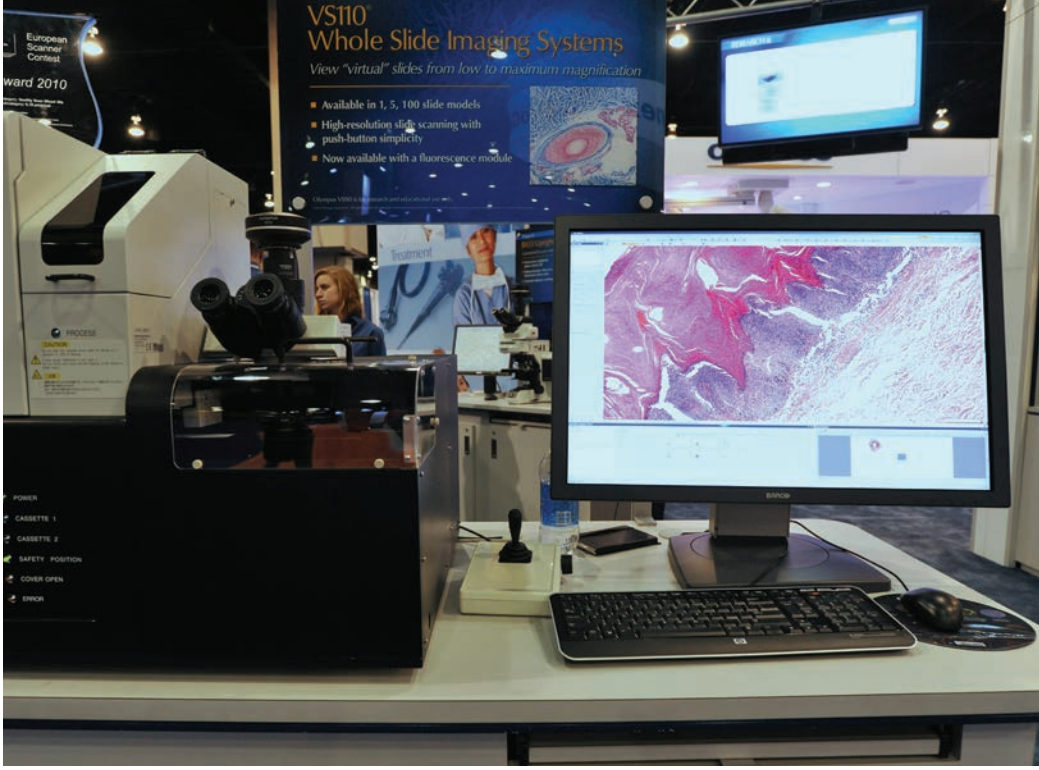


Reference

1. *University of Michigan (2022). Available at: http://bit.ly/3DqBbXt.*

A Library of a Million Slides

How do we access thousands of whole-slide images quickly whilst retaining important clinical information? The answer could lie in deep learning...



Credit: Ed Uthman/Flickr.com

As pathology becomes increasingly digitized, practitioners have never had larger libraries of whole-slide images (WSIs) at their fingertips. There's just one problem: how do we make these vast collections of slides easy to use? How can we take advantage of gigapixels' worth of samples in a way that isn't just fast and intuitive, but also technically accurate? According to one team of researchers, the answer lies in deep learning.

Currently, if a pathologist wants to search a WSI repository for a certain morphological feature, the speed of the search is ultimately tied to how many images it has to look through (the bigger the library, the slower the search). This inverse relationship between size and speed ultimately affects clinical and research applications. So how do we resolve it?

A recent investigation indicates that a form of self-supervised deep learning can be used to quickly locate images that match certain criteria regardless of overall library size (1). Rather than use standard methods to teach systems whether two or three images are similar to one another, the self-supervised image search for histology (SISH) algorithm looks at WSIs as integers and binary code, meaning that it requires no pixel or region of interest-level annotations.

The results of this approach seem to speak for themselves. SISH achieved accurate results in both general and rare diseases and offered rapid, consistent search speeds. Interestingly, the system can be used for not only WSIs, but also image patch retrieval.

One caveat of the SISH model is that it uses images, rather than words, to make a search query – limiting its applications for widespread use. The authors readily accept this and subsequently call for a multimodal version to be developed in which WSIs are paired with patient data, allowing pathologists to use written search terms on huge repositories in the future.

Reference

1. *C Chen et al., Nat Biomed Eng, [Online ahead of print] (2022). PMID: 36217022.*

A Tumor-Agnostic Prognostic Tool?

ctDNA tumor fraction acts as a prognostic biomarker across four advanced cancer types

Using a cohort of patients with one of four advanced cancer types, researchers have investigated the prognostic value of elevated circulating tumor fraction (TF) calculated using ctDNA analysis. TF levels of at least 10 percent were closely associated with lower overall survival in univariate analyses across all cancer types; the biomarker's prognostic impact is independent of most clinical features on multivariate analysis. However, certain clinical features formed an exception to this rule. The authors found that brain metastases, for instance, increased patient morbidity, but did not increase TF levels because these tumors may not shed ctDNA. Exploratory analysis further found that TF is a successful prognostic biomarker across a range of different cutpoints, although more research on relevant cutpoints within each cancer type is still needed.

The researchers concluded that ctDNA TF can act as a biomarker for prognosis across multiple common cancer types in a real-world dataset. They hope that – with additional research – ctDNA TF can be incorporated into point-of-care settings to provide cancer therapy based on patient-level tumor biology.

Reference

1. *ZR Reichert et al., Ann Oncol, 34, 111 (2023). PMID: 36208697.*

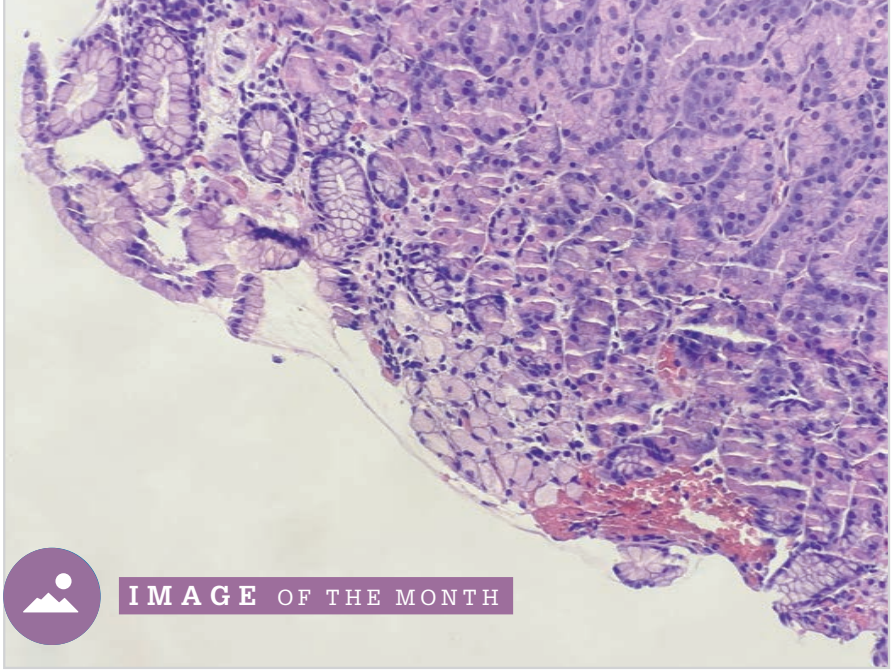


IMAGE OF THE MONTH

A fascinating example of a rare stomach cancer

This slide, taken from a prophylactic gastrectomy, shows a small focus of signet-ring cell (poorly cohesive) gastric adenocarcinoma involving the stomach body in a patient with a *CDH1* germline mutation. This rare cancer is highly aggressive and its characteristic signet-ring cells feature mucin-filled vacuoles with eccentrically placed nuclei, grow in sheets, can be difficult to identify, and present a challenge for noninvasive diagnostic approaches.

Credit: Alan A. George, private practice gastrointestinal pathologist in Florida, USA.

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

QUOTE of the month

"I don't think it's controversial to say that global medical culture has too much toxicity, stress, stiffness, and difficulty for people to practice medicine. We need a detoxification. That means more emphasis on the human side and less on the achievement side. Less competition, more collaboration. Less of medicine saturating bright minds and more of bright minds saturating medicine. Fewer clichés about our work as a "calling" and a new philosophy about its being a profession full of capable minds who are doing the best they can. Medicine needs a stat injection of creativity and wandering, instead of continuing the IV drip of aggression."

Syed T. Hoda, Clinical Associate Professor and Director of Bone and Soft Tissue Pathology at NYU Langone Health, New York, USA

Does Dyslexia Have a Genotype?

Researchers have found 27 new genetic variants associated with dyslexia, paving the way for further explorations into the biology and even expanded diagnostic capabilities

Previous familial studies suggest a strong genetic predisposition for dyslexia, yet few genetic markers have been identified that prove the correlation. To investigate further, an international team of researchers have conducted the largest genome-wide association study of dyslexia to date.

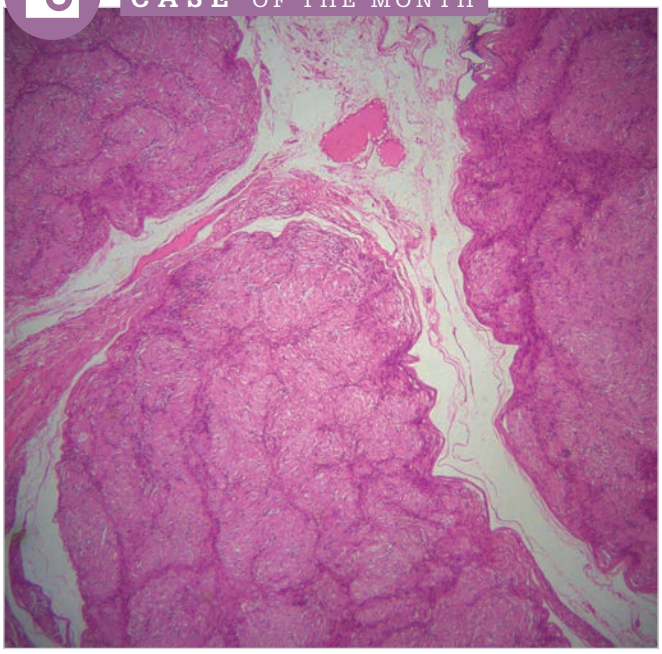
The study included 51,800 adults with a dyslexia diagnosis and over a million controls. A total of 42 genetic variants were found to be associated with dyslexia; of these, 15 have been previously linked to cognitive ability and educational attainment, but the remaining 27 were newly identified.

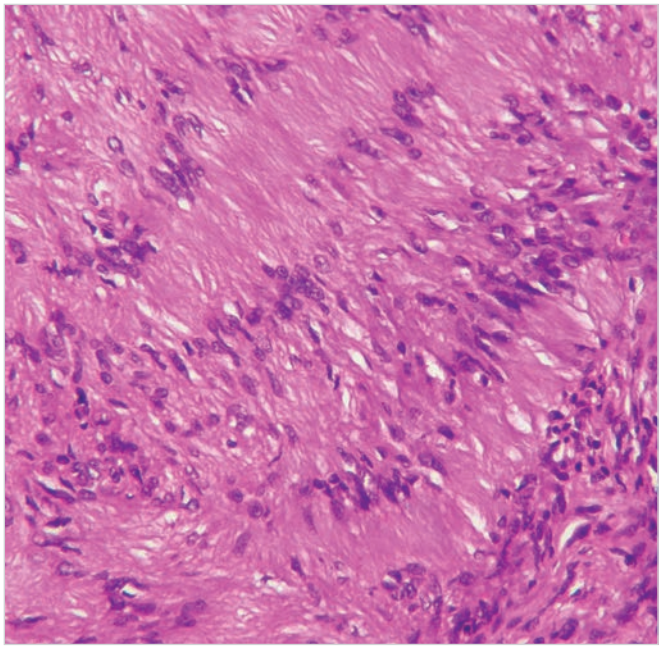
The work also found a positive genetic link between dyslexia and ambidexterity, as well as a "moderate" genetic correlation between dyslexia and ADHD. The researchers hope that the new variants will be prioritized for further investigation to increase our understanding of the biological underpinnings of dyslexia.

Reference

1. *C Doust et al., Nat Gen, 54, 1621 (2022). PMID: 36266505*

CASE OF THE MONTH





A firm nodular lesion of the lower lip

A 14-year-old female presents with a firm nodular lesion on the lower lip. She has no significant previous medical history. A representative biopsy of the lesion is shown.

Given the morphologic findings, what is the most appropriate diagnosis?

a) Plexiform neurofibroma
b) Malignant peripheral nerve sheath tumor
c) Plexiform schwannoma
d) Palisaded encapsulated neuroma

Answer to last issue's Case of the Month…

c) Stomach

Primary signet ring cell adenocarcinoma of the colon is a rare subtype of colorectal carcinoma most commonly located in the stomach (2). Histologic findings include pools of extracellular mucin and the characteristic proliferation of signet ring cells with intracellular mucin displacing nuclei to the periphery. Designation of the subtype requires a morphologic component of 50 percent signet ring cells or greater (3). A 2011 literature review concluded that signet ring cell adenocarcinoma demonstrates genetic alterations from conventional colorectal carcinoma, including lower *KRAS* and higher *BRAF* mutation rates, lower expression of p16 and p53, higher CpG island hypermethylation of tumor suppressor genes, and microsatellite instability (5).

Submitted by Erina McKinney, University of Kansas School of Medicine, Kansas City, Kansas; Gang He, American Diagnostic Consultation & Services, New York; and Ting Zhao, Department of Pathology, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA.

See references online at: tp.txp.to/0223/case-of-the-month

To register your guess, please go to http://tp.txp.to/0223/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.

21-25 May

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25th european Congress of Clinical Chemistry and Laboratory Medicine
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Context Matters

How spatial biology is advancing cancer biomarker discovery

Nicole Johnson, Miltenyi Biotec

Recent advances in immuno-oncology research and biomarker discovery are staggering and have resulted in life-saving therapies. Yet, challenges remain. This is particularly true for solid tumor cancers as they contain many different cell types in a dynamic local environment.

To better understand cancer biology, a thorough characterization of the spatial context of the heterogeneous tumor microenvironment (TME) is needed. The TME includes malignant and non-malignant cell populations that play a role in immunotherapy. A vast number of markers are required to effectively characterize the location and relationships between immune infiltrates, tumor-specific markers, and structural components of the tumor.

A spatial biology approach that can elucidate the variety and function of different cell types is critical to unravel this complexity, identify new target candidates, as well as predict and monitor the response to therapeutic intervention.

Overcoming challenges in spatial biology

Spatial multiomic approaches can reveal new insights into disease mechanisms and potential therapeutic targets. While spatial transcriptomic technologies have been widely adopted, analyzing more than a few proteomic markers on the same tissue section is a more recent, and challenging, development.

Multiplex immunofluorescence (mIF) and imaging mass cytometry (IMC) allow for varying degrees of multiplexing over classical immunohistochemistry (IHC). These spatial methodologies all rely on highly specific antibodies for accurate tissue staining and imaging. However, in some cases appropriate antibodies are not commercially available for some highly multiplexed spatial proteomic platforms.

Consequently, certain techniques require time-consuming and costly antibody conjugations with metals or oligonucleotide tags that can take months to validate. Other technologies are limited in their capacity to analyze the number of markers needed for comprehensive phenotyping and discovery.

Furthermore, since highly multiplexed experiments are often exploratory, and researchers may want to analyze the same tissue sample downstream. With some technologies, tissue samples are destroyed, rendering them unusable for further analysis.

The MACSima™ Imaging Platform was developed to address the challenges of navigating complex tissue environments, such as the TME. This system is unique in its ability to automatically stain and image a virtually unlimited number of targets using MACSima Imaging Cyclic Staining (MICS) technology. This non-destructive approach leaves the tissue intact for additional staining or downstream applications.

A broad array of immunologically relevant antibodies are qualified for formalin-fixed paraffin-embedded (FFPE) and frozen tissues on the MACSima Imaging System. These reagents are commercially available as individual antibodies or pre-configured plates. The flexible platform also allows the use of fluorescently tagged antibodies from other sources. Optimization may take mere days or weeks, empowering scientists to begin experiments sooner.

Hyperplexed imaging experiments generate large amounts of data that contain a treasure trove of complex information. Analysis and interpretation of large, multi-dimensional data sets require advanced tools designed to evaluate spatial relationships among multiple markers.

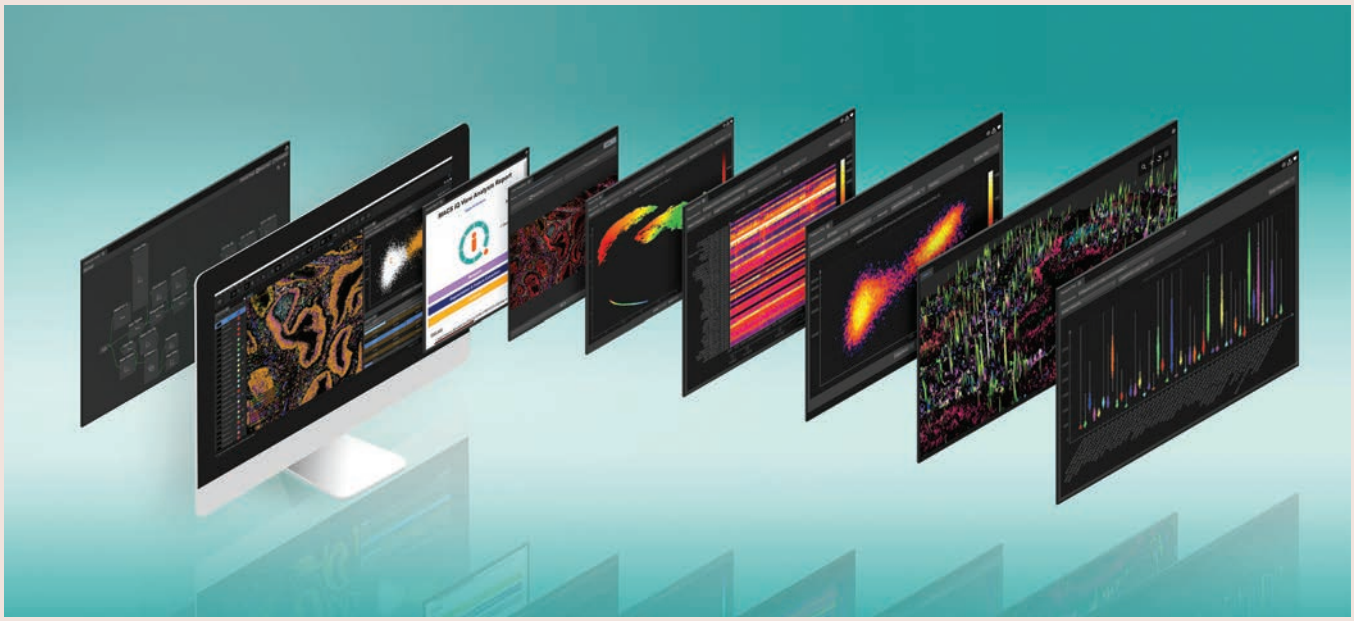
MACS® iQ View Imaging Analysis Software was developed for this purpose. It provides effective cell segmentation, flexible gating, and useful visualization tools to clearly identify marker co-expression and localization. Distance mapping, heat maps, and dimensionality reduction, among others, are advanced plotting options that help to reveal insights held within large and complex data sets.

Identification and validation of chimeric antigen receptor (CAR) target candidates and combinatorial pairs

Recent studies have incorporated high-content proteomic spatial analysis to extend and better understand observations generated by single-cell analysis.

In one example using a holistic approach, researchers combined single-cell and spatial analysis with comprehensive bioinformatic and experimental evaluation for off-tumor expression to identify

Miltenyi Biotec



pancreatic adenocarcinoma (PDAC)-specific cell surface markers.[1] Automated cyclic IF staining and analysis of 50 prioritized surface antigens were performed with the MACSima Imaging System, and CAR constructs were designed for further evaluation. The MACSima Imaging System was also used to assess the therapeutic efficacy and confirmation of target expression on healthy tissues, revealing a novel comprehensive workflow for target candidates.

Another strategy for CAR T cell therapy involves targeting cancer cells using co-expressed markers to circumvent tumor-escape mechanisms or to reduce off-tumor toxicity.

For example, the MICS-based screening of 96 markers was applied to glioblastoma multiforme (GBM) tissue samples from high-grade serous ovarian carcinoma (HGSOC), and PDAC plus normal tissue samples. Tumor marker expression was also quantified on a single-cell level for healthy tumor tissue. Data were analyzed for marker combinations and the most effective were selected as potential targets for further study.[2]

In addition to cancer biomarker strategies focused on cell-surface markers, we can also look at combined targeting of soluble molecules such as chemokines to enhance CAR T.

In one such study, researchers assessed the spatial distribution of the membrane-bound form of TGF-β and its co-localization with more than 90 surface markers within the TME of human ovarian cancer. The findings indicated that latent TGF-β is a potential antigen for CAR T cells to target desmoplastic areas of solid tumors. They were able to develop a novel technique that allows Adapter CAR™ (AdCAR) T cells to respond to soluble factors. This technique could lead to the development of new AdCAR T cell-based approaches for targeting solid tumors.[3]

The impact of ultrahigh-content spatial biology on cancer biomarker discovery

Spatial biology is a powerful tool that promises to advance our understanding and treatment of cancer and other diseases. Having spatial context for dozens of markers, or more in a single tissue, will enable us to fully characterize the complexity of the TME and evaluate potential cancer biomarkers.

When used as part of a comprehensive approach, an ultrahigh-content spatial proteomic technology such as the MACSima Imaging Platform is well-suited to play an important role in the discovery of new biomarkers with therapeutic potential.

References:

1. *Schäfer D. et al. (2021) Identification of CD318, TSPAN8 and CD66c as target candidates for CAR T cell based immunotherapy of pancreatic adenocarcinoma. Nat. Commun. 12(1453).*
2. *Kinkhabwala A. et al. (2022) MACSima imaging cyclic staining (MICS) technology reveals combinatorial target pairs for CAR T cell treatment of solid tumors. Sci. Rep, 12(1911).*
3. *Weechau N. et al. (2022) Combined targeting of soluble latent TGF-ß and a solid tumor-associated antigen with adapter CAR T cells. Oncoimmunology. 11(1):e2140534-3.*

Learn more about the MACSima spatial biology platform

In My View

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

Reliable Synthesis Theory: A Call for Future Leadership

How can pathology educators produce resilience in the training environment?

By Kristine McCluskey, Assistant Professor, Baylor College of Medicine's Departments of Pathology and Immunology and Education, Innovation, and Technology and Department of Pathology, Ben Taub Hospital-Harris Health System, Houston, Texas, USA.

There are many ways for educators to act as leaders. There's the traditional route in which they pass on expertise to their students – or there is the symbolic way in which people lead by good example or by instilling confidence in those around them. It may surprise you to learn that, in my work, I focus on the latter – why? Because finding leaders for pathology residents and pathologists' assistant students is crucial to set the standard for future professionals. For these future practitioners, effective training relies on the interactions between leaders and learners within an academic institution's culture.

Through the years, the concept of "culture" has evolved. In the past, culture was simply an organization's climate or the interactions between members in their physical environment – including combating external stressors, developing customs and traditions, and embedding skills. However, we now see culture as an increasingly complex organism. Due to outside factors affecting pathology's culture, educators must adapt and overcome obstacles with resilience by demonstrating valid, reliable behavior. This is a key proposal to ensure optimal patient care.

I have noticed a common thread across the works of many important figures and researchers: the image of the reliable leader. Vulnerability expert Brené Brown, organizational culturist Edgar Schein, John Kotter, Karl Weicke, Kathleen Sutcliffe – all these people cross disciplines and fields, but the reliable leader appears in all their works. For them, the reliable leader is trustworthy, deflects errors and stagnation, prevents loss of communication, and drives experiential learning and change. Using these experts' suggestions, we can construct a "reliable synthesis theory" for educational leaders to address the training deficiencies discovered in the literature over the past 20 years or longer (1, 2).

How we learn

To formulate the reliable synthesis theory, we must first understand how learners absorb information. Fundamentally, a student interacts with their environment to learn (3). This applies to both childhood development and adult learning. Infant learners often resort to chewing exploration – demonstrating sensorimotor intelligence, preoperational thinking, and systematic problem solving (4). Adults tend to engage a little differently! We learn through experiences that result in knowledge acquisition; actions, images, and language all help commit learning to memory (5). Adult learning in the pathology setting is no different; surgical specimens can be presented to trainees who actively explore, review resources, and may even teach other trainees under observation. Recent literature has noted that repetitive observation in this cycle results in students who are more mindful and actively aware. Instead of the traditional "see one, do one, teach one," it's much more powerful to "see many, do many, teach many" (6).

Cultural scientists have defined culture as an "accumulated shared learning over time as a group solves problems of external adaptation or integration; which is considered valid and, therefore, to be taught to new members as a correct way to perceive, think, feel" (7). In our pathology context, this means learners eventually value the importance of grossing, performing an autopsy, generating accurate diagnoses, learning educator skills, and becoming embedded in their culture by reliable leadership. The result? Sufficiently trained practitioners – whether they function in private practice or pass their skills on in academia.

A common feature

Schein and Brown write that, to accomplish goals, we need humble inquiry (8) and daring leadership (9). Temporary subordination is a great example. Whena leader becomes dependent or vulnerable, it creates psychological safety, builds trust, and facilitates sense-making in others. For example, the educator can dispense information by asking instead of telling. When a trainee asks, "How do I gross a kidney?" some may respond with, "Just take the margins and the tumor." A better response would be, "What is the history and what are you attempting to demonstrate? Can you show me?" By employing a humble inquiry, the educator offers direction and gauges the learner's understanding of the task at hand. Interdependence occurs because the trainee depends on the educator to offer guidance and the educator depends on the trainee to discover deficiencies in training by asking and not telling. Similarly, Brown encourages people to seek more information, rather than create a story. Through daring leadership, she suggests that leaders have a "soft front" – that is, be curious and vulnerable. By keeping the lines of communication open, these leaders help us evolve as we gather information, communicate, and remain curious. In places where this philosophy is put into practice, we quickly see that shared learning occurs, relationships are built, communication improves, and reliable leadership is established.

Situations requiring mindfulness, vulnerability, and eventual leader reliability are those within organizational cultures where safety is valued – places such as air traffic control, nuclear power stations, and yes, even laboratories. Sutcliffe and Weick propose that error reductions occur in high-reliability organizational (HRO) settings where safety is essential (10). The HRO process includes monitoring impending error, deferring to experts, recognizing organizational complexity, and committing to competency, all in a bid to reduce error. By adopting these principles, the leader becomes highly reliable. In another study, medical workplaces that valued safety – dubbed "safety cultures" – were examined in hospital nursing units (11). In this study, upholding safety values was enabled by "supportive leadership." Again, we see that reliability is a common feature of effective leaders.

A call to action

There have been recent indirect calls to action by the Association of Pathology Chairs (APC) and the College of American Pathologists (1, 2). Both pathology residency and PA programs revealed a decline in people pursuing pathology residency and training (12) – both related to cultural and environmental factors (13). These findings show that a variety of solutions are needed: a commitment to resilience, faculty development, and an effective monitoring and distribution of resources. Another important point raised is that grossing has shifted to Pathologists' Assistants as residents focus more on didactics and less on the value of grossing. So what behaviors should education leadership demonstrate to combat this issue? We need to develop staff so that they can appropriately instruct, monitor, and encourage the importance of grossing – and then introduce a new training cycle considering educational constraints. The adoption of high reliability characteristics in teaching has the potential to mend educational gaps and reduce error, making those characteristics a valuable safety feature in pathology's culture.

Reliability leads to change

One possible remedy to the problems in our discipline's culture is to follow the leadership style of John Kotter and implement his eight-step leadership model (see "The Eight Steps for Leading Change"). The model describes the process leaders can use to institute change and begins with immediate action, creating a sense of urgency to instill belief in the community (14). You might notice a similarity to HROs' shared learning with commitment. Through models like these, teams can develop a plan, strategize, and communicate their vision among themselves. Once cultural buy-in occurs, obstacles can be removed and short-term wins can induce long-term change – all anchored into the culture by the oversight team.

"By employing a humble inquiry, the educator offers direction and gauges the learner's understanding of the task at hand."

There appears to be a common theme among leadership theorists; the reliable synthesis theory is proposed as a way to codify it. There is room – and need – for future investigation into this theory, because although the concept of reliability has been drawn from current theorists, little study has been conducted. But if we are ever to address the trainee deficiencies in our discipline, it is my hope that this theory can help guide educators to become effective leaders.

See references online at: tp.txp.to/reliable-synthesis

Setting Your Priorities Straight

Choosing a pathology residency program should come with some non-negotiables

By Sarah Glogowski, Hematopathology Fellow at UT Southwestern Medical Center, Dallas, Texas, USA.

The first time I learned about pathology was during my undergraduate histology course; a classmate was talking about the field with genuine enthusiasm and it just clicked for me. When I interviewed for medical school and mentioned I was interested in pursuing pathology, my ambition was mostly met with confusion – a sentiment I also got from my classmates or the preceptors I rotated with. Despite the less-than-positive response from those around me, I feel fortunate that I knew about pathology early on because I was able to pursue it as my only third year elective – and that helped me solidify my decision when applying for residency early in my fourth year.

My best advice for people approaching this career stage? First and foremost, find a residency program that supports your needs. Case variability is always important but, for me, a supportive culture was crucial – and this applies to both your staff and co-residents. The people around you become your family. Being able to count on your co-residents to help you out when something unexpected arises helps make stressful situations more manageable. Having a "we're all in this together" mentality not only helps you, but is also better for your patients. The "pay it forward" mindset gets instilled early on and perpetuates throughout your training years.

From a staff perspective, you want your colleagues to be genuinely interested in your development as a pathologist in training. The ability to confide in your program director and tell them if something isn't working and what you think might help is invaluable. When I decided I wanted to get involved in the Resident Forum Executive Committee with the College of American Pathologists, I felt comfortable going to my program director and saying, "This is what I would like to do but I'll need to take time out during workdays for calls and to take days off to go to meetings – would you support me through that?" I was fortunate that the support was there because, without it, I wouldn't have had the opportunity to pursue leadership or make so many connections within pathology.

There are increasingly more barriers to recruiting for pathology residency – not least a problem that echoes the saying, "If you're not at the table, you're on the menu." Due to budget neutrality, we are constantly fighting reimbursement cuts against our other clinical colleagues and, though we have successfully negotiated smaller reductions over the past few years, a permanent solution is urgently needed. We need to support the expansion of pathology residency slots to address the growing physician shortage and cement our seat at the table. One option may be to expand the Conrad 30 Waiver Program to make it easier for hospitals to obtain sponsorship by their state health department – allowing more J-1 visa-holding medical professionals to provide care in our medically underserved areas. But these changes won't happen unless there's a collective voice supporting them – so, no matter where you are in your career, get involved and speak up!

"When I interviewed for medical school and mentioned I was interested in pursuing pathology, my ambition was mostly met with confusion – a sentiment I also got from my classmates or the preceptors I rotated with."

Inclusion Inroads

The future of pathology and laboratory medicine is ours to shape

By E. Blair Holladay

At the end of 2022, we wrapped up an outstanding year for ASCP. Not only did we celebrate the 100th anniversary of the American Society for Clinical Pathology, we also concluded what was undeniably one of the most exciting years we've had as a society. Our members continued to endeavor, create, innovate, and lead through the ever-changing landscape of healthcare, solidifying the role of pathology and laboratory medicine as leaders.

All that we accomplished in the past year has set us up to make strides in the coming year, and that momentum will be necessary as we make inroads into the issues we face in pathology and laboratory medicine. A continued press on fostering environments that embrace diversity, equity, and inclusion is imperative in order to create a workforce that better represents the populations we serve, as well as imbue within the profession diversity of thought, experience, and insight.

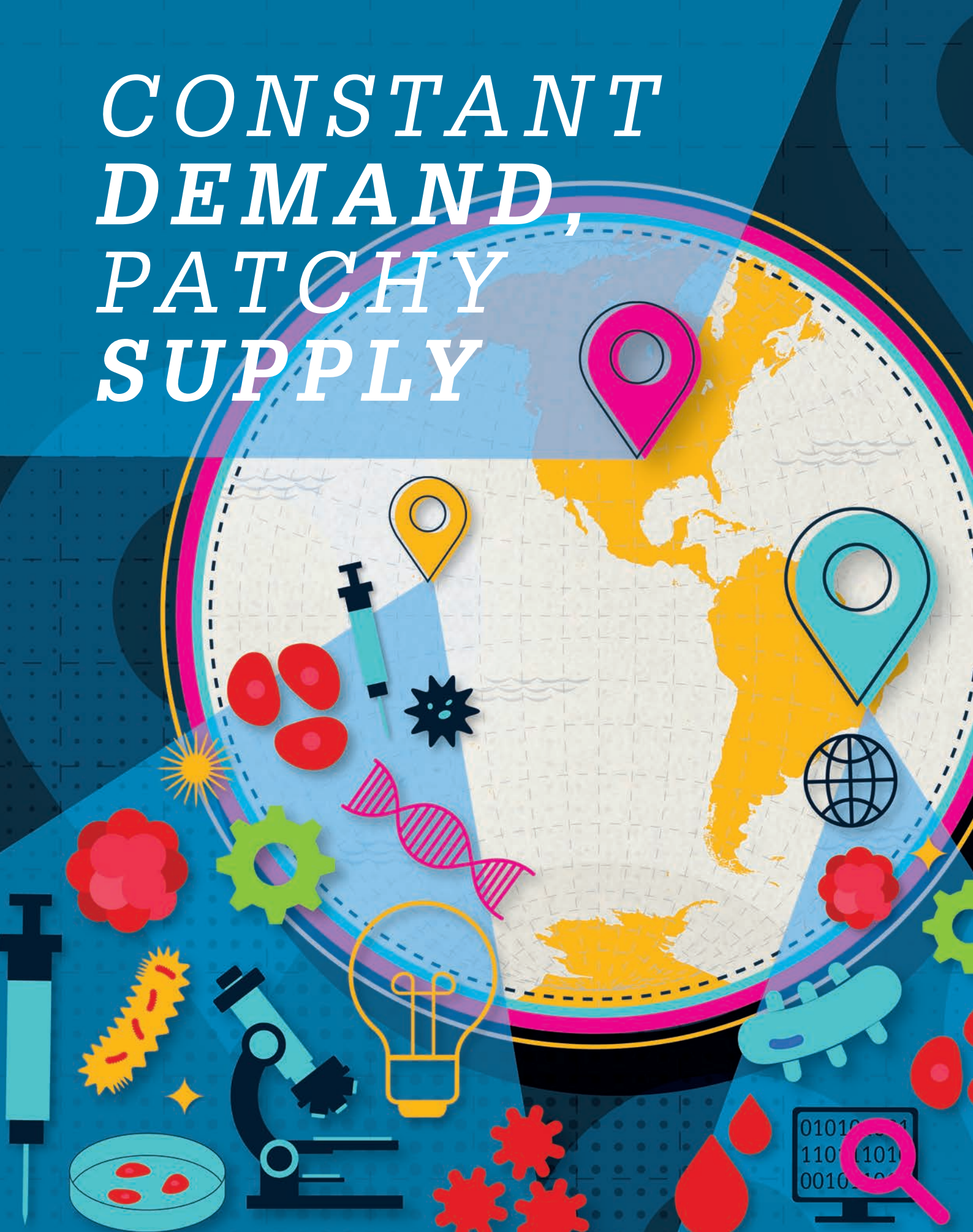
As the healthcare professionals involved in just about every patient's healthcare journey, pathologists and medical laboratory scientists have a responsibility to understand what patients need not only in their own country or region, but around the world. Strengthening the global presence and influence of the laboratory in the coming year is essential in helping lower- and lower-middle-income countries provide the high-quality care they need.

Although it is often said that the COVID-19 pandemic catapulted the laboratory into the spotlight, we can't let it end there. The visibility of the laboratory – the hub of healthcare from which all other patient care stems – can't be raised enough, and there is no limit to how high we can lift it up. Keeping the laboratory in the spotlight it has long deserved is a constant exercise, and one we cannot let lag.

These are not easy tasks we've set for ourselves, yet there is no doubt that we are up to the challenge, particularly when so much is at stake. Do we slow our pace when patient lives are on the line? Do we cede control to others within healthcare when the knowledge we have, and the laboratory provides, is what informs high-quality care? To do either of these things would be detrimental for the members of the laboratory team just as much as it would be for patient health and safety. Recognizing that the laboratory is in a unique position to tackle issues we face within the profession and in healthcare overall, and ultimately affect change worldwide – this is a torch we gladly carry.

We can't know the future, but we can certainly shape it. Understanding what pathology and laboratory medicine need to continue providing high-quality care for patients means looking at where we currently stand – and then taking the necessary steps and leaps forward to advance the profession and advance patient care. As we dive deeper into 2023, we must be resilient, we must be confident, and most importantly, we must be bold, to continue being the healthcare leaders we are.

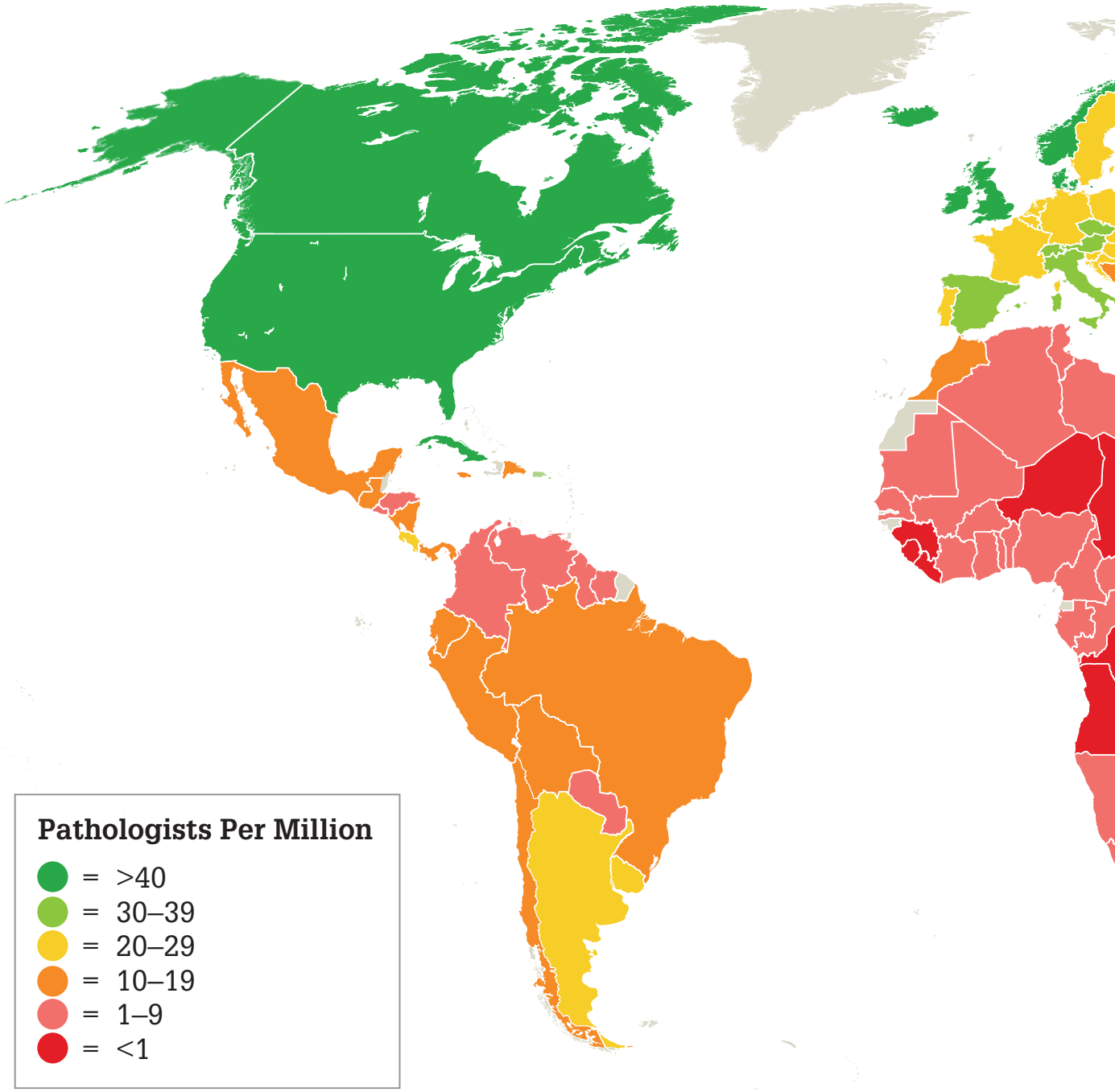
CONSTANT DEMAND, PATCHY SUPPLY

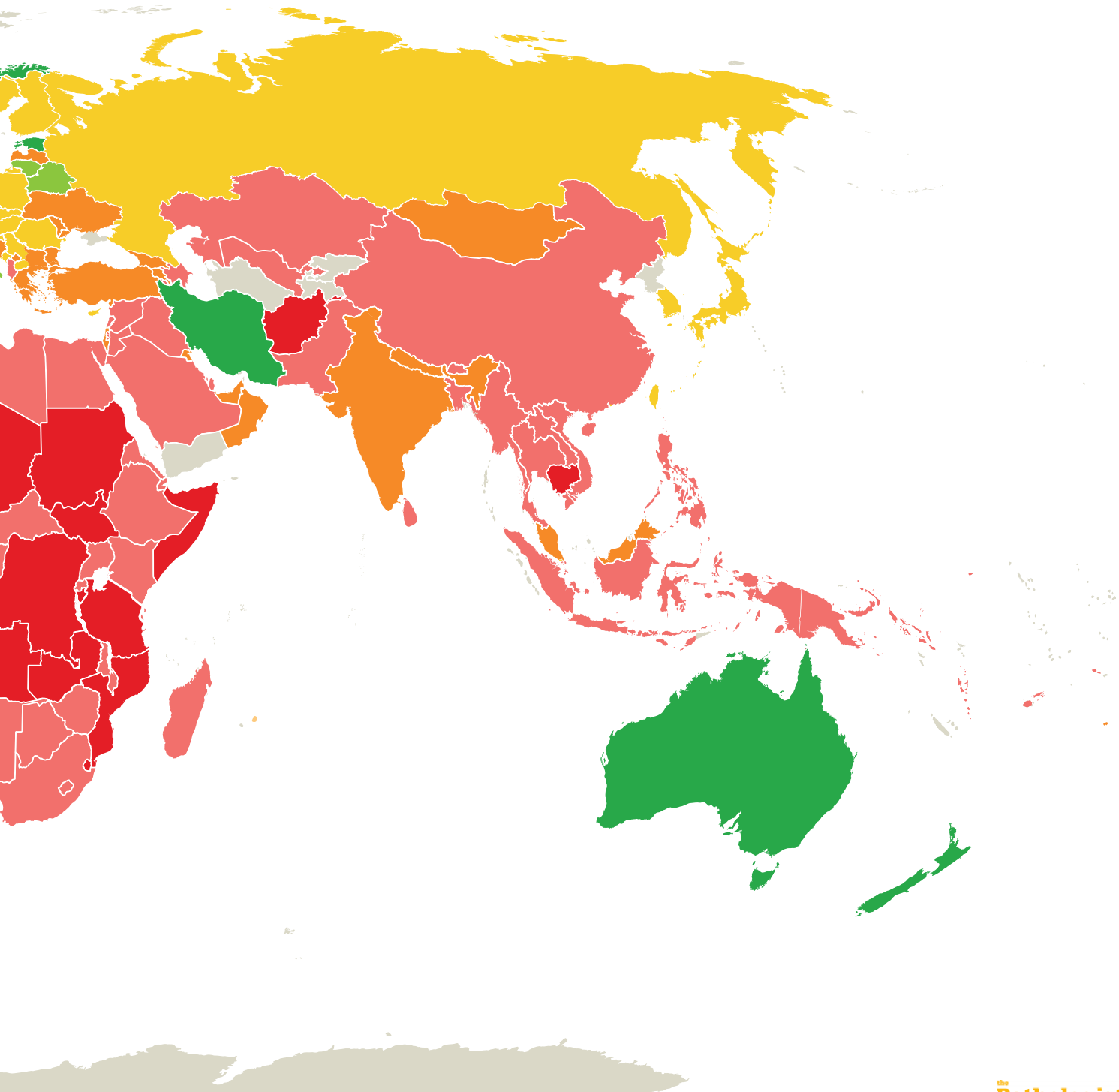


The first comprehensive study on the global pathologist workforce both identifies key disparities in pathologist supply and prepares the ground for correcting these imbalances

By Andrey Bychkov and Michael Schubert

A World Map of Pathologist Density





Our Panelists

Stanley Robboy is Professor Emeritus of Pathology, Duke University, Durham, North Carolina, USA.

Bruno Märkl is Director of the Institute for Pathology and Molecular Diagnostics, University Medical Center, Augsburg, Germany.

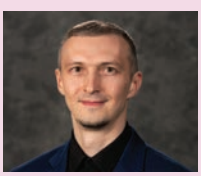
Michael Wilson is Professor and Vice-Chair at the University of Colorado Anschutz Medical Campus, Aurora, and Director of the Department of Pathology and Laboratory Services at Denver Health, Denver, Colorado, USA.

Joshua Kibera is an anatomical pathologist, Founder and CEO of The Pathology Network, Nairobi, Kenya.

René Buesa is retired; formerly Histotechnologist and Pathology Laboratory Manager at Mount Sinai Medical Center of Greater Miami, Florida, USA.

Ann Nelson is Senior Advisor and Director of LIS Programs at Pathologists Overseas, Infectious Disease Pathology Consultant at the Joint Pathology Center and Visiting Professor of Pathology at Duke University, Durham, North Carolina, USA.

Mike Osborn is President of the Royal College of Pathologists and Consultant Histopathologist for North West London Pathology at Imperial College Healthcare NHS Trust, London, UK.



Andrey Bychkov is Director of Digital Pathology at Kameda Medical Center, Kamogawa, Japan.

An ever-increasing workload and an insufficiency of pathologists; it's an old story and we know it well. At least, we think we do – but how many of us know the actual numbers behind this received wisdom? And does the numerical imbalance stay the same from region to region, country to country? The truth is, nobody has ever defined the details of this broadly appreciated, but vaguely understood, narrative of the shortfall in trained pathologists – until now, that is.

This groundbreaking map represents the first-ever attempt at a global quantification of pathologist numbers: over 108,000 individuals in 162 countries and territories, representing about 98.5 percent of the world's population (data collected in 2019–2022 by Andrey Bychkov). It also reveals glaring disparities; the mean number of pathologists per million population is 14, but people in the United States enjoy 65 pathologists per million, whereas those in Africa have access to, on average, fewer than three pathologists per million. The 10 countries with the highest number of pathologists account for over two-thirds of the total pathologist workforce worldwide – a list is topped by the US, India, China, Iran, and the UK. Worldwide, the WHO estimates the number of medical doctors at approximately 13.2 million, indicating that about one in every 120 doctors (0.8 percent) is a pathologist.

Quantifying the problem in this way is essential, but represents only part of the value of these data; crucially, they provide a baseline for future investigation and may help direct personnel recruitment plans in countries across the globe. In brief, they represent an essential first step in correcting the significant international imbalances in pathologist supply.

Tell us about your contributions to understanding the pathology workforce…

Stanley Robboy: During the time I headed the College of American Pathologists (2009–2013), our board recognized that American medicine was in a crisis and about to undergo a massive change. No one knew what form that would take – but, wanting to be proactive, we embarked on reviewing all aspects of pathology, including the workforce. I headed that thrust.

The two obvious elements of workforce are supply and the functions we serve. We now know that the numbers we established in 2013 (1) were too low, because the Association of American Medical Colleges (AAMC) ignored pathologists who subspecialized. What we did correctly identify was the beginning of the retirement cliff, although the name was poor. It was not a cliff, but a gradual slide in which the number of people entering the profession was consistently lower than the number retiring. The highest rate of entry was from the 1960s to the 1980s; after that, the number of retirees overshadowed

the number of new pathologists – and has, since 2000, been stable at about 600 each year.

A subsequent paper in 2015 (2) explored several important new facets. One was the taxonomy of pathologist activities – the settings of their work and functions. It became evident that this taxonomy was much more complex than anyone had previously conceived – but has proven crucial to developing workforce projections. A second was our ability to quantitatively project the demand by subspecialties. This understanding involved more than simply the numbers of specimens examined annually; it had to explore the technology needed to examine the specimens, which improved year on year. We also published how to measure those changes (3).

We are currently working with the AAMC to better understand the outdated methodology it used to provide workforce numbers for pathology and, I suspect, for all medical specialties. Our first joint publication is expected to emerge shortly.

Bruno Märkl: Wondering why it was so difficult to hire board-certified pathologists in Germany, I started to collect data such as total numbers of working pathologists, numbers of physicians in training, gender proportions, and so on. I discussed my insights with colleagues who encouraged me to publish – so I validated my data and compared the German results with numbers in other European countries and in North America (4).

Michael Wilson: Most of my work was on a pathology workforce survey via the group African Strategies for Advancing Pathology (ASAP) (5), the Lancet series on pathology and laboratory medicine in low-income and middle-income countries, (6), and most recently the Lancet Commission on diagnostics (7).

Joshua Kibera: I am an anatomical pathologist and have practiced for eight years in Kenya. I spent four years as Head of Department at the Kenya Methodist University, then established my own anatomical pathology lab in 2017, which later merged with a cancer center servicing the Kenyan town of Meru and its environs. I have traveled to and been involved with pathologists in South Africa, Uganda, Botswana, Tanzania, Ethiopia, Somalia, Zambia and Kenya, so I am familiar with workforce challenges in sub-Saharan Africa.

Rene Buesa: From my arrival to the USA (from Cuba) in 1983 until my retirement in 2002, I worked first as histotechnologist, then as pathology laboratory manager. In that time, I made a number of contributions to the field in terms of safety and efficiency. After my retirement, I decided to share my managerial experience – which included running numerous surveys to determine workloads, staffing benchmarks, turnaround times, and productivity figures for every histology and cytology position and task in the USA and multiple other countries.

Ann Nelson: I have worked in pathology development in Africa since 1986 – I set up the first AIDS pathology lab in Kinshasa, Zaire. I have collaborated with Association of Pathologists of East, Central and Southern Africa (APECSA), the International Academy of Pathology, and other organizations to increase pathology capacity and utilization in Africa. With colleagues, we did a comprehensive survey of anatomic pathology workforce and capacity (8). I have also collaborated with and mentored many pathology leaders in sub-Saharan Africa.

Mike Osborn: The College has repeatedly raised the issue of workforce shortages across pathology services with the UK government and devolved nations' administrations. We achieve this by attending parliamentary meetings, submitting responses and evidence to parliamentary groups, briefing parliamentarians to raise awareness of pathology, asking them to raise issues in parliament and with government on behalf of the profession, and responding to government consultations. In addition, we are closely involved with a range of other organizations directly and indirectly involved in workforce planning and resourcing. The groups consist primarily of high-level National Health Service (NHS) committees and other relevant stakeholder groups, but the College will work with any suitable stakeholder to highlight workforce issues and try to resolve them.

Issues raised have included calling for sufficiently trained staff, including increased numbers of biomedical scientists supporting medically qualified pathologists in integrated teams to achieve maximum productivity; improving retention of consultants and lab staff (having the right number of diagnostic staff in the right places, working in a supportive culture, is

key to the delivery of an agile and resilient pathology service with patients at its heart); and building resilience in workforce by ensuring that staffing levels are sufficient to meet service expectations. This is not possible where staffing is aimed at covering minimum or average workloads.

Do you think the map accurately reflects pathology's status in your region?

Andrey Bychkov: Data was collected from national registries with the assistance of local pathologists, international and local journal publications, and communication with local societies. The information was verified through personal communication with pathologists from the respective countries whenever possible. After validation, the data were classified as reliable, acceptable, or questionable, with questionable data excluded from the final analysis. All subspecialties were included, but residents and trainees were excluded.

SR: It is difficult for me to say whether it is high, correct, or low; at best, I can say it works. However, even though we are now seeing the rise of automation and artificial intelligence, there is little question that the incoming supply of US pathologists in the years to come will remain less than those retiring. For many years, pathology graduates could not find jobs. Suddenly, over this past year, I now continuously see the number of open positions far exceeding anything experienced for decades. Currently, there is an insufficient workforce – but we don't control residency slots, so it is difficult to make predictions.

BM: Yes, the map appears accurate for my region.

MW: Yes, but the challenge is that workforce data are largely lacking for many regions – particularly in areas such as sub-Saharan Africa, where there are no formal registries or databases in most countries.

JK: For sub-Saharan Africa, the data appear more or less correct.

AN: The data include anatomic and clinical pathology, disciplines that are not combined in much of Africa – but the relative numbers seem correct.

MO: The heat map appears to show that there are enough pathologists in the UK – but this was not the case even before COVID-19 and the associated backlog and the situation has worsened since the pandemic. In addition, there are significant variations between regions and specialties. Northern Ireland, for example, currently has no pediatric consultant pathologists, and many rural locations across UK face greater workforce pressure with pathologist recruitment and retention than more urban centers.

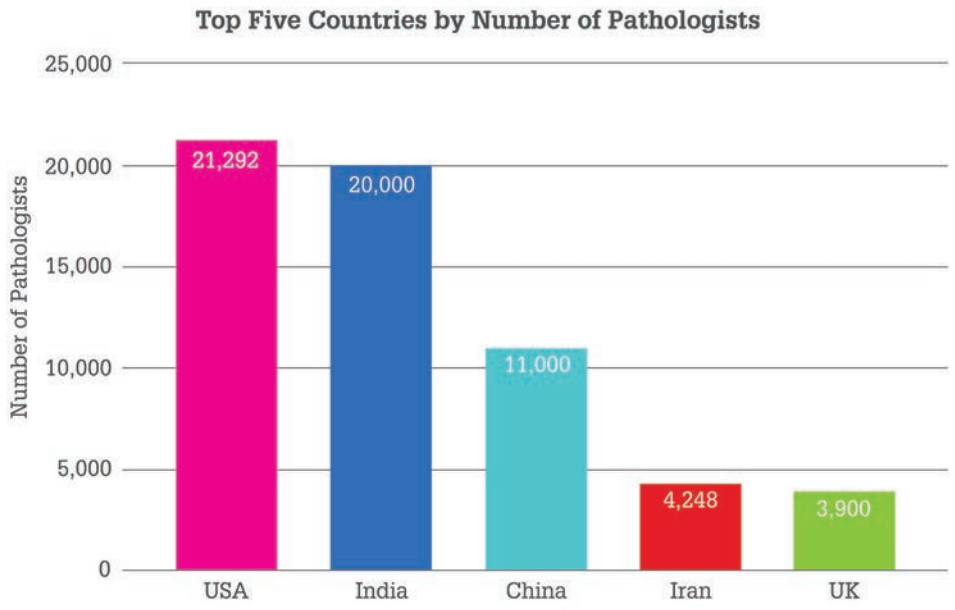
AB: The UK data include not only histopathologists – also known as surgical or anatomic pathologists (AP) – but also other subspecialties, such as clinical pathologists (CP), microbiologists, chemical pathologists, and so on. The AP:CP ratio in the UK is 1.5:1, which is five to 10 times lower than in countries that don't use the British system of pathology education and nomenclature. Furthermore, in many European countries, CP-equivalent jobs are occupied by other specialties, such as medical laboratory scientists, who are not pathologists and sometimes not even medical doctors. The UK has a histopathologist density of 23 per million people (a shortage; this would be yellow on the map). Projecting to the global level, my estimation would be that out of 108,000 practicing pathologists, only about 90,000 to 100,000 are surgical pathologists.

It's important to add that our data don't include residents or trainees, who perform a significant amount of work in pathology labs, but who are not board-certified. The number of residents varies widely by country, from less than 10 percent to up to 50 percent of all pathologists. For example, the USA offers a fixed number of just over 600 pathology residency slots each year, whereas India has recently raised that number to 2,350. I predict that, in just a few years, India will top the list.

> "FOR MANY YEARS, PATHOLOGY GRADUATES COULD NOT FIND JOBS. SUDDENLY [...] THE NUMBER OF OPEN POSITIONS FAR EXCEEDS ANYTHING EXPERIENCED FOR DECADES."

What does the pathology workload and pipeline look like in your region?

SR: The workload for individual pathologists has increased over the years and I'm concerned about the dangers inherent in the rise.



In the early 1970s, a committee I headed for the Massachusetts Society of Pathologists specifically addressed workload numbers. The number we felt comfortable for an average pathologist at a secondary or tertiary center to handle annually was about 2,500 (one or two highly involved operations per day; three or four larger specimens; the rest biopsies). I now hear that pathologists commonly are expected to examine over 4,000 – sometimes considerably more – cases a year. That means the time per case becomes unbearably short, which I fear will lead to burnout and errors. A study we recently published reports that burnout rates for people with more than three years in practice have jumped significantly (9). This occurred whether or not the person was anxious or experienced burnout in residency. Burnout is now becoming the norm and I attribute this to unhealthy workloads.

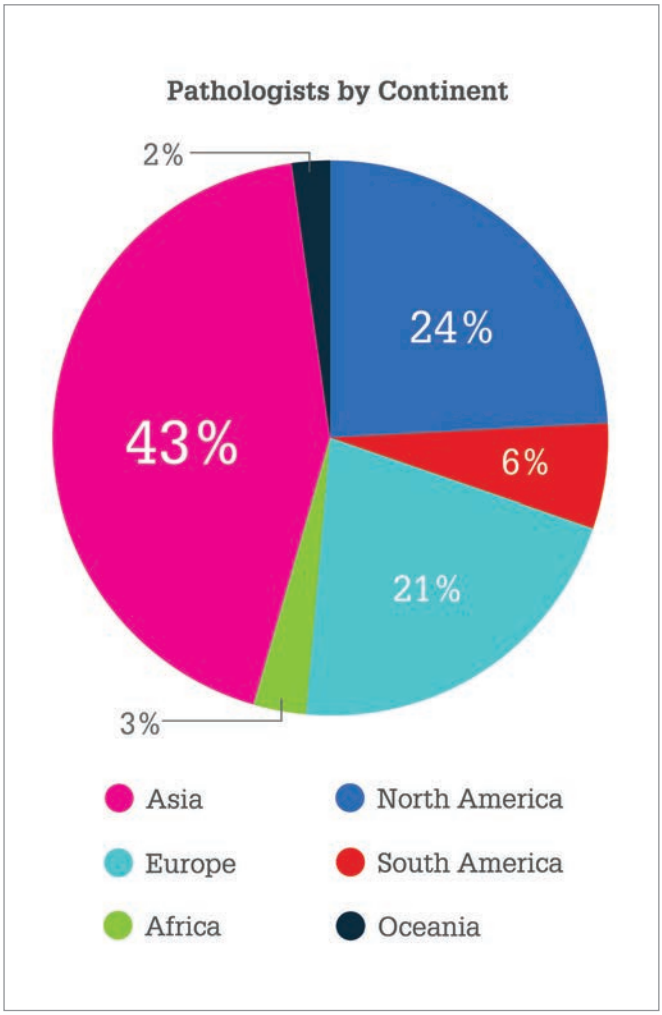
BM: In Germany, we maintain the number of working pathologists. However, the rate of part-time workers is growing while full time equivalents are decreasing. I have no validated data concerning workload, but I estimate that the average number of cases per pathologist per year is around 10,000.

MW: The situation in most of Africa is woefully inadequate; the number of pathologists per population is a small fraction of what is needed to deliver necessary services at a population level. The average workload of a pathologist is highly variable, but in general low (except in some urban areas) due to inadequate healthcare systems, funding, and infrastructure – and a lack of awareness of the importance of diagnostics.

JK: Africa is a large continent whose different countries have operated in silos for historical reasons. Sadly, these silos extend into medical practice, where there is generally very little professional interaction between practitioners across the continent. Regional professional bodies have grown in strength over the last two decades because of geopolitical and economic unions such as the Southern African Development Community, the Economic Community of West African States, and the East African Community. APECSA has been instrumental in strengthening bonds between pathologists across the eastern and southern parts of Africa. Multinational pathology laboratory chains have played a role in elevating the status of pathology and further cementing relationships between pathologists in these regions. I am most familiar with eastern and, to some extent, southern Africa, so my opinions and observations are limited to these regions.

That said, there is a severe shortage of pathologists in East Africa (Rwanda, Burundi, Tanzania, Uganda, Kenya and Somalia) and across southern Africa. There is currently relatively free movement of medical professionals across East Africa – a region that contains 200 million people served by just 300 pathologists. Training in East Africa tends to focus on creating general pathologists who can serve as administrators and practitioners in remote government hospitals. It's expected that over half of these pathologists' work will be in forensic pathology, so training is heavily oriented toward forensic pathology, hematology, and microbiology – the laboratory disciplines expected to make up the bulk of practice.

Most pathologists in eastern and southern Africa hold two or three jobs and are very busy. They often shy away from surgical pathology because of its sensitivity and because their training generally gives them limited exposure to histopathology. In Kenya and Uganda, most surgical pathology work is done by pathologists in the private sector or shipped abroad. Many



surgeons consider it a luxury, so – in my estimation – 80 percent of samples are either not collected or are thrown away, even in Kenya (where surgical pathology uptake is highest).

RB: The USA averages are adequate, but pathologists are retiring and new MDs prefer better-paid specialties, so it is very likely that, by 2040, there will be shortages. In Cuba in 2020, there were 400 pathologists working in 110 departments across the country, along with 500 cytotechnicians and cytopathologists. The only workload information available was a total of 366,285 autopsies from 1991 to 2002, for an average of 30,524 per year and 3,330 per site.

Official US government statistics say that, in 2019, there were 21,292 active pathologists and 171,400 histotechnologists working in 9,111 histopathology and 3,995 cytology laboratories. The number of pathologists increased 13 percent from 2011 to 2019; histotechnologists are expected to increase 12 percent from 2016 to 2026. In 2011, there were 621,811 tests completed in those labs for an average workload of 68,248 tests per lab. Pathologists in the USA have a median of 3,000 cases per year; in Latin America, excluding Cuba, the mean is 2,100 cases per year.

AN: The pathology workforce has increased significantly in the past decade and there are more trainees, but there is still a deficit.

MO: Though there is variability across the 17 pathology specialties that the College covers, pathologists in general face great pressures through rising workloads and the increasing complexity of their work. Vacancies are also currently 10–12 percent and rising. The significant pressure on laboratory staff affects turnaround times for results, particularly in less automated specialties such as histopathology, a discipline in which requests to laboratories have increased by around 4.5 percent year on year since 2007.

Though some specialties are relatively stable when it comes to workforce, others are facing acute shortages – for example, pediatric pathology, with 24 consultant vacancies across the UK – creating considerable pressures on the service.

What future challenges do you anticipate in staffing and recruitment?

SR: Each staff member means a significant expense, and with reimbursements consistently dropping, all CEOs of hospitals and hospital chains will endeavor to prune payroll. If a national laboratory can do the same work at 75 percent of the in-house cost, why wouldn't CEOs outsource the lab? Fortunately, many realize their own pathologists are critical intermediaries when clinicians need help understanding a patient's disease, whether further treatment is needed, or even what expensive laboratory test should (and should not) be ordered. In-house pathologists often save hospitals bundles of money with their advice.

BM: I predict a systemic shortage of qualified staff over the next 10 to 15 years. By my calculations, we would need at least double the number of residents in training to cope with the growing workload.

MW: The pipeline for pathologists is small in many countries and, as a result, we are not even replacing the existing workforce as pathologists move, retire, or leave the profession. There are a few examples of small-scale successes, but the number of people entering the profession globally is far lower than necessary to expand the workforce.

JK: There will be a shortage of lecturers to train medical students in universities. We are not producing enough pathologists to fill this gap. There is already a chronic shortage of clinical and anatomical pathologists and the pace of training does not match population growth, increasing cancer testing, or the volume of surgeons, gynecologists, and endoscopists being trained.

RB: Unfortunately, my surveys don't indicate the numbers of pathologists or supporting personnel needed per site or position. Without that knowledge, it is impossible to foresee future staffing and recruitment challenges, let alone the steps needed to address them locally or globally. We also cannot see

whether or not present pathologist numbers are adequate or, if not, how many are needed – a question complicated by the fact that many international pathologists migrate to the USA in search of better salary or working conditions.

AN: Recruitment and retention are issues due to funding, priority, and the stability of governments and supply chains.

MO: A UK-wide survey of histopathologists conducted in 2017 found that only 3 percent of histopathology departments reported enough staff to meet clinical demand. Laboratory staff are under pressure to provide slides, which should happen within 24 hours, but regularly takes longer – in some places, up to 10 days. This directly and detrimentally impacts patient care.

Taking a broader view, 95 percent of patients will have a pathologist involved at some point in their healthcare journey. Evidence points to pathology services constituting 2–4 percent of the healthcare bill, meaning that the value of pathology services far outweighs their cost.

Our workforce is an aging one; around one-third of UK pathologists are 55 or over. When our most senior consultants retire in the next five to 10 years, there will not be enough trainees to replace them in numbers, let alone in knowledge and expertise.

The COVID-19 pandemic brought into sharp relief the vital need for pathology services. We must ensure that we learn lessons to ensure that the global pathology community has the resources it needs to help manage and mitigate the next global health emergency.

What is the most important action we can take today to ensure pathology's future?

SR: The pathologist workforce in the hospital – and in local, state, and national pathology societies – must remain strong and provide the leadership and arguments to maintain good staffing.

BM: First, raise awareness of the issue. Second, increase of the number of residents in training. Third, heighten training efficacy – and consider reducing timelines (for instance, in Germany, five years instead of six). Finally, implement digital assistance systems.

MW: Advocacy. Until policymakers and governments make access to diagnostics a priority and provide the necessary funding, workforce challenges will not change. The lack of visibility of diagnostics is the single most important barrier to increasing the workforce; until it is addressed, little progress is possible.

JK: We need to rethink both pathologists' training and the rules governing pathology practice. We should explore the possibility of training pathologists using digital slides, which would greatly increase the volume of pathology residents. We probably need to expand the scope of training of pathologists' assistants and cytologists. The use of AI and assistive technology would be helpful increasing the efficiency of individual pathologists. Without increasing adoption of technology, Africa will never close the diagnostic gap.

RB: Every university pathology laboratory should accept pathology students on the condition of being trained in histology procedures. Also, increase the number of histology schools, both brick-and-mortar and online, to ensure the necessary auxiliary personnel.

AN: Continued emphasis on providing accurate, accessible, and on-time reporting of results. If pathology is an essential component of patient care and there are funds to pay staff, purchase consumables, and maintain infrastructure, it will be successful. Long-term, sustainable local (national) funding is needed.

MO: More training places for pathology specialties under pressure, better IT systems and connectivity, and digital pathology transformation programs.

We need to ensure that there are sufficient training places to meet future demand, so the College works closely with the government and organizations responsible for creating training places to ensure that pathology specialties are represented and included in plans to improve the overall number of trainees. We also need to attract medical undergraduates to take up pathology as a career despite stiff competition from other specialties. We have invested in an active program of engagement to encourage medical undergraduates to consider careers in pathology.

Digital pathology has the potential to improve patient care and support the pathology workforce by making the diagnosis and monitoring of disease much more efficient. In addition, it facilitates high-quality teaching. We need more investment in better IT for day-to-day work and to implement digital pathology more widely so that staff can work more efficiently and flexibly.

Digital pathology, and developments in technology-enhanced learning provide unique opportunities to support future training models (attracting high-caliber trainees), multidisciplinary learning, and new educational resource for trainees, practicing pathologists, scientists, and those in pathology-linked roles.

Pathology services underpin health systems around the world, but pathology is often overlooked. The global pathology community has a critical role in raising awareness among political leaders and policymakers to make the case for pathology for the benefit of patients.

Disclaimer: all data provided in this article are estimates. If you would like to add to or amend the data provided in this article, please contact Andrey Bychkov at bychkov.andrey@kameda.jp

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Foundation
Molecular Pathology

By our powers combined… A newly created framework – "sc-linker" – combines single-cell RNA sequencing, epigenomic SNP-to-gene maps, and genome-wide association study (GWAS) statistics to identify the cell types and cellular processes genetic variants use to influence disease. The team detected subtle differences in SNP-to-gene mapping between tissues, with strong differences in disease heritability across cell types (1).

Two-faced collagen Type I collagen remodeling is associated with differing outcomes for patients with pancreatic ductal adenocarcinoma (PDAC). Matrix-metalloproteinase-cleaved type I collagen activates discoidin domain receptor 1 (DDR1), signaling tumor growth; the intact protein triggers DDR1 degradation and hinders tumor growth (2).

Clear-headed hepatic health Analysis of 9,491 cases combined with proton density fat fraction from 36,116 liver images has revealed 18 sequence variants associated with non-alcoholic fatty liver disease (3). Four variants linked with cirrhosis were found. Loss-of-function variants were found in *MTARC1* and *GPAM*, indicating they may have potential as future drug targets.

Something to ASPYRE to A highly sensitive model to detect gene fusions, called ASPYRE, shows rapid and consistent results even with low sample sizes. The method eliminates multiple instrument runs and uses pyrophosphorolysis to detect gene fusions from RNA and DNA simultaneously. The workflow and equipment are similar to standard PCR assays, with turnaround times under 24 hours (4).

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IN OTHER NEWS

Testing for treatment
Antibody-drug enfortumab vedotin's target – NECTIN-4 – is frequently decreased in mUC and 39.4 percent of metastases exhibit no membranous NECTIN-4 expression at all (5).

AML expansion pack
An expansion of the first proteogenomic characterization of acute myeloid leukemia bone marrow blasts has confirmed the proteomic Mito-AML subtype and mapping AML's proteomic landscape (6).

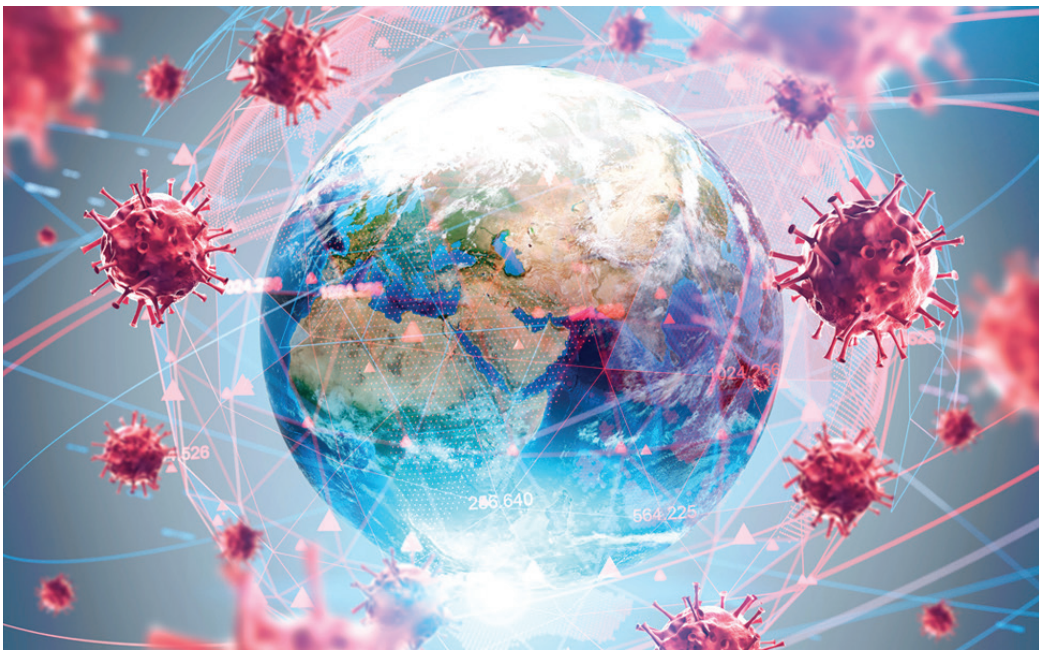
Lay of the molecular land
96 mutations found in 124 common chronic lymphocytic leukemia patients, with roughly half having at least one mutation. Thirty-six patients showed just one pathogenic variant, while 88 had between two to four (7).

A tale of two DLBCLs
Primary refractory diffuse large B-cell lymphoma (prDLBCL) makes up six percent of newly diagnosed DLBCL cases – with high frequency of TP53 alterations and MYC copy (8).

A Perfect Molecular Match

To tackle the growing threat of global infectious disease outbreaks, we need to optimize molecular testing and establish pandemic preparedness networks

By Anona Bamford



Few of us these days can say we're unfamiliar with the threat of a pandemic – or the long tail of recovery after one. But how can we use emerging technologies to stay ahead of that threat? Molecular diagnostics offer us an opportunity to monitor populations, quickly identify and address infectious diseases, and even distinguish between multiple illnesses with similar or nonspecific symptoms. To take full advantage of these tests' capabilities, we need to ensure that all people have equitable access to them – and we need to establish a pandemic preparedness infrastructure that allows us to act quickly on the information they provide.

Our pathogenic future

Pandemics are nothing new – but, with four influenza pandemics in the last 100 years, the regularity of such events is of great concern. The swift response to COVID-19 – particularly with respect to the development of diagnostics and vaccines – prevented a much worse outcome, but there have been more lethal and contagious pandemics in the past and preparation for the next one is really key to future success.

Simultaneous disease outbreaks in different areas of the world are to be expected due to our increasingly globalized economy, air travel, and increased opportunities for zoonotic transmission of pathogens to humans. That's why it's paramount to not only maintain global surveillance, but also invest in an infrastructure for a global pandemic preparedness system that nurtures research and capabilities in this area so that, when the next outbreak arises, our responses are swift and coordinated.

One way to do this in the fight against viral pathogens is to screen for common viruses with similar symptoms using so-called "syndromic tests" (so-called because symptoms that consistently occur together, forming a diagnostic entity, are called syndromes). Available syndromic tests enable the qualitative detection of multiple viruses at once – allowing pathology laboratories to distinguish between SARS-CoV-2, influenza, and respiratory syncytial virus (RSV) infections despite their similar symptoms. Although vaccination is key to reduce the spread of these pathogens and to prevent severe disease, syndromic testing is also valuable for rapid diagnosis, so that those with active infections can be isolated quickly to prevent further spread and receive appropriate treatment for the specific virus faster.

Diagnostics takes center stage

Diagnostic professionals are at the forefront of testing and diagnosing infected patients – so it's important that they are consulted in the choice and implementation of diagnostic tests to ensure the best possible outcome for patients. When deciding on the type of test to use, several factors are at play, including the stage of the outbreak, the resources required, and the laboratory workflow in operation. During peak respiratory disease season, running single-target tests may result in a difficult-to-manage workload. Switching to syndromic testing, which combines multiple targets into a single test, can reduce overall workload and enable faster reporting – speeding up measures such as isolation and treatment.

Molecular diagnostics play an important part in the prevention and early response to outbreaks from many angles: identifying infected individuals, understanding community levels of immunity, and also monitoring the evolution of variants so that appropriately targeted vaccines can be developed. When designing diagnostic tests, it is vital to avoid viral genes prone

to mutation so that infected cases are not missed. A rigorous process of research and development identifies optimal target regions that are then bioinformatically analyzed using primer design algorithms to select appropriate sequences. Following this, the sequences are tested to ensure the best possible sensitivity and specificity performance metrics are achieved by adjusting cycling parameters so that precise results can be obtained within an acceptable turnaround time.

Applying molecular tests

Molecular diagnostics are an extremely valuable tool when used correctly in the presence of appropriate clinical symptoms. They offer specificity and sensitivity with ease of use and interpretation, whether that's through a single-target assay or a syndromic panel in a diagnostically challenging situation. However, their value is maximized when each test's advantages and limitations are understood, so that the right test is used in the right circumstances.

PCR-based assays are still considered the gold standard in infectious disease diagnostics because they use common laboratory equipment and tolerate a wide range of input sample types. With the recent mpox outbreak and the constant threat of new and emerging viruses, broader syndromic tests are an excellent tool for building a global pandemic surveillance strategy.

PCR-based tests allow for high sensitivity and specificity. They use equipment already present in most labs and results can be obtained from a noninvasive nasal, nasopharyngeal, or saliva sample. Such workflows lend themselves to mass community testing because, with the addition of laboratory automation, throughput can be increased considerably. Modular, scalable extraction and liquid handling platforms allow labs to respond to surges in demand by removing bottlenecks such as sample accessioning and reformatting primary sample tubes into workflow-compatible consumables. At the same time, these platforms allow for full traceability of the sample to the patient result, thereby improving turnaround time.

"When designing diagnostic tests, it is vital to avoid viral genes prone to mutation so that infected cases are not missed."

But not all diagnostic settings are equal. PCR obviously involves the use of laboratory equipment, lab space, and sample collection logistics. Although it can be deployed to remote or underserved settings using mobile labs, that's an expensive undertaking – and the workflow takes time to run. Increasing the speed with rapid extraction and PCR protocols results in less time to result, but also less sensitivity, so this needs to be balanced to mitigate the likelihood of false negative results. Rapid point-of-care testing in the form of lateral flow tests, for example, offers speed and convenience without requiring laboratory equipment, but these types of tests have a wide range of sensitivity and specificity and are generally most appropriate during the acute phase of infection. If patients are tested too early or too late, their results may not be reliable even with a high-quality rapid test.

I believe that molecular testing will become increasingly syndromic. Pathogens that present with similar symptoms will be tested for in a single panel or as a combined, multiplexed, one-tube test. Though single-target assays offer speed and sensitivity, the clinician needs to know what pathogen(s) they are looking for to ensure success. In the future, syndromic tests and panels will include a wider array of target pathogens – and I anticipate that we will see faster testing and ever more streamlined workflows.

What's next?

With the changes in our climate becoming more apparent every year, vector-borne diseases are of great concern. Increasingly warmer and wetter weather supports the life cycles of mosquitoes and ticks, which can carry diseases between infected and uninfected animals – including humans. Such diseases include Zika, Chikungunya, yellow fever, malaria, dengue, and many others. In fact, the World Health Organization recognizes eight neglected vector-borne diseases that pose a huge burden of morbidity and mortality worldwide (1). Surveillance and early diagnostic testing are vital to effectively manage infected people and curb the spread of disease – and molecular testing approaches are key to catching the emergence of any novel pathogens.

Molecular diagnostics for routine testing and surveillance are a powerful armory against outbreaks of known pathogens and in the detection of new and emerging threats. Yet their success on the global stage is dependent upon partnership and collaboration within and between countries. We need adequate funding and resources to develop and distribute molecular tests – and, alongside that testing, we need collaborative, cross-functional research to create pandemic preparedness networks that will endure into the future.

Anona Bamford is Regional Segment Leader, Applied Genomics at PerkinElmer, EMEAI.

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Feeling the Selective Pressure

Key genetic differences may have determined who survived the Black Death pandemic – and how our immune system respond to diseases today

Infectious diseases have placed intense selective pressure on the human and animal population throughout history, with many of these involving immune response genes. The problem, however, lies with linking cause and effect – which pathogens caused specific adaptations?

In the mid-14th century, the Black Death wiped out up to 50 percent of the global population – cementing its place as one of the deadliest pandemics recorded in modern history. In an effort to understand whether *Yersinia pestis* – the bacterium responsible for the second plague pandemic – triggered a case of natural selection, researchers have analyzed the DNA of victims and survivors who lived in Denmark or London before, during, or after the Black Death (1). By their reasoning, variants associated with susceptibility or protection should display opposite frequency patterns across the sampled timepoints; variants conferring increased susceptibility should be high in frequency in individuals who died during the Black Death then decrease in post-pandemic survivors or descendents, whereas variants associated with protection should rise after the Black Death

By tracking genetic variants that became more common throughout the pandemic, they found key genetic differences associated with plague protection or susceptibility. In particular, changes in *ERAP2* allele frequencies were implicated; people with two identical copies of the protective *ERAP2* allele were about 40 percent more likely to survive the pandemic than individuals homozygous for the deleterious variant. This allele is linked with increased *ERAP2* expression and production of the canonical, full-length protein ERAP2, which the researchers suggest is associated with an increase in *Yersinia*-derived antigens to CD8+ T cells. They also found that macrophages from individuals with the protective allele yield a unique cytokine response to infection and better limit replication in vitro.

After the Black Death, plague outbreaks continued to occur in waves up until the mid-19th century, but these often wreaked less havoc than their predecessors. Why? Possible explanations span changing health, sanitation, and cultural practices, but it could also be that, because more people with protective variants survived the Black Death, their descendents will have inherited the survival advantage and been protected against future waves of the bubonic plague.

Fast-forward to modern day, and the research demonstrates how historical natural selection can impact current susceptibility to chronic inflammatory and autoimmune diseases. When stimulated with a range of pathogens, *ERAP2* was transcriptionally responsive and demonstrated its key role in immune response regulation – suggesting that the selective pressure from *Y. pestis* likely impacts immune response to other pathogens or diseases. The paper cites that the advantageous *ERAP2* variant against *Y. pestis* is actually a known risk factor for Crohn's disease and some communicable diseases. Perhaps the *ERAP2* variant protected our ancestors through the Black Plague, but this may have come at a trade-off for immune disorders in the present day – or "a long-term signature of balancing selection," as the researchers state.

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Pathology Versus Pandemics

How lab medicine professionals stepped up to the plate in the fight against COVID-19

Michael Schubert interviews Sir Jonathan Van-Tam and Mike Osborn

Tell us about the very early days of the pandemic…

Jonathan Van-Tam: In the very early days, we were looking at China and thinking, "We haven't got much information here. Is this real? What does it represent? Does it or does it not feel like the start of another pandemic?" The point at which I knew it definitely was and that it was coming our way was January 16, 2020. My next realization was that we had a clearly severe disease heading toward us at 100 miles per hour and we were going to take a big hit, but we still had to get other politicians to realize it was real and not just a scaremongering story.

What were your initial priorities when you realized the extent of what was coming at you?

JVT: It was already too late to avoid the problem, so my initial priority was to get the National Health Service (NHS) as ready as we could; it already looked like bed availability in intensive care was going to be an issue. The other thing that immediately came to mind was that we need to get a vaccine – there is no time to delay.

Mike Osborn: At the Imperial College Healthcare NHS Trust, we were taking our lead from national healthcare professionals; of course, we are health professionals, but this was a pandemic accompanied by a nationwide response and therefore you have to listen and follow the advice of specialists in that area. I was talking several times a week with high-level people and royal medical colleges; we would discuss the situation and specialists would share how the colleges could work together.

For the NHS and government organizations to best prepare and deliver the country's COVID-19 response, individual groups were tasked with jobs that catered to their skill set. For example, my predecessor at the Royal College of Pathologists, Jo Martin, along with other members of the college, produced a national strategy for COVID-19 testing. She wasn't in charge of the national policy, but we were able to provide data and guidance on how tests function, the various ways of using different tests, and what to look for in samples.

Other medical colleges and organizations provided guidance on infection control, how to diagnose and define the disease, and how to protect against it, while some colleges had input on how to carry on surgery during the pandemic, while protecting surgical patients. It was a mutual effort and there was a huge amount of collaboration that was critical to the success of the response.

When you were setting up your initial response, what role did you think pathologists and laboratory medicine professionals needed to play?

JVT: First of all, it was a new organism, so there were no readily available diagnostic assays – and those that were available were labor intensive, unsuitable for large-scale use, and required highly specialized staff. The need to upscale as much as possible was clear – and the laboratory medicine professionals at the heart of testing played an enormous role, swinging into action to significantly upscale diagnostic capacity across the world in record time.

Two and a half years on, our understanding of SARS-CoV-2 has changed a great deal – how have priorities shifted?

JVT: My main two priorities now are learning to live with COVID-19 in a way that wasn't possible in early 2020 and recovering the health service and


Professor Mike Osborn


Sir Jonathan Van-Tam

its staff. We also need to think of our next move with SARS-CoV-2 vaccines; our current vaccines are based on a form of the spike protein that is closely related to the wild-type variant, but we need to continue development to keep up with the virus' evolution.

What lessons can we learn from COVID-19 for future pandemics?

JVT: We can't predict the future, but, because of our increasingly close proximity to animals on an increasingly crowded planet, I have no doubt that there will be future zoonotic pandemics. Younger pathologists need to be careful not to dismiss COVID-19 as something that happened way back in 2020 and won't happen again in their professional lifetime.

We have demonstrated the need for large-scale diagnostics in public health and infectious disease control, and we understand that we might need that kind of response again. I don't think it's possible to say the COVID-19 pandemic is over in the UK and that we won't have problems with variants of concern in future, so we also have to be ready to upscale and reignite those widespread testing facilities we had during peak pandemic times.

Like many previous pandemics, we also learned that the way out of such crises is through vaccination and there is a clear need to develop more robust manufacturing infrastructure – not only in the UK but worldwide.

MO: These zoonotic events are inevitable, so you have to be prepared to deal with them; however, no two events are going to be alike. And that means you must learn broad lessons; for example, how to deliver messaging to politicians in a concise, defined, reliable way so they are best positioned to make public health decisions on a national level. They then need to make the public aware and keep them informed of what this means for them, their duties, and their responsibilities for maintaining their own health and the health of their families. Messaging needs to provide people with enough information to deal with the pandemic on a personal level, but needs to stop people from panicking and worrying. It helps to justify any dramatic policies, such as lockdowns, by giving intelligent – but simplified – information. Furthermore, relaying information around the importance of vaccination and how it is going to work has proved to be particularly useful.

During the pandemic, pathologists were involved in performing post-mortems on patients who had succumbed to COVID-19. And we have a post-mortem portal at the College that holds anonymous information on autopsies we have performed. Additionally, our members set up tissue banks around the world to store COVID-19-based tissue that, with consent, could be used for research or to develop vaccines or treatments. Importantly, these banks also hold post-mortem tissue – a valuable resource when dealing with a disease that can result in such varied outcomes, from mild illness to death. Certainly, it's easy to acquire serum samples from less severe and recovering patients who are in hospital, but the tissue bank enabled researchers to explore very severe cases and compare and contrast both ends of the disease spectrum to gain a more complete picture of the disease. Going forward, we can use this same resource and apply it to future emerging threats.

How are pathologists helping advance COVID-19 knowledge?

MO: Pathologists and laboratory medicine professionals have played a huge role in learning about COVID-19, but let's not forget that they play just as large a role in learning about diseases every day. We do this all the time and we will continue to develop our skills so that whenever the next threat arises, we'll be ready for it. We have forged close collaborations with industry partners so that we can rapidly develop robust tests and roll them out on a national level. Many of these technologies were developed for COVID-19, but they are now being used for a range of diseases.

It's important to realize that, although we live on this planet, we share it with millions of other species that have various bugs, diseases and bacteria – some of which can jump over to humans, like COVID-19. Veterinary pathologists investigating zoonotic diseases and transmission have always been vital, but this area is something that we now need to focus on even more.

Let's talk about information and misinformation. What role should healthcare professionals play?

JVT: The UK's response has always been to avoid engaging with misinformation because, when you respond to it, you amplify it and make it the center of attention. In my opinion, the best thing to do is to not engage with it directly; instead, release effective counter-messages that are clear, accurate, and speak in lay terms. Healthcare and research professionals tend to play to the professional language agenda and forget that complexity is not required when communicating with the public. Though it may appear demeaning to talk about science in ultra-simplistic terms, if you speak with the public enough, you come to understand that they're looking for something they fully understand. As healthcare professionals, we forget that it isn't just what we say, it's how we say it – the whole communication package is important.

MO: Agreed. Messaging needs to be plain and simple, if you want it to strike home. Interestingly, that is also true when dealing with politicians; they need to understand what is going on and your points need to be backed up with proper data. When Chris Whitty and Patrick Vallance gave the daily COVID-19 briefings on national TV, they communicated their messages with charts and graphs. An image speaks 1,000 words in a way that everyone can understand.

The public eye is now cast more firmly on pathology and related disciplines – how do we keep it there?

JVT: The pandemic has drawn these professions into the public eye – and applications for these careers are rising. Now, we need to engage with the young people who are showing an interest and put together engagement activities to keep them interested. It's not necessarily a once-in-a-lifetime opportunity, but we need to seize it now to draw in the next generation of budding scientists and laboratory medicine professionals.

MO: Realistically, the focus of the public eye moves all the time. During the COVID-19 pandemic, it was all over pathologists, laboratorians, doctors, and nurses; next week, it will be on the latest reality show or football scores. However, I think we're in a good position to build on the level of understanding and appreciation to maintain a relationship with the media and discuss topics and issues that are pertinent to the population. Keeping our messaging relevant, simple, and interesting will keep people interested in our health communications. For example, monkeypox has kept lab medicine professionals in the public eye by making sure stories are sensibly covered with good messaging from people who can communicate well. When the gaze fully turns back to us, we'll be in a position to build on it and not let it fade away.

What single key message would you like to send to the pathologists and laboratory medicine professionals – or the general public?

JVT: Pathologists and laboratory medicine professionals have put in a great shift during the pandemic. And, although it isn't the most glamorous work, we really have needed and depended on you during these times. What I'd like the public to know is that some of the more silent professions in medicine have done an enormously fantastic job behind the scenes. We cannot thank them enough.

MO: You do a fantastic job; what you do underpins all healthcare. Pathologists conduct all blood, infection, and cancer testing (and more!) – even if you go to a primary care doctor, it's still pathologists analyzing the tests and making a diagnosis. So you may not think you're interacting with patients and other healthcare professionals, but you are; you're fundamental to everything. The public appreciates and understands this and you should be proud of and champion what you do because it's fantastic. Healthcare would be on its knees without you.

For the public, I would say that we are here for you; you may not see us much in the background, but you wouldn't have healthcare without us.

"We can't predict the future, but, because of our increasingly close proximity to animals on an increasingly crowded planet, I have no doubt that there will be future zoonotic pandemics."

Sir Jonathan Van-Tam is the Pro Vice-Chancellor of Faculty of Medicine and Health Sciences, University of Nottingham and former Deputy Chief Medical Officer of the Department of Health and Social Care, UK.

Professor Mike Osborn is the President of the Royal College of Pathologists and Consultant Histopathologist for North West London Pathology at Imperial College Healthcare NHS Trust, London, UK.

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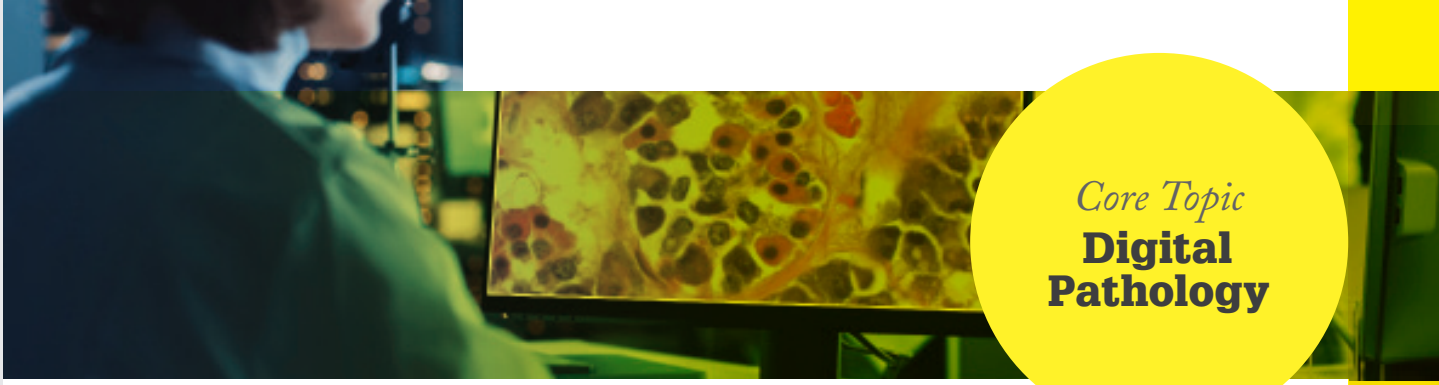


Core Topic
Digital Pathology

Blood Bots

By leveraging the power of AI, computers can detect leukemia in blood samples – with accuracy to match their human counterparts

By George Francis Lee

The discourse on the marriage of artificial intelligence and pathology is hardly fresh at this point. If you're a keen reader of The Pathologist, you'll be familiar with the many articles we've published on the matter. Demonstrating real-life applications of AI in clinical settings, for instance, is still a fledgling branch of research. And though they are starting to increase in number, it feels like each new analysis of AI's importance in the diagnostic pipeline takes us one step closer towards a new era of healthcare.

One such study is offered by Carsten Marr, Director of the Institute of AI for Health at Helmholtz Munich, Germany, and his team, who used the increasing availability and capabilities of AI to support diagnostic decision making in hematopathology (1). In this case, the aim was to assist pathologists in spotting acute myeloid leukemia (AML). I spoke with Marr to find more about the study and the implications it could have on hemepath as a whole.

First, could you broadly explain your work and how you arrived there?
Today, my team develops machine learning and mechanistic models to boost diagnostics and understand stem cell kinetics. How did I get here? I studied physics in Munich, did my PhD in network biology, and transitioned from bioinformatics to clinical data analysis and health AI during my time as postdoc and group leader. Later, I got involved in computational hematopathology as it was quite clear to me – based on my discussions with clinicians and pathologists – that the amount of data in histopathological slides was a perfect use case for health AI.

What work have you been doing in blood diagnostics?
We trained several models with different blood datasets to address questions such as: Can we automatically discriminate blood cells? Can we predict the disease or subdisease? The genetic alteration? From blood, bone marrow smears, and histological sections?

If so, with what accuracy? And based on which morphological features?

How were you able to train an AI system to detect different AML subtypes?
With the help of a large enough data set, sufficient computing power, and dedicated students – ha!

AI worked well in cases of leukemia. Will this approach work for other blood diseases? Do you expect difficulties in other areas?
I expect it to work wherever pathologists and cytologists can do the job. What these experts train into their brain over years of education, we train into the parameters of our artificial neural networks. It becomes particularly interesting when we can identify diseases where experts fail.

Your system's classification accuracy was comparable to human experts. Is this a huge deal for diagnostics or should we hold back our excitement?
I think it's great. To make a difference in the clinics or the lab, we have to make sure algorithms work with real-world data (and not particularly selected datasets), can deal with data from different labs, and are efficiently integrated in the existing workflows.

Your AI was able to detect even very rare forms of cancer, where less data is available. Are there any pitfalls?
The more difficult the problem, the more data we need. However, if some cancer cells are very different from all others' data, models can also work with a limited number of examples (2).

How do we bring these AI models into clinical settings?
Optimize workflows. Make sure it makes the experts' lives easier. Evaluate workflows with algorithms against traditional ones and measure time and performance. Plus, we need hardware companies to join in.

You've spoken about a healthcare data "explosion" in the near future. Is this purely a positive thing or are there any negatives to this glut of info?
I think there is really a great deal we can learn, once we are able to analyze our health data. Of course, we need to make sure that individuals have control over their data, which they currently do not have. I suggest moving forward with caution but note that we should definitely move now.

See references online at: tp.txp.to/0223/blood-bots

Picture Perfect: Embracing Digital Pathology 2.0

Technological restraints have been a historical barrier in the lab but, thanks to innovative tech, a new age of digital pathology is here

By Prasanth Perugupalli

Part one of our six-part "Barriers to Adopting Digital Pathology" series.

Advances in semiconductors and computing technology have transformed the way we think about images. For example, when snapping photos on our mobile phones, we rarely adjust the lens or consider the lighting – we just point and shoot. With high-resolution cameras, increasingly small storage devices, lightning-fast data handling, and mathematics for real-time parsing of data from millions of pixels, the choices we now make tend to focus on how data should be handled to preserve the most valuable information.

"The pathologist's ideal is for every part of the tissue to be visualized in its most pristine clarity, often defined as 'in focus.'"

In embracing innovation, pathology labs are aggressively evaluating the available options for digital transformation of their reporting work – from the moment a slide is placed on the pathologist's desk to the final report's appearance at the treating physician's office.

The pathologist's ideal is for every part of the tissue to be visualized in its most pristine clarity, often defined as "in focus." Recent advancements offer pathologists supreme confidence that the microscope-only days will not be missed, because the next generation of digital pathology is increasingly unaffected by variability in slides, stains, or tissue cuts. Next-generation whole slide imaging (WSI) scanners are smart machines that will make in-line intelligent decisions about scanning and image parameters to output super-high-fidelity WSIs without the need for perfect glass slides. They would also automate the quality control process based on metrics they generate on various aspects of WSI quality, including focus, stitching, banding, color fidelity, and more. This would significantly reduce the burden and cost that would otherwise be involved in filtering out scans that are unusable for practical purposes.

The new norm in digital scanning will augment the WSIs with first-pass content detection. The outcome can be remarkably precise computational advice on WSIs, identifying macro and micro elements of interest – from tuberculosis bacteria to tumor islands. This would herald tremendous efficiency in identifying the most important slides for pathologists' expert review.

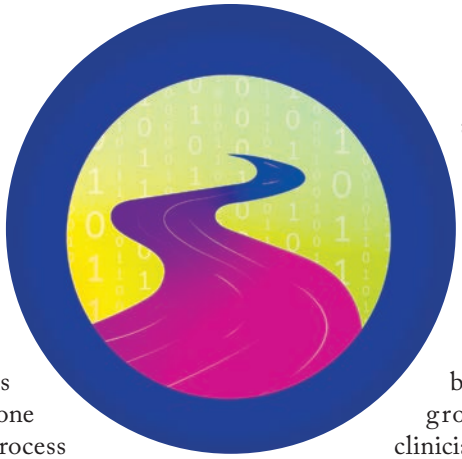
With these new advancements in digital pathology, labs would have a drastically lowered barrier to adopt a digital workflow that is as simple as snapping a picture-perfect photo with your phone.

Prasanth Perugupalli is Chief Product Officer at Pramana, Cambridge, Massachusetts, USA.

Looking Through a New Lens

It's time to make the leap from digital pathology to digitizing pathology

By Catarina Eloy, Junya Fukuoka, Anil Parwani, and Colin White



The COVID-19 pandemic has been a significant driver of digital pathology adoption. Labs worldwide rapidly adopted, or expanded their adoption, of digital technologies and telepathology as a means to remain operational during pandemic-induced lockdowns. In 2020, we estimate that about five percent of pathologists were asking questions not about how to scan slides, but about what they could do with the scanned image. Now, that number is more like 25 percent. This is good news!

Unfortunately, the transition happened so fast that it is not proving sustainable. As we settle into the post-acute phase of the pandemic, we see labs beginning to revert to traditional glass slide-driven pathology. Although this may feel comfortable, it is also a mistake. We must maintain our forward momentum. In that spirit, we propose a focus on digitizing pathology, rather than on digital pathology. This is not wordplay; on the contrary, adopting this language compels a shift in mindset and encourages acknowledgment of our vital role in patient care.

Why is this warranted? Pathologists are in a sweet spot. We are in the right place at the right time because we can now make use of digital images to expand our positive impact on quality and patient care. Technology is available to capture, store, retrieve, and share pathology images. Solutions range from simple image capture on cell phones to sophisticated scanning devices. A patient can have their sample reviewed in real time by a pathologist. We recognize, of course, that there is much work to be done to optimize the process of digital transformation, especially for those with limited personnel and financial resources – but, that said, our work can't begin and end within the pathology department. If it does, we're shortchanging patient care.

Digitizing pathology is a journey we must take as a global pathology community. We believe that something on the order of 10 percent of labs currently have the technology, expertise, and leadership to digitize pathology. We need to connect that first 10 percent to the other 90 percent who are earlier in their journeys. Doing so will benefit all. New platforms, such as Digital Pathology Connections, allow pathologists from all over the world to learn together. Pathologists just starting their journey can now easily access and connect directly with those farther along the path. Developed and developing countries can learn from one another. Academic centers can share knowledge with private provider practices.

The phrase "digitizing pathology" accurately reflects the continuum of work we must undertake, which stretches far beyond a switch from glass slides to digital images. Our remit includes not only that transition, but also work to establish quality policies and standards, to agree on "ground truth" data sets and computational models for use worldwide, and to align on outcome measures, including new types of measures such as impact on lab workflows or patient disease. Although it's still early days, we are starting to see the publication of peer-reviewed studies that document the benefits of digitizing pathology. As this body of evidence grows, patients and clinicians will demand the use of such tools to improve patient care. This will take time, of course, but we anticipate an acceptance trajectory similar to what we experienced with immunohistochemistry. Digital pathology is a tool – but digitizing pathology is a process change and people engagement journey with the end result of improving patient care and outcomes.

Robert Frost's well-known poem, "The Road Not Taken," extols the potential of the untraveled road. We concur – and we recognize that pathologists need to walk the road to digital together on behalf of our patients and our profession.

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Targeting the Forgotten

How to empower patients in histopathology diagnostics as we navigate the emergent digital era

By Angelene Berwick, Bradford Power, and Nicolas M. Orsi

It is now well recognized that histopathology is facing a challenging future characterized by a global decline in the number of pathologists coupled with an increased diagnostic workload (1, 2). Though compromised service delivery under such pressure seems almost inevitable, help may be at hand. Over the last two decades, major innovations in histopathology have centered on the implementation of digital scanning and whole slide imaging (2). Centers investing in digital pathology have the potential to reap benefits such as streamlined workflows, increased pathologist efficiency, rapid/cheaper second opinions and external consultations, and faster diagnostic turnaround times – all while creating opportunities for remote working (3). These benefits may extend further as the foundation of image-based infrastructures tantalizingly promises to support the development and deployment of artificial intelligence (AI) solutions to lighten the diagnostic burden – the incipient so-called 'third revolution' in pathology (4). That said, adoption of digital pathology varies worldwide. In this regard, the UK leads in Europe (5), while other countries, such as the US, lag behind. But what we lack are comprehensive evaluations of the technology's adoption in the field.

A pathologist-focused agenda?

To date, studies on the acceptability of AI and related technologies have focused on the opinions of histopathologist end-users (6), while neglecting the views of the end-beneficiaries: patients. This mindset may partly reflect the clinical immaturity of these technologies and the fact that patients typically have very limited interactions with pathology services, as opposed to other clinical disciplines where there is a greater stakeholder oversight of public and patient involvement (PPI). Nevertheless, given the cross-sectional relevance of pathology and its system-critical impact on other clinical disciplines (2), such involvement is key.

Another contributing factor may be differences in healthcare systems, for which the UK and US offer markedly contrasting examples. In the former, the National Health Service (NHS) represents a government-funded, single payor system, wherein patients often have minimal involvement in diagnostic processes, with many being unaware of the clinical role of histopathologists. By contrast, the US system has a fragmented reimbursement pathway where patient management is heavily influenced by insurance coverage. In the US, the risk for many is that reimbursement strategies and policies may dictate diagnostic analyses performed.

Similarly, the understanding of PPI is also subject to national interpretation. In the UK, PPI depends on willing volunteers representing a disease area (such as cancer), who are driven by a desire to help patients gain knowledge of complex medical matters, which informs their input into their own clinical management decisions and personalized treatment options. Moreover, it aims to offer a patient-centric view for researchers investigating novel diagnostic and treatment solutions, and their subsequent clinical adoption.

In the US, patient advocacy is driven by organizations that lobby on behalf of communities with more specific disease types (for example, breast cancer). Their activities are guided by a combination of funded research and philanthropic donation-based opportunities, community need, government and regulatory lobbying, and the provision of knowledge for educational services, patients and caregivers. PPI involvement (typically by the Patient and Family Advisory Council, PFAC) extends to healthcare providers, payors, and pharmaceutical companies, and provides evidence of involvement of patients and caregivers in their programs. Despite these differences, the goal of both UK and US-based patient advocacy organizations should align in offering patients faster, reliable and, ideally, more affordable diagnoses without unduly burdening diagnostic services.

Thinking ahead: involving patients

In recent years, the UK in particular has witnessed a concerted effort in adopting a holistic, patient-centered approach in healthcare and service user-led research in the wake of changing patient attitudes to established biomedical authority – notably, following a number of well publicized medical scandals (7). There are, as such, the founding principles underpinning the legitimacy of PPI centered on moral, policy-based and, in the case of research, methodological grounds. As such, empowering patients has been enshrined in the UK's National Institute for Health and Care Excellence (NICE) PPI policy's progressive key principles. First, lay people and their advocates should have opportunities to contribute to developing guidance, advice, and quality standards with a view to supporting their implementation. Second, this contribution should inform NICE's guidance and ensure that products are focused and relevant to those stakeholders most directly affected by its recommendations (8).

The benefits of PPI involvement

are tangible, with various studies demonstrating how patients can effectively contribute to service improvement as well as better health outcomes and patient experience (7, 9, 10, 11, 12). This success has translated into NHS England's commitment to empower patients, their caregivers, and advocates to participate in making informed decisions about their individual care and treatment (13).

Actively considering PPI engagement in the digital pathology space, especially regarding AI and its potential clinical adoption, now seems very timely. From our ongoing UK-based studies, we understand that patients and their advocates are not only increasingly cognizant of the potential personal and clinical benefits of such technologies; they are also prepared to embrace their clinical adoption, albeit as diagnostic adjuncts combined with histopathologist input. This viewpoint may offer a comforting message to any clinicians concerned that they may be at risk of being replaced by diagnostic algorithms.

A future framework

The benefits of PPI engagement for validating patient support in research and clinical utility evaluations are easily conceived and can offset any practical issues pertaining to establishing advocacy groups – and the same applies in the adoption of AI in digital pathology. In an ideal setting, PPI should be incorporated at all stages of research (such as grant applications, ethics review, publication), clinical evaluation, cost-to-benefit analyses, and clinical adoption. Each stage should provide opportunities for iterative feedback – a model that the UK, at least, is increasingly moving toward. Importantly, such an interactive, inclusive, and transparent system will build trust with both end-users and beneficiaries. And just as importantly, by giving patients a voice in cutting-edge medical advances, we ensure that the research/clinical adoption of these new technologies remain grounded in achieving a positive impact on patients and their advocates. Active, engaged, and educated patients get better outcomes – and so, regardless of whether institutions listen, patients should speak more.

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See references online at: tp.txp.to/0223/targeting-the-forgotten

Profession

Your career
Your business
Your life

For Your Reference

Identifying reference standards to improve immunohistochemistry

Michael Schubert interviews Keith Miller

Have you ever wondered how accurate your immunostaining really is? It's a subject of deep interest to everyone from pathologists to regulators – but, until now, the ability to verify that accuracy has been limited due to a lack of universally available reference standard controls. Without such standards, it can be difficult to determine test sensitivity, ensure consistency and repeatability, and compare results between laboratories. To address this gap, a new group – the Consortium for Analytic Standardization in Immunohistochemistry (CASI) – aims to identify objective, quantifiable analytic sensitivity guidelines for immunohistochemistry (IHC) assays and establish reference materials to help laboratories ensure accurate, consistent testing for all patients.

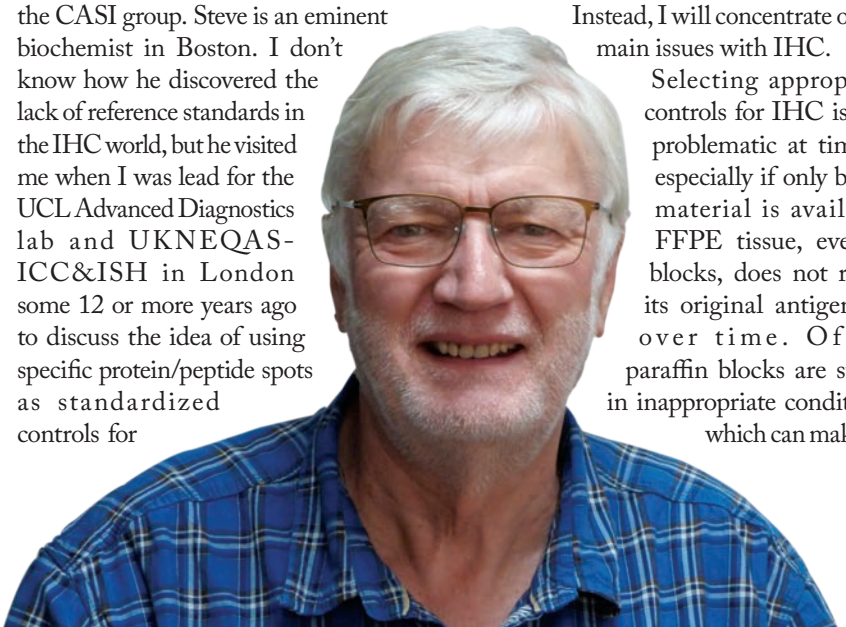
Can you describe CASI's work?

The CASI team is working on developing and validating a series of standardized controls for some of the companion diagnostic immunohistochemistry (IHC) tests and other important diagnostic IHC antibodies. The individual controls are made up of measurable amounts of target antigen (in the form of a specific protein created for a specific antibody) added to microbeads. There will be a range of concentrations of the specific protein developed for each specific test.

At present, the CASI team is focusing on having four control spots for each target on a slide next to the test section. The specific protein concentration ranges are aimed at encompassing the entire detection range, from lower to upper limit. This is still early days, but some tests may also need a spot that should be beyond the lower limit of detection with an approved assay. If this control lights up – for example, with a HER2 assay – it should indicate that the patient test section in question may be overstained, warning the pathologist that there is a risk of over-calling the case. If, on the other hand, the spot whose protein concentration is at the upper limit of detection fails to stain properly, this will provide a warning that there is a risk of under-calling.

What prompted the group's launch?

It was Steve Bogen's excellent idea to launch the CASI group. Steve is an eminent biochemist in Boston. I don't know how he discovered the lack of reference standards in the IHC world, but he visited me when I was lead for the UCL Advanced Diagnostics lab and UKNEQAS-ICC&ISH in London some 12 or more years ago to discuss the idea of using specific protein/peptide spots as standardized controls for IHC. My colleagues and I were absolutely delighted by the proposal – but the ability to develop his idea and use some sort of digital slide analysis was beyond us at the time. Just before I retired in 2018, Steve got in touch again to see if we could work together and develop this project. Microbeads had been added to his proposal by then and, with all the technological developments that had taken place since Steve first visited, I felt sure the tools were now available to get his project up and running. I suspect others thought the same.



In your opinion, what are the major analytical challenges currently facing IHC?

I will avoid going into detail about the issues with formalin fixation and paraffin sections because there are just too many. Instead, I will concentrate on the main issues with IHC.

Selecting appropriate controls for IHC is very problematic at times – especially if only biopsy material is available. FFPE tissue, even in blocks, does not retain its original antigenicity over time. Often, paraffin blocks are stored in inappropriate conditions, which can make the

loss of target antigen even worse. Paraffin sections, too, can lose their antigenicity if not stored appropriately.

FFPE cell lines are available for many targets, but not all. For a lot of clinically important targets, there are no cell lines available with the appropriate range of IHC staining.

Manufacturers have difficulty at times in eliminating batch-to-batch variation that affects their companion diagnostic kits. This is simply because either the control material they use is deteriorating or they must source other FFPE blocks that have been fixed differently to the batches of controls they employed previously.

The commonly used automated IHC instruments are not able to incubate every slide with specific IHC reagents for exactly the same amount of time as specified by the onboard staining protocol. I was once informed by one eminent IHC instrument engineer in the field that this is because only a single robot delivers the main IHC reagents for up to 30 slides and it is not possible to ensure exact timings for all the different tests that can be on board at one time. These small timing differences between slides can affect the staining result. Add to this the batch variation of IHC staining kits and the fact that there are now targeted cancer therapies licensed for use when a relatively small amount of target antigen is detected and it is quite clear that the IHC staining variation problem can potentially be catastrophic for some cancer patients.

To further explain, because many laboratories like to use controls that show relatively strong staining for a given target, it is possible that a weak positive case could become an undetected false negative. Target antigen-rich controls can often show good staining even if the assay concerned is a little less sensitive than normal, which can happen for a variety of reasons. This risk applies to tests such as HER2, PD-L1, and *ALK*.

Another problematic area associated with companion diagnostics can be interpretation, especially when small amounts of protein must be identified and converted to a percentage of tumor cells positive within a given section. Having an IHC quality baseline provided by reference standard controls might help the development of some wonderful AI digital slide technology that could assist with more complex interpretation.

I believe that CASI's work will overcome many of the issues affecting the sourcing of IHC controls today. There will be those who say the protein spots will not provide information on localization of the target antigen with a given IHC assay, but adding an appropriate FFPE cell line can overcome this issue.

How should pathologists and analytical scientists interact to further the consortium's goals?

Our first step is to get the message about CASI out there. Publications alone will probably not get the message across at first – but we have a website in development that might also help.

My feeling is that we need to introduce the existence of CASI and its work at national and international pathology meetings before the various reference standard controls and related analytical software are ready for clinical use. I believe that, by doing this, we can highlight some of the problems that affect IHC testing today and explain why reference standards are needed.

UK pathologists are reliant on their scientists when it comes to understanding the weaknesses with IHC. Unfortunately, a lot of the older scientists who were around when IHC was developed into a significant diagnostic and predictive tool have now retired. Today, the younger generation are using push-button technologies and, in some cases, lack a thorough understanding of why an IHC test may go wrong. Worse still, a small number will not even recognize when a particular test result might be false.

A lack of appropriate training is the main problem and this is unlikely to be rectified soon due to resource limitations. Having said this, the UK's EQA Scheme, like other EQA programs around the world, is helping educate all in the field.

Read the full version of this interview at tp.txp.to/for-your-reference

Meet the Group

Steve Bogen, Boston Cell Standards Inc., Boston, Massachusetts, USA
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David Dabbs, PreludeDx, Laguna Hills, California, USA
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Keith Miller, University College London, London, UK
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Suzanne Parry, UKNEQAS, London, UK
Matthias Szabolcs, New York Presbyterian/Columbia University Irving Medical Center, New York, USA
Clive Taylor, Retired, Keck School of Medicine, University of California Los Angeles, California, USA
Emina Torlakovic, University of Saskatchewan, Saskatoon Health Authority, and the Canadian Biomarker Quality Assurance Saskatoon, Saskatchewan, Canada

A Connected Future for Pathology

How a virtual pathology interest group for Chinese medical graduates became a platform for all those invested in the discipline's diverse future

By Chuan Chen, Yi Zhu, Xingchen Li, Wangpan Shi, Axin Yu, Casey P. Schukow, Kamran Mirza

For international medical students and graduates seeking to build a life and career in a new country, getting started can feel like an impossible task. This is particularly true for those who are beginning their medical careers in a new language, with a new alphabet, or in a medical system completely different to the ones they've grown accustomed to during training. To overcome the many obstacles a move to the United States presents, we conceived CMG23PathGroup – a virtual pathology interest group to help with residency applications and promote workforce diversity, equity, and inclusion.

Who are CMGs?

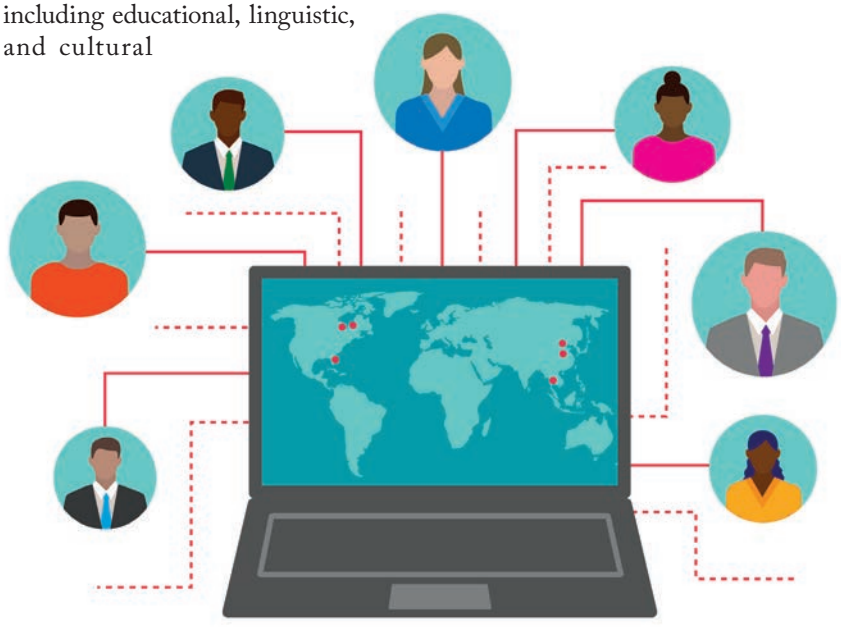
Chinese medical graduates (CMGs) currently represent a small portion of the active US physician workforce (less than 1 percent in 2017), but one whose top practicing specialty is pathology (1). And the numbers are only increasing – in 2017, 571 (10.8 percent) of all US-based CMGs were pathologists (2), but by 2022, this had increased to 1,520 (19.4 percent).

CMG applicants for pathology residency training fall mainly into three categories: i) candidates with an advanced graduate degree after completing medical education in China, ii) candidates who practiced pathology or other specialties in China, and iii) fresh medical graduates and medical students. We refer to all Chinese applicants as CMGs. Regardless of their background in medicine, these candidates develop their passion for pathology in their research or clinical work and then pursue a career in the United States for a variety of reasons.

Challenges and opportunities

Like other international medical graduates (IMGs), CMGs face challenges when applying for US pathology residency, including educational, linguistic, and cultural differences; limited US clinical experience; and issues with visas or work permits.

In China, medical school takes five to eight years, depending on the specific program's training track. Pathology is typically introduced in the second year after anatomy and histology courses, but medical students do not evaluate slides under microscopes in real clinics and, as with many US undergraduate medical programs, pathology clerkship is not mandatory (3). These factors limit students' exposure to pathology and may contribute to the misperceived idea that pathologists are "not doctors" (4, 5).




Axin Yu


Chuan Chen


Yi Zhu


Wangpan Shi


Casey P. Schukow


Xingchen Li


Kamran Mirza

"Our long-term goal is to promote the pathology profession and bring in new perspectives and skills to enrich the diversity of the US pathology workforce."

A key difference between Chinese and US pathology is the scope of clinical practice. Pathology graduate medical education in the US consists of anatomic pathology (AP) and/or clinical pathology (CP) but, in China, "pathology" typically refers to the AP arm only. CP professionals in China – including biochemistry, microbiology, transfusion, and coagulation – are trained in a separate laboratory medicine track and are not considered "pathologists." In medical school, CP is primarily taught in laboratory diagnosis and internal medicine courses. These differences narrow the scope of pathology in China and generate confusion when CMGs apply for pathology residency in the US.

Another challenge for CMGs is language. In China, pathology courses (and medical curricula in general) are taught in Chinese, which generates a significant language barrier for those who hope to practice in the US – for instance, when preparing for the USMLE exams and during clerkship training (6).

Finally, CMGs, like other IMGs, have limited access to US mentorship and clinical rotation opportunities. US clinical experiences and letters of recommendation from these experiences are two key documents for residency application that CMGs often lack. The COVID-19 pandemic further decreased the availability of US clinical experience and prevented international travel, even though the need for health care professionals increased worldwide during the pandemic (7). Another consequence of the pandemic is the permanent cancellation of the USMLE Step 2 clinical skills (CS) exam. IMGs are now required to undergo the Pathways for ECFMG Certification, including passing the Occupational English Test and a structured clinical examination, instead. For example, Pathway 6 requires that the applicant's clinical skills be evaluated through six clinical encounters by at least three licensed physicians using ECFMG's Mini-Clinical Evaluation Exercise. These new evaluations add additional layers of uncertainty, as well as financial and time costs, for IMGs.

But challenges and opportunities come hand in hand. To overcome the barriers and help CMGs match into US pathology residency programs, we initialized the CMG23Path Group, a virtual pathology interest group for all CMGs applying for residency in the 2022–23 cycle. The group aims to encourage pathology learning, shared observership opportunities and experiences, and residency preparation. Our long-term goal is to promote the pathology profession and bring in new perspectives and skills to enrich the diversity of the US pathology workforce.

CMG23Path Group achievements

The group has two subgroups, PathStudy and PathConnection. The PathStudy team is responsible for scheduling weekly group study sessions via Zoom. The sessions, which take place most Saturdays at 10 pm EST to accommodate both US- and China-based participants, typically last one to two hours. The topics and format are flexible. For example, we review textbook chapters covering bone marrow, soft tissue, liver, brain, and so on. Members are encouraged to share their clinical experience (for instance, tips on specimen grossing). We also hold group case studies in which attendees are encouraged to describe the microscopic features and give diagnoses to the unknown slides. Residents and faculty are invited to join and teach as well – for example, we invited Mengxue Zhang, a PGY-1 pathology resident at the University of Chicago, to host a medical renal unknown conference. The flexibility in format and content allows speakers to deliver or discuss topics of personal interest. Live question-and-

answer sessions are encouraged and unanswered questions are addressed in the group chat after the meeting. This peer-to-peer group learning has been interactive, engaging, and fruitful!

The PathConnection team is responsible for connecting with peers, residents, fellows, and faculty members. For example, in July 2022, we invited Guannan Zhang, a PGY-2 pathology resident at the University of Miami/Jackson Health System, to host a live session to answer pathology residency application questions. In September, we invited Kamran Mirza, an associate professor of pathology at Loyola University, to give a mentoring session on "Demystifying Pathology Residency Interviews" (see Figure 1). These invited talks attracted and served audiences worldwide, with attendance numbers up to 80 per session – about 12 percent of total IMG applicants (8).

The PathConnection team also organized a program search during the application season. Each volunteer selected between five and eight programs and filled out an informational form, including USMLE Step score requirements, year of graduation cutoff, number of open positions, and more, using the programs' official websites and cross-referencing online databases such as FREIDA and medmap.io. The forms are updated if additional information is explained in the program's open house and serves as a reference for group members to promote individualized application and reduce costs.

Through these activities, CMG23Path Group members develop a robust collegial relationship, which is maintained and strengthened after entering residency and beyond.

Where are we heading?

CMG23Path Group is growing and attracting IMGs from other countries. In August 2022, we opened the CMG23Path Group to all aspiring pathologists interested in learning, sharing, and connecting. CMGs, IMGs, and US medical students and graduates (UMGs) are all welcomed and we have expanded our social media groups to different platforms, including WeChat, Twitter, and WhatsApp. Our group has therefore become more inclusive. We kept the name CMG – but the "C" took on a new meaning: Connected.

CMG23Path Group is now working on a number of things to herald a supportive community. First, we propose collaborating with Path_Sig, a virtual pathology student interest group founded by Kamran Mirza. CMG23Path Group and Path_Sig complement each other; CMG23Path Group members are mostly IMGs, whereas Path_Sig members are mainly UMGs. Collaboration between the two groups can only promote diversity, equity, and inclusion within pathology education and the workforce. Second, we plan to collaborate with the Pathology Outreach Program (POP) founded by Ahmed Aadil and co-ambassadored by Casey P. Schukow. POP aims to engage and empower high school students to learn about pathology. Collaboration with POP can enrich current applicants' volunteer experience and enhance the future pathology workforce in the long run. In our opinion, the more connected aspiring and early-career pathologists become, the better our discipline will be for years to come.

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See references online at: tp.txp.to/a-connected-future

A Unique Perspective

Sitting Down With… Sylvia Asa, Consultant in Endocrine Pathology, University Hospitals Cleveland Medical Center and University Health Network (Toronto) and Professor of Pathology, Case Western Reserve University, Cleveland, Ohio, USA

What led you to pursue pathology?

I wanted to specialize in internal medicine and really enjoyed endocrinology, so I followed that path – but then I switched to pathology, which gave me a unique perspective on both disciplines. When I told my department head that I was switching to pathology, he said, "You don't look like a pathologist." I asked, "What does a pathologist look like?" And he said, "An old man in a wrinkled suit, with stains on his tie, stuck in the basement with pickled body parts." This description stayed with me and, when hiring professionals for my department at the University Health Network in Toronto, Canada, I looked for people who had strong personalities and weren't afraid of social interaction. I pushed them to interact with the patients who regularly came to our offices to meet their pathologists.

Why are you passionate about digital pathology?

I believe that digital pathology results in better outcomes. In 1909, Canadian clinician William Osler said, "As is our pathology, so is our practice" – and that hasn't changed. If you get the right diagnosis fast, the patient's treatment is likely to work better, their hospital stay will be shorter, and they will have fewer complications. The secret is to persuade the decision-makers and budget-holders that the scanners, software, and AI systems we use all affect those variables. The world of digital pathology has grown; with so many technological advances available, we have to gather the data to prove that digital pathology saves money not only in the lab, but also outside it. It's not easy, because the benefits can be hard to quantify without direct comparisons.

A great thing about digital pathology is that we can show patients their slides on our computer screens; on double-headed microscopes, they often only see their eyelashes. Digital images make it easier to explain to patients what we see in their slides, why they need a specific treatment, or that they may have a genetic disorder and need further testing.

How has pathology changed over the course of your career – and what changes will it see next?

I recently went to the Pathology Visions Conference in Las Vegas, where I saw 800 people deeply involved in digital pathology. Their energy was palpable. It was a far cry from the time I was told I would be sued for using digital pathology.

Many of us were told in training that pathology was a pattern recognition exercise and we were expected to offer a diagnosis based on that alone. These days, we need to understand not only pathophysiology, but also clinical manifestations – whether inherited or somatic – and help guide the right treatment for each patient. As a community, we must recognize the importance of the depth of our knowledge and the role we play – not only in identifying the pattern and the diagnosis, but also in understanding disease mechanisms and the biology of targeted therapies. Those are aspects that medical professionals may not be trained in or may not have time to explore in depth. Nobody can learn everything, and that's why I advise my trainees to subspecialize, focus on their chosen area, and become an integral member of the clinical care team. We need to move away from just doing "pattern recognition," or else algorithms will replace us.

There are two possible scenarios for digital pathology and AI. One is that pattern recognition algorithms do the job pathologists have trained them to do exceptionally well and, without adapting, pathologists disappear. It seems that many people are afraid of this scenario. But the more optimistic alternative is that we do our job better with the algorithms' help. For me, digital pathology with AI is not just a challenge, but also a tremendous opportunity for advancement. Doing things differently ensures the survival – and the importance – of our discipline.

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How can labs with limited resources go digital?

My current laboratory doesn't have a lot of funds, so my team had to convince decision-makers that implementing digital pathology would save money in the longer term. It's a hard calculation for those in charge of budgets, but for us, it's quite intuitive. We see how much time is spent looking for slides that may have been misfiled when they need to be reviewed again; that goes away when the slides are available digitally. In an academic center with residents, the requests for slide recuts quickly add up; it's much easier to share a digital file. Algorithms that accurately replace our most tedious manual tasks not only save valuable time and money, but also make our work more enjoyable and fulfilling.

How do you balance a busy career and a personal life?

My children would tell you I don't have a personal life! My husband is an endocrine oncologist, so we both see our work as our life. We love our jobs. When you love something, you live it. This is why my four kids grew up learning a lot about pathology and endocrinology. They have all grown up to be extremely well-adjusted, independent, and self-sufficient, and I'm now also a happy grandmother.

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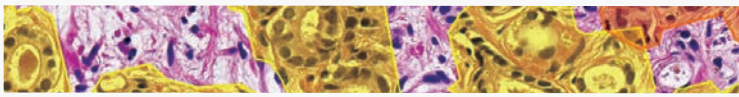

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