JANUARY / FEBRUARY 2022 # 82

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Ki-67 IHC MIB-1 pharmDx (Dako Omnis) Scoring Session

Monday, March 21 at 1:00 pm PST - Live session at USCAP with Dr. Sunil Badve

Tuesday March 29 at 1:00 pm EST - Virtual session (open to all) with Dr. Miglena Komforti

Scan here to register.

News on Resolution Bioscience Liquid Biopsy and NGS for the Pathology Lab

Monday, March 21 at 3:00 pm PST - Live session at USCAP
Training on NGS for the Pathology Lab with Jana Blackett

Tuesday, March 22 at 3:00 pm PST - Live session at USCAP
Introduction to Resolution Bioscience with Jana Blackett

PD-L1 IHC 22C3 pharmDx Combined Positive Score (CPS) Session

Tuesday, March 22 at 1:00 pm PST - Live session at USCAP with Dr. Sunil Badve

Tuesday, April 5 at 12:00 pm EST - Virtual session (open to all) with Dr. Allen Gown

This information is subject to change without notice.

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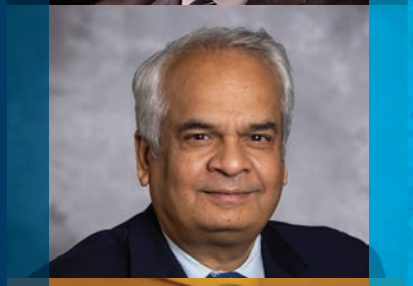

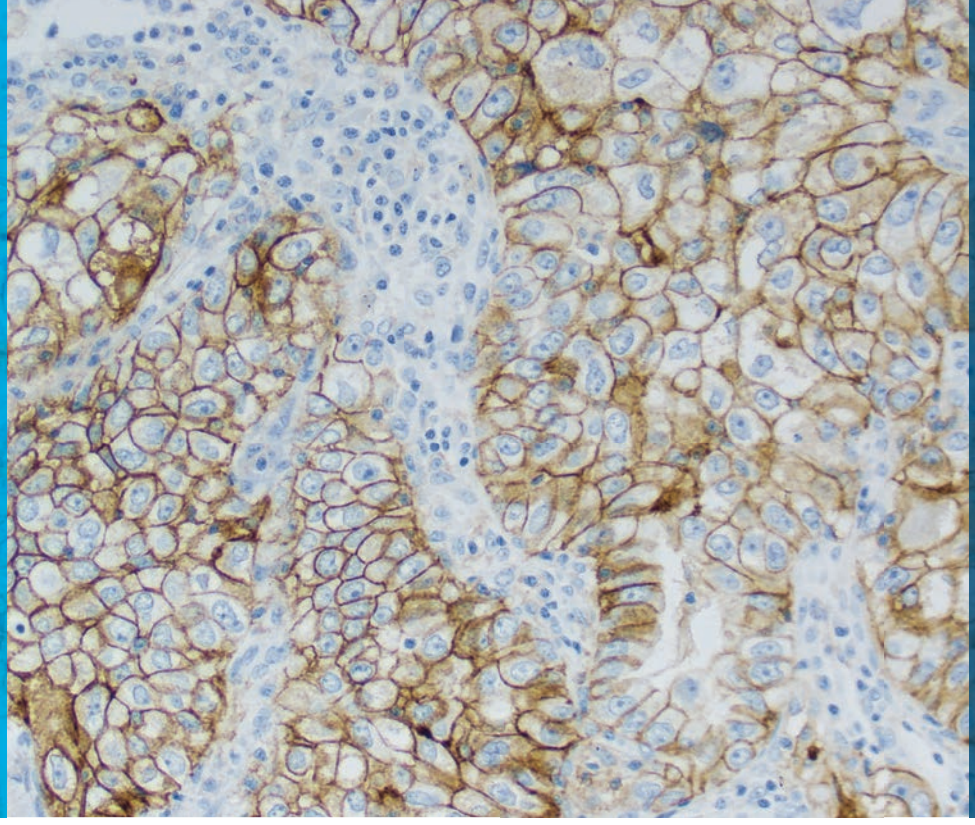

USCAP 2022 Agilent Symposium

Update on TNBC: Biomarkers Landscape and Real-World Experience with PD-L1 Testing and Patient Management

Monday, March 21

5:30 pm PST - 7:00 pm PST | Room #4

Scan here to register.

Meet the speakers

Dr. Romualdo Barroso-Sousa
Medical Oncologist at Hospital Sírio-Libanês Brasília, Hospital Sírio-Libanês in Brasília, Brazil

Dr. Sunil Badve
FRCPath Vice Chair, Pathology Cancer Program at Emory University School of Medicine, US

Dr. Allen Gown
Founder of PhenoPath Laboratories and Clinical Professor of Pathology at the University of British Columbia, Vancouver

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An Identity in Danger

Pathology doesn't just need a place in medical school curricula – it needs to be prepared to take advantage of that place

The article "Our Own Worst Enemy" (1) will undoubtedly give rise to many opinions on pathology's future. As someone who has been around for quite a few years, I would like to share something the article did not consider.

The most telling sentence in the article is, "We need a distinct place in the medical curriculum that shows pathology as a clinical specialty." During my time in medical school, such a "place" was available – but pathology departments never knew how to take advantage of it. Our eight-month pathology course was a comprehensive tour de force that gave me great respect for pathologists – but there were two reasons I didn't consider pathology as a career. The first is that pathology departments never showed us that pathology is a clinical specialty choice; the second is that nowhere in either the traditional or revised curricula are students exposed to actual pathologists doing their everyday jobs.

In my fourth year of medical school, I liked all my clerkships, but none of them fit my interests enough to make me desire a career in any of them. I knew that I enjoyed making diagnoses more than treating them and expressed this to my faculty advisor. He and a surgical pathologist friend helped me arrange a surgical pathology elective at another medical school – and it turned out that the surgical pathologist was not just a brilliant diagnostician, but also an incredible role model. After half a day of the elective, I knew I wanted to spend the rest of my life doing surgical pathology.

And that's exactly what I have done for the past 49 years. During much of that time, I have tried to be a resource for medical students interested in pathology. I think the single most important thing I ever did in this regard was formulate a surgical pathology elective students attended either in their second year as a group or in their fourth year as an individual. This was done at a time when systemic pathology courses had become absorbed into interdisciplinary courses and pathologists were losing even more of their identities to new curricula. If we do not address this identity loss, one day there will be no identity.

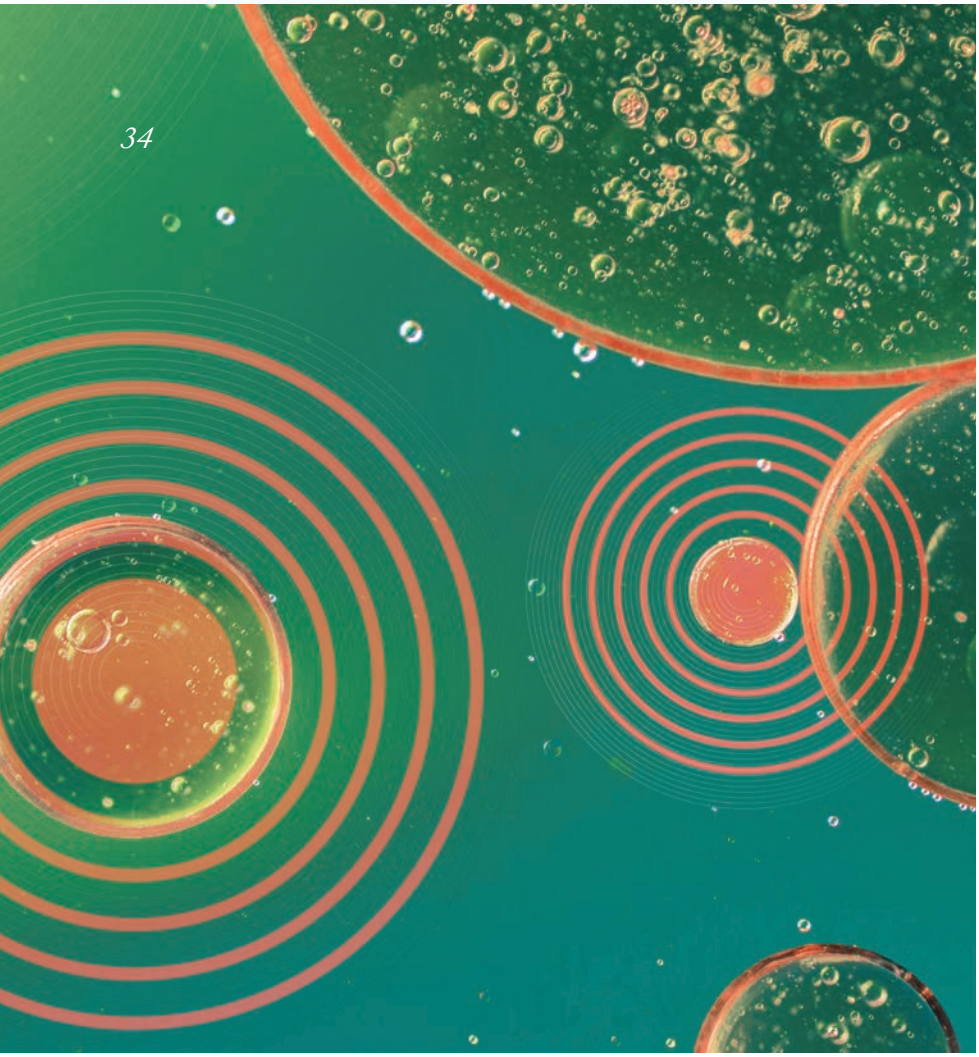
Michael J. Klein

Michael J. Klein is Professor of Pathology and Laboratory Medicine at Weill-Cornell College of Medicine and Pathologist in Chief Emeritus at the Hospital for Special Surgery, New York, USA.

Reference

1. *Olivia Gaskill, "Our Own Worst Enemy," The Pathologist (2021). Available at: https://bit.ly/3okE18f.*

Contents



On The Cover

Patients step out from behind the slide to meet their pathologists. Credit (for people): shutterstock.com.

Upfront

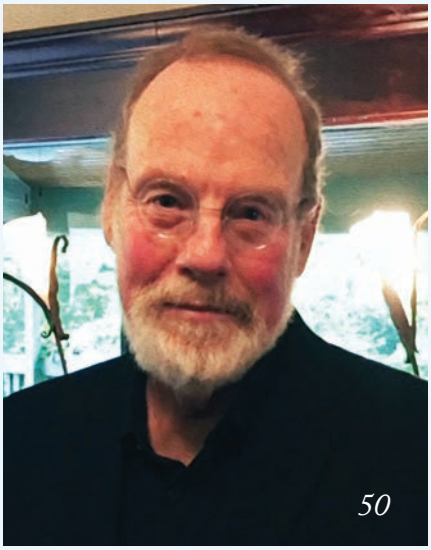
In My View

From The ASCP

Feature

the Pathologist
ISSUE 82 - JAN/FEB 2022

Foundations



Profession

Reports

Sitting Down With

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Distribution: The Pathologist (ISSN 2055-8228), is published bi-monthly by Texere Publishing Limited, Booths Park 1, Chelford Road, Knutsford, Cheshire, WA16 8GS, UK. Single copy sales $15 (plus postage, cost available on request info@thepathologist.com). Non-qualified annual subscription cost is available on request.

Upfront

Research
Innovation
Trends

Diamonds Are a Diagnostician's Best Friend

A diagnostic sensor for rapid, cost-effective, and accurate detection of SARS-CoV-2

Credit: Matthias Weinberger from flickr.com

We are almost two years into the COVID-19 pandemic and, though both point-of-care and lab diagnostics have come a long way, there is always room for improvement. Recognizing this, researchers from the Massachusetts Information Technology and the University of Waterloo have developed a new approach to testing for SARS-CoV-2 – based on theoretical quantum effects (1).

The approach involves coating nanodiamonds that contain nitrogen vacancy centers (atomic-scale defects that are highly sensitive to tiny alterations) with a magnetically coupled material that bonds only with the RNA sequence of SARS-CoV-2. Presence of virus-specific RNA disrupts this magnetic connection and changes the fluorescence of the diamond, which is then detected by a sensor. In the paper, the authors state that the rapid method is "fast and promises to reach a sensitivity down to a few hundreds of RNA copies with a false negative rate of less than one percent."

"The proposed approach is appealing both for its generality and its technological simplicity," said David Glenn, senior research scientist at Quantum Diamond Technologies Inc., though he was not associated with the research (2). "The sensitive, all-optical detection technique described here requires minimal instrumentation compared to other methods that employ nitrogen vacancy centers."

What's next? The team now hopes to translate their mathematical simulations into a working device that can be used in the lab to confirm their predictions. "Even if complications arise in translating the theoretical analysis into a working device, there is such a large margin of lower false negatives predicted from this work that it will likely still have a strong advantage over standard PCR tests," said senior author Paola Cappellaro (2). "And even if the accuracy were the same, this method would still have a major advantage in producing its results in a matter of minutes, rather than requiring several hours."

References

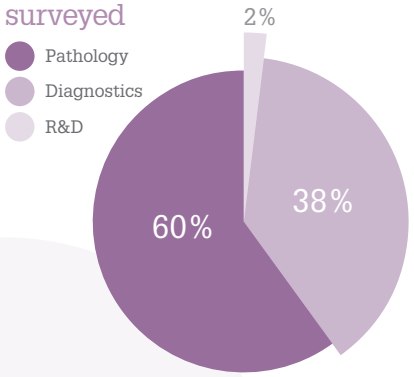
1. *C Li et al., Nano Lett, 22, 43 (2021). PMID: 34913700.*
2. *David L. Chandler (2021). Available at: https://bit.ly/3IwL9qx.*

INFOGRAPHIC

Can Automation Save the Lab?

Senior lab teams feel that automation could help support increasing diagnostic demands

40 senior UK laboratorians surveyed



Top challenges in the sector

Finances, exhaustion, and staff morale
95%

Human error
65%

Replication of results
48%

IMMUNOLOGY INSIGHTS

The latest research in pathology and laboratory medicine

Drivers of Development

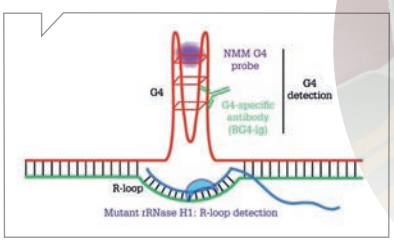
New research has uncovered insight into how the loss of TET enzymes plays a role in B cell lymphoma onset (1). Deleting *TET2* and *TET3* in mature B cells in a mouse model of lymphoma led to marks associated with double-strand breaks, which were then associated with increased G-quadruplexes and R-loops.

Immuno Insights

Researchers have investigated dendritic cell immunoreceptor (DCIR) activity underlying inflammatory diseases (2). "We have identified a novel functional ligand of DCIR, likely involved in the pathogenesis of arthritis and other autoimmune diseases like multiple sclerosis," said senior author Yoichiro Iwakura (3). Their work could advance research into immunology and glycobiology in inflammatory diseases.

Matters of the Heart

High blood pressure, atherosclerosis, and heart attack have been found to lead to structural and functional changes in the blood vessels in human bone marrow and mice (4). This resulted in an increase in white blood cells – causing inflammation throughout the body, including the arteries and heart.



Credit: Shukla et al.

Oxygen Observations

Scientists have used two-photon phosphorescence lifetime imaging microscopy to measure oxygen concentration in live mice (5). "Through this study, we suggest a new approach to understand the physiological mechanisms of living organisms by accurately measuring the concentration of biomolecules deep in biological tissues," said lead author Keizo Nishikawa (6).

Testing Peto's Paradox

Ever wondered why elephants and whales have low rates of cancer despite their large size and cell populations? An intense evaluation of Peto's paradox has found that, across species, risk is largely independent of body mass and life expectancy (7). However, a carnivorous diet is associated with increased cancer-related mortality.

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

"Pop" Goes the Sensor

A new device could help scientists identify signs of arrhythmia, heart attack, and cardiac fibrosis

Engineers have developed a tiny pop-up sensor that directly measures the electrical activity of cardiac muscle tissue at the single-cell level (1). "With this device, we can zoom in to the cellular level and get a very high-resolution picture of what's going on in the heart; we can see which cells are malfunctioning, which parts are not synchronized with the others, and pinpoint where the signal is weak," said senior author Sheng Xu (2).

The device's 3D array of microscopic field effect transistors (FET) makes it unique – allowing it to penetrate cells without damaging them. "It can have two FET sensors penetrate inside one cell – with minimal invasiveness – and allow us to see which way a signal propagates and how fast it goes," said first author Yue Gu (2). "This detailed information about signal transportation within a single cell has so far been unknown."

References

1. *Yue Gu et al., Nat Nanotechnol, [Online ahead of print] (2021). PMID: 34949774.*
2. *Liezel Labios (2021). Available at: https://bit.ly/33nK19o.*

Top challenges in the lab

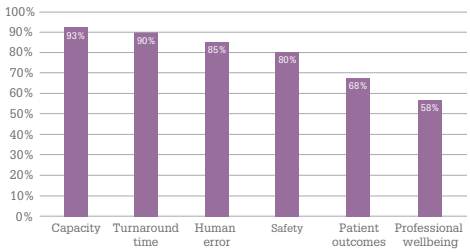
Staff shortages **95%**

Meeting current demands **65%**

Time pressures **60%**

What's getting worse?

Automation could positively impact...



Reference

1. *Health Tech Digital (2021). Available at: https://bit.ly/3GCMAD7.*

Sequencing Access for All

An affordable genome sequencing pipeline for low- and middle-income countries

Though the first bacterial genome was sequenced over two decades ago, the technology has largely been limited to high-income countries – creating a disparity between the need for bacterial sequencing and its accessibility. Now, a worldwide consortium of scientists has developed an inexpensive pipeline for collecting and sequencing bacterial pathogens – for less than US$10 per genome (1).

The consortium used *Salmonella enterica* to test their method. "The number of publicly available sequenced *Salmonella* genomes reached 350,000 in 2021," said study author Neil Hall (2). "However, limited genome-based surveillance of *Salmonella* infections has been done in [low- and middle-income] countries and the existing dataset did not accurately represent the *Salmonella* pathogens that are currently causing disease across the world."

The LITE (Low Input, Transposase Enabled) pipeline has a low DNA requirement – reporting that, for *Salmonella*, 1 ng is equal to over 150,000 copies of the genome. With a diverse collection of 10,419 bacterial isolates, the researchers successfully generated 6,117 high-quality *Salmonella* genomes that have already been used in published studies. "Our pipeline represents a cost-effective and robust tool for generating bacterial genomic data […] to allow investigation of the epidemiology, drug resistance, and virulence factors of isolates," said Darren Heavens, who developed the whole-genome sequencing pipeline.

Overall, the work represents the value of global collaboration to tackle future epidemics and pandemics. Going forward, the authors suggest that "early investment in the development of a shared, protected, and version-controlled database for the storage of epidemiological information" is needed to implement approaches like theirs worldwide.

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1. *BM Perez-Sepulveda et al., Genome Biol, 22, 349 (2021). PMID: 34930397.*
2. *University of Liverpool (2021). Available at: https://bit.ly/3GwmPo1.*

Improving Risk Stratification

Two genes have been identified that may be linked to prostate cancer outcomes

Prostate cancer is one of the most common cancers in men – and one of the leading causes of cancer-related deaths. Unfortunately, due to the heterogeneity of the cancer, it's difficult to properly stratify risk in diagnosed patients. Though some tissue changes have been found, the information has not yet led to improvements in diagnosis and treatment.

Previously, the STAT3 protein has been associated with tumor suppression in prostate cancer. Scientists have now built on this research to identify novel markers that indicate poorer survival in patients with aggressive prostate cancer (1). In a STAT3 cohort, they found that high expression of *NDUFS1/ATP5O* was linked to earlier biochemical recurrence of prostate cancer, indicating that the genes could be used to identify high-risk patients.

Reference

1. *R Wiebringhaus et al., Cancers (Basel), 13, 6036 (2021). PMID: 34885151.*

When Pathology Goes 3D

This image shows a 3D pathology dataset of a prostate biopsy stained with a fluorescent analogue of H&E (left). The researchers perform deep learning-based image translation to convert the H&E dataset into a synthetic dataset that looks like it has been immunolabeled to highlight a cytokeratin biomarker (brown) that is expressed by the epithelial cells in all prostate glands. In turn, this synthetically immunolabeled dataset allows for relatively straightforward and accurate 3D segmentation of the prostate gland epithelium (yellow) and lumen spaces (red). This also allows the researchers to extract the "skeleton" of the branching-tree gland network (magenta). To read the full caption, visit: tp.txp.to/pathology

Credit: Jonathan T.C. Liu, University of Washington, Seattle, Washington, USA

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

QUOTE of the month

"We need to provide our colleagues with information on the meaning of COVID-19 test results in our reporting systems so that tests are not overinterpreted. This issue also needs to be communicated to the public so that testing is not overutilized – stressing the ability to provide testing to those who need it – or overinterpreted. An example of overutilization would be getting serology on everyone who was vaccinated, because such results are not predictive of the 'degree' of the immune response and, except in some specific clinical situations, would not alter the care of a patient or drive revaccination."

Louis M. Weiss is Professor of Pathology and of Medicine (Infectious Diseases) and Codirector of the Einstein Global Health Center at Albert Einstein College of Medicine, Bronx, New York, USA.

The Big Freeze

How cryobioprinting could maximize the shelf life of bioprinted 3D tissues

3D bioprinted tissues hold promise for the future of medical research and patient care – but they are currently limited by their short shelf life. Challenges in fabrication and storage mean such tissues survive only days or even hours – so rapid transportation is necessary to ensure that they are viable at their destination. But a new cryobioprinting strategy simultaneously fabricates and stores 3D tissues in cryogenic conditions – meaning they can be preserved for longer, with cryoprotective bioinks helping to maintain cell functionality (1).

Cryobioprinting also allows scientists to print more intricate shapes than traditional methods. "The bioink filament freezes within milliseconds of reaching the cold plate, so it has no time to lose its original shape," said lead author Y. Shrike Zhang (2). "Then you can build layers on top of each other, eventually creating a freestanding 3D structure that can withstand its own weight."

References

1. *H Ravanbakhsh et al., Matter, [Online ahead of print] (2021).*
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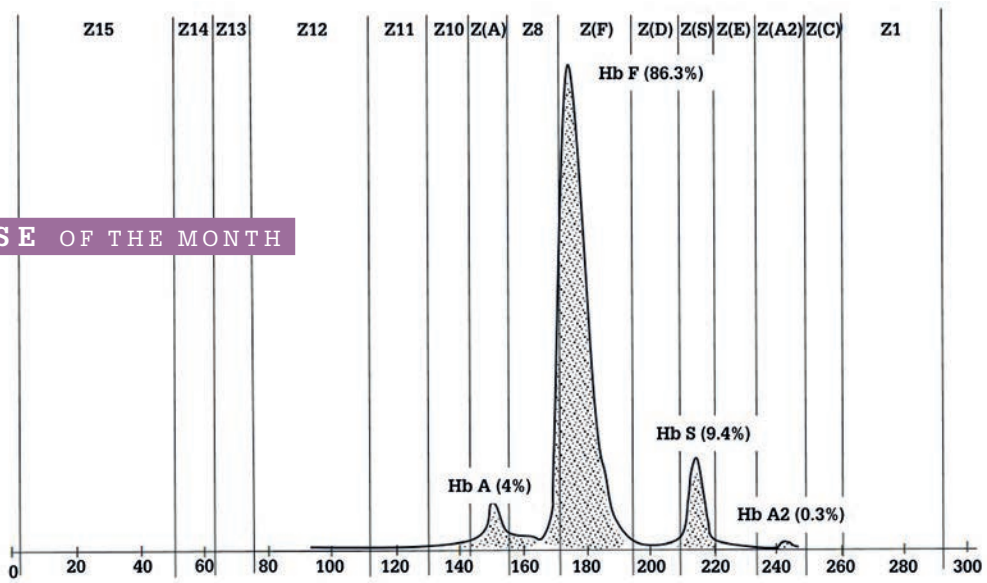
CASE OF THE MONTH



Capillary Hemoglobin Electrophoresis

	Patient value	Reference range
RBC	5.68	3.9–6.6 · 10^{12}/L
HGB	186	135–225 g/L
HCT	0.506	0.42–0.67 L/L
MCV	89.1*	95–121 fL
MCH	32.7	31–37 pg
MCHC	368	290–370 g/L
RDW	15.5*	11.4–14.5%
Ferritin	412	20–200 µg/L

What is your diagnosis?

a) Sickle cell trait (Hb AS)
b) Sickle cell anemia (Hb SS)
c) Sickle beta-plus thalassemia (Hb Sβ+ thalassemia)
d) Sickle beta-zero thalassemia (Hb S/β0 thalassemia)

Answer to last issue's Case of the Month…

c) Verrucous pseudonevoid melanoma

Histopathology revealed marked epidermal hyperplasia and papillomatosis overlying a broad, atypical melanocytic proliferation. Melanocytes proliferated in a confluent fashion in both nests and solitary units at and above the dermo-epidermal junction. An uneven, sheet-like proliferation of small, uniform-appearing melanocytes was seen in the upper dermis. Melanocytes arranged in parallel cords with surrounding sclerosis were observed. Rare dermal mitoses were identified and Ki-67 stain revealed a proliferation index of approximately 10–15 percent in the dermal melanocytes.

Nevoid melanoma is a rare entity that presents significant diagnostic difficulty on both clinical and histopathological grounds. The verrucous subtype has features that may distinguish it from a papillomatous nevus: broad, exophytic growth pattern with verrucous epidermal hyperplasia; continuous proliferation of melanocytes along the dermal-epidermal junction; confluent sheets of small- to medium-sized melanocytes in the dermis without evidence of true maturation; and low, but appreciable dermal mitotic activity.

Submitted by Rand Abou Shaar, Department of Pathology; Joseph McGoey, Department of Dermatology; and Ben J. Friedman, Department of Dermatology, Henry Ford Health System, Detroit, Michigan, USA.

To register your guess, please go to http://tp.txp.to/0222/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.

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Your Newest Colleague?

The need for AI-based end-to-end biomarkers in oncology

By Jakob Nikolas Kather, Assistant Professor of Medicine, University Hospital RWTH Aachen, Germany

The diagnosis of cancer is an unexpected, life-changing event for most patients – and the therapeutic path can be complex and confusing. This can be traumatic for patients and difficult for the healthcare system to manage. Complex diagnostic and therapeutic pathways cause stress, increased cost, and suboptimal outcomes (1). Addressing and reducing this burden starts with the foundation of cancer diagnostics – histopathology.

Much of a histopathologist's day is absorbed by tedious and repetitive tasks, such as searching for tiny nests of tumor cells in prostate biopsies or counting mitotic cells in tumor tissue (2). Considering the global shortage of pathologists, an obvious step is to use AI to automate such tasks – a move that could also mitigate problems of intra- and inter-observer variability in histopathology (3). Some AI-based image analysis systems for automation of tedious routine tasks are already approved by regulatory institutions.

Although the digitization of routine pathology workflows requires significant financial and organizational investments, it enables a return on a potentially massive scale. In digitized pathology workflows, software can not only be used to view and assess images, but also to automate tedious manual processes in histopathology. However, automation of existing components in a complex diagnostic pathway can only make incremental improvements to the system as a whole. Fortunately, AI's limits extend beyond simply automating existing steps in a diagnostic cascade. AI can be applied to complex diagnostic tasks in an end-to-end approach – all the way from raw image data to clinically actionable recommendations.

The aim of all oncology diagnostics is to improve patients' quality of life and survival time – and, sometimes, the best way to help individuals is to improve the system. Multiple academic publications have demonstrated a direct route from AI technologies to improved diagnosis and prognosis through end-to-end AI systems. In addition to automating specific steps in the diagnostic cascade, these systems can make clinically actionable predictions directly from raw pathology images (4). For example, instead of training an AI to detect lymphocytes in cancer and use this number to forecast response to a particular immunotherapy drug, AI can be trained directly on images to learn which phenotypes are predictive of drug response (5). Without expert guidance, such end-to-end approaches usually rediscover known morphological features – but these systems can, in principle, also be "smarter" than their inventors; they can discover new morphological features in pathology slides and can detect cancer and predict subtypes better than the human eye (7,8).

In the last five years, academic research groups have pushed the frontier of AI in histopathology from basic technical studies to clinically relevant applications (2). Researchers at universities and cancer centers have shown that AI can extract a wealth of information from routine slides – far beyond what was generally assumed only five years ago (9). But, although the academic system can come up with innovative new technologies, they cannot immediately be applied to patient care. Regulatory approval for diagnostic software requires a multi-year effort and significant funding. On the other hand, the potential yield is enormous. Not long after the first academic studies were published, companies began to build products around AI technology. Currently, tech-savvy researchers and pathologists can download state-of-the-art computer code from scientific publications and apply it to their own problems. Soon, any pathologist or researcher will be able to use commercial AI solutions to extract useful information from slides. Ultimately, this technology has the potential to enable new scientific discoveries, enhance clinical trials, and improve patient outcomes in oncology and beyond.

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

The Rise of MALDI

Now's the time to realize the many advantages of mass spectrometry imaging in clinical research

By Mike Easterling, Imaging Business Manager, Bruker Daltonics, Billerica, Massachusetts, USA

All pharmaceutical scientists share a common goal – to accelerate drug discovery and development efforts through a deeper understanding of biomarkers and the etiology of a disease. Matrix-assisted laser desorption/ionization (MALDI) imaging is becoming increasingly important in clinical research, particularly when we consider its impact in the study and management of cancer. Over the past couple of decades, as we have uncovered specific molecular markers of disease, we have gradually augmented traditional diagnostic histopathology with the use of molecular labels and probes. If we combine this with the knowledge provided by the Human Genome Project in the 1990s and early 2000s, The Cancer Genome Atlas (TCGA) program that began in 2006, and the development of accessible sequencing technologies, we create a new discipline – clinical molecular diagnostics.

Looking back on these developments, one review stated that "pathologists will become pilots for precision medicine cancer therapy through their unique ability to combine morphological and molecular findings (1)." Put simply, pathologists are pioneers in bringing new cancer drugs to life.

Current tools to analyze the tissue microenvironment of disease and determine the locations and interactions of cellular components that dictate disease outcomes include immunohistochemistry, spatial transcriptomics, and imaging mass cytometry. Although each of these techniques offers useful targeted information about proteins in tissues, they also have challenges – for instance, their inability to capture the variety of post-translational modifications in the proteome.

In contrast, MALDI imaging presents a label-free tool that captures information about the spatial proteome and additional spatial omic signatures unique to the local cell neighborhood. No prior knowledge of the compounds is required – the technique provides true untargeted molecular analysis in a spatial context. Equally as important, tumor-associated biomolecules that are missed at the gene level can be visualized. Further to this, the MALDI imaging workflow is compatible with standard histological procedures, maintains spatial resolution of around 10 µm, and preserves the tissue section under examination for further study. Its in-depth spatial proteomic, lipidomic, and metabolomic insights complement traditional genomic and transcriptomic methods and can help identify new predictive or prognostic biomarkers and classify heterogeneous tumor subpopulations, yielding important contextual clues to tissue-level communication networks integral to cancer growth and treatment success.

Two recent technological breakthroughs are now being applied to MALDI imaging. First, ion mobility separation has greatly broadened the range of biomolecules that can be analyzed by pre-separation ahead of mass analysis. Second, novel laser-induced post-ionization technology has delivered a quantum leap in MALDI imaging sensitivity – by up to three orders of magnitude.

"It's not hard to see the potential of this technology in providing a top-down, disease-centric view of tissues."

Clinical research has led the way in using MALDI imaging technology, taking advantage of a label-free analytical tool that can fill in the broad gaps left by spatial transcriptomics and genomics in molecular investigations on tissue samples. It can provide valuable information when it comes to protein modifications after gene expression and visualize additional compounds, such as metabolites, glycans, and lipids – all of which play a role in disease pathology.

In my view, it's not hard to see the potential of this technology in providing a top-down, disease-centric view of tissues that can inform therapeutic strategies, support diagnosis, and improve patient outcomes. Additional developments to the technology will boost measurement speeds, increase sensitivity (without compromising spatial resolution), and even offer deeper molecular content – important factors that may help accelerate the adoption of MALDI imaging in the routine clinical environment.

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1. *L Müllauer, "Milestones in pathology—from histology to molecular biology," Memo, 10, 42 (2017). PMID: 28367253.*

A (Consistently) Bright Future

Enabling cytogenetic automation for the modern clinical diagnostics lab

By Matt Sergent, Director of Sales, Molecular Diagnostics, BioDot, Inc., Irvine, California, USA

The ongoing evolution of genomics data as a key driver for improved patient outcomes through personalized medicine is raising the bar for clinical laboratories. Although cytogenetic testing is valued for its high specificity and accuracy – and its compatibility with a variety of protocol and sample types – these techniques are often time-consuming and require advanced training. Chromosome analysis, with incremental advancements in sample processing and automation, has been the tried-and-true approach for cytogenetics labs looking for a broad view of the complete genome over the last 50 years. And, ever since its arrival on the scene, fluorescence in situ hybridization (FISH) has become the chosen tool for evaluating many biomarkers and is now a key platform for researching disease biology and monitoring progression in cancer patients. Indeed, despite emerging technologies, such as next-generation sequencing, FISH remains the go-to tool for detecting many genetic abnormalities.

What if cytogenetics labs could take advantage of FISH assays and chromosome dropping – while overcoming traditional bottlenecks and drastically reducing both labor and reagent costs? And what if such a transformation allowed highly skilled technologists to focus their attention on the complex analysis needed to interpret cytogenetic assays? In my view, combining these tried-and-true methods with process optimizations and automated systems will allow clinical labs to enter a new era of cytogenetics.

And there are other drivers to consider; ever-changing reimbursement models are pushing laboratories to explore creative methods of reducing costs – and a shrinking pool of highly skilled laboratory technologists have put many laboratories in crisis mode. Instead of a one-sample – and largely manual – workflow, labs will increasingly need to adopt efficient, high-throughput approaches to make their processes faster and more cost-effective.

Fortunately, there are solutions! Non-contact, quantitative fluid dispensing technology miniaturizes and automates slide preparation for both karyotype analysis and FISH, taking cytogenetic testing to the next level. Slide preparation from fixed pellets for karyotype analysis has been completely automated – from normalizing cell pellets to dropping onto slides in a controlled environment for optimal results with minimal sample input requirements. And the ability to precisely dispense nanoliters of fluid onto glass slides allows cytogenetic labs to tackle many of the inefficiencies of classical FISH by enabling fast, reliable testing of much smaller sample sizes without the need for constant user oversight – and, at the same time, generating fewer pieces of glass to process and analyze.

And there are more cost savings: with ultra-low-volume dispensing technology, reproducible assays can be performed using 500–1,000 cells per sample, with eight individual samples per slide. This significantly reduces the volume of expensive fluorescent probe required (whereas traditional methods use up to 10 microliters of probe per assay, automation can achieve the same results with just 0.4 microliters). Given that probe costs make up a significant portion of the laboratory budget, these savings will have an impact on the overall cost of healthcare.

Automated dispensing technology can be used to process various matrices, diluting or concentrating samples automatically prior to printing them onto the slides. The increased reproducibility enables reliable automation of analyses and reduces turnaround times to keep laboratories efficient. Furthermore, many automated systems have built-in sample management tools, such as barcode readers that help track each sample from collection to result without undue user burden.

"I believe laboratories will need a continued focus on standardization, automation, and miniaturization to increase efficiency and throughput."

Applying precise automated dispensing technology, on-the-fly normalization, and strict environmental controls to chromosome dropping offers equally important advancements in chromosome slide preparation processes. It's not hard to see how standardization through automation offers more reproducible results, improved scanning, and higher image resolution.

If you work in a clinical diagnostics laboratory, you will be no stranger to relying on technology and processes to overcome traditional bottlenecks and challenges. To keep up with growing demand, I believe laboratories will need a continued focus on standardization, automation, and miniaturization to increase efficiency and throughput. Just like many other lab processes before it, FISH has now been transformed to function in the modern cytogenetics diagnostics lab – and simple, cost-effective automated processes can help secure the technique's continued future as the gold standard for cytogenetic testing.

Supporting the Laboratory Starts Here

The lab is in the spotlight – but it's our job to use that attention for good

By E. Blair Holladay

The past two years, as we've battled a global pandemic, the world has become well aware of the role the laboratory plays in patient care. Prior to the pandemic, patients – and even other members of the healthcare team – may not have known or understood the depth of knowledge and care pathologists and medical laboratory scientists provide. As testing and diagnosis for COVID-19 continues to increase and we continue to develop vaccines and conduct the essential research needed to continue the fight, the laboratory is no longer in the shadows.

And we have not sat back and basked in the glow of attention. We knew that this was a time to capitalize on our spotlight by ensuring that, once the pandemic recedes, the laboratory remains a very visible part of a patient's journey and is understood as an essential partner in healthcare. One aspect of this effort entails leveraging the research and insight we've gathered and applying it to the advocacy we do on behalf of pathologists and medical laboratory scientists around the world.

In 2021, the American Society for Clinical Pathology (ASCP) completed a groundbreaking clinical research study with the University of Washington Center for Health Workforce Studies that provided insight into the needs of the laboratory and the laboratory workforce (1). The study offers innovative strategies to address these needs and provides guidance for continued support and advocacy for pathologists and medical laboratory scientists; it has been widely disseminated to educate and advise our healthcare colleagues and the industry as a whole on the critical needs – and the importance – of the laboratory. Pathology and laboratory medicine are facing a workforce shortage exacerbated by the pandemic. This is not widely recognized by healthcare leaders, but it should be. Ultimately, a lack of qualified medical laboratory scientists will have a grave impact on health systems and patients' healthcare journeys. Those systems and healthcare partners who do not recognize that fact and act on that do so to their own – and their patients' – detriment.

ASCP also recently released its 2020 vacancy survey of medical laboratories in the United States (2). This biennial survey is critical to informing our advocacy efforts and our most recent data shows how the pandemic has disrupted the staffing of clinical laboratories and the flow of new graduates into the workforce. Further data shows that the laboratory has already lost a good deal of employees who harbored a wealth of experience. Without a steady pipeline of qualified new employees, patients are at risk. How we can better develop a strong and sustainable workforce is central to our efforts in supporting the laboratory.

There is still a lot of work to be done – to develop a solid laboratory workforce, to raise the visibility of the laboratory, and to leverage the influence pathologists and medical laboratory scientists have on patient care. We look forward to the challenges that lie ahead and to the knowledge we will gain by overcoming them. As we do so, we know we will be creating a field that is #StrongerTogether.

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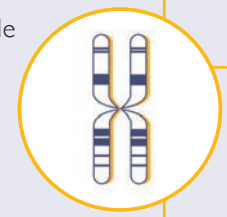
Enriching Our Understanding of Multiple Myeloma

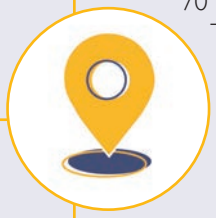
Plasma cell enrichment can increase FISH sensitivity for detecting high-risk cytogenetic abnormalities, which may help improve risk stratification and patient management when combined with clinical follow-up data (1)

A GLIMPSE OF MULTIPLE MYELOMA



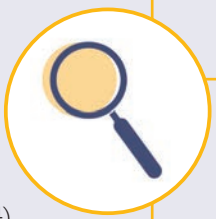
A cancer of the plasma cells, multiple myeloma (MM), is a heterogeneous disease in which patients have one common characteristic – almost all exhibit karyotypic abnormalities, with some studies showing an average of 8–10 changes present at diagnosis (2,3). The most common of these are translocations and hyperdiploidy (4) – but they do not stand alone; secondary cytogenetic events in MM may warrant repeat cytogenetic testing (5).

IgH TRANSLOCATIONS IN MM



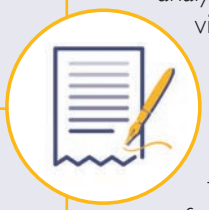
IgH translocations most likely occur in 50 to 70 percent of all MM cases (6). These translocations result in derivative chromosomes that may place enhancers next to oncogene promoters – thus increasing the activation of oncogenes (7).

CYTOGENETIC TESTING



Cytogenetic testing is one component in the assessment of MM and related conditions. One reason is risk stratification; knowing a patient's disease-specific mutations may help in understanding prognosis (5,8). Karyotypic abnormalities, such as t(6;14) or t(11;14) translocations or hyperdiploidy, are considered standard risk. t(4;14), t(14;16), t(14;20), and del(17p) place patients in the high-risk group according to Mayo Clinic mSMART 3.0 risk stratification guidelines (9-12). Standard risk is defined as having an indolent course of disease and lengthy survival, and high risk is defined as experiencing a more aggressive course and shorter survival (11,12). Both the National Comprehensive Cancer Network (NCCN) and the International Myeloma Working Group (IMWG) currently recommend cytogenetic analysis for all MM patients at the time of diagnosis (5,8).

APPROACHES TO CYTOGENETIC TESTING



1. *Conventional karyotyping* is widely available and commonly used, but requires cells to be in metaphase (13,14) – a unique challenge in myeloma due to the cells' low proliferation rate – and has a success rate of only 30–40 percent in detecting cytogenetic abnormalities in MM (14–16).
2. *Fluorescence in situ hybridization* (FISH) can be used on plasma cells in interphase and has a high (>90 percent) detection rate when using enriched plasma (16). Additionally, FISH analysis can detect IgH translocations not visible using conventional karyotyping (10,17). However, its success depends heavily on probe selection (7,18); IgH break-apart probes can help clearly identify the presence of an IgH translocation, while dual-color, dual-fusion probes can be used to definitively identify the specific type of IgH translocation (19,20).
3. *Next-generation sequencing* (NGS) may perform as well as FISH and may provide a more comprehensive, cost-effective approach in the near future (21,22).

ENHANCING SENSITIVITY

The College of American Pathologists recommends improving sensitivity with either plasma cell enrichment or cytoplasmic immunoglobulin-enhanced FISH (1,23). Plasma cell enrichment can improve detection of cytogenetic abnormalities threefold when used with FISH and may be achieved in one of three ways:

1. Flow cytometric analysis is useful for comparison and quality control of plasma cell enrichment to ensure adequate CD138 expression if performed before plasma cell separation (24).
2. Magnetic-activated cell sorting (MACS) enables positive CD138 selection (25) but with MACS, timing is important; cells may lose CD138 expression outside the bone marrow environment (26). One analysis found that MACS-enriched plasma cell concentration from a single specimen declined from about 58 percent on day two to about 13 percent on day eight (24).
3. Fluorescence-activated cell sorting (FACS) offers more pure plasma cell separation than MACS and permits the analysis of specimens with decreased CD138+ expression (24).

Because aspirates typically do not contain a large number of plasma cells, timing is sensitive and multiple tests may be needed; close communication among laboratories, pathologists, and oncologists is crucial (27).

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NOT JUST A SAMPLE

Patient–pathologist interactions are vital – and both sides must work together to make the connection

By Michele Mitchell

In 2006, I was diagnosed with breast cancer.

I received the tentative diagnosis at work. That day, I went home and told Ray, my husband of less than a year. He agreed to help me in my fight – but, just half an hour later, Ray had a stroke. A month later, I took him off life support. One week after burying him, I began my battle with breast cancer.

I was treated at the University of Michigan's Comprehensive Cancer Center. My treatment plan included a lumpectomy surgery, chemotherapy, radiotherapy, an additional surgery, and years of anti-hormonal "pills." I am now in remission – having completed the final phase of my treatment plan in 2015 – but, like many cancer survivors, I still suffer from the side effects of treatment and I continue to struggle with thoughts of recurrence. A cancer journey is a lifelong marathon, not a sprint.

How it began

Waiting for the results of my biopsy was agonizing. It took two weeks. I couldn't sleep or eat; I worried every hour of every day. Ray was in intensive care. I wondered, if he lived, how would I care for him and manage my own breast cancer journey at the same time? What would my life be like? I wanted to get the tumor out of me. Finally, my oncologist called with the results of my core needle biopsy, which confirmed the ultrasound report from weeks earlier. It was a "malignancy." I heard the words "breast cancer" – and then my mind went somewhere else. I was numb. I had so much on my plate at that point that the news was totally overwhelming.

I still remember the day I decided I wanted to look at my own pathology slides. I already had the honor of being a patient advisor and the co-chair of UMich Pathology's Patient and Family Advisory Council. The chair of the committee, a pathologist, offered to show me my cancer and review my pathology report. At this point, it had been 10 years since my diagnosis and one year since I had completed my treatment plan.

What made me curious? When I was diagnosed, I never saw my pathology report or slides. I was told that my breast cancer had been caught early. What I knew was that I had an invasive ductal carcinoma with no lymph node involvement. It was stage I and small – 0.9 cm. My oncologist said my prognosis looked "good." Over the years, I had done a lot of research on my own – but I still had a lot of questions and looked forward to learning more.

Seeing my slides

First, the pathologist showed me "normal" tissue. Next, he put a digital slide of my tumor on the screen. He explained how they stained the slides and determined the tumor's characteristics. My tumor was "luminal A" (ER/PR+, HER2-). He explained how they determined the grade of the tumor. I had never heard of tumor grading before. I thought, "Wait a minute – I had a stage I tumor. What's a 'grade?'" My pathologist explained that the black dots I saw on the screen were cancer cells. He said they count the number of cancer cells to determine the grade of the tumor and that the grade defines the tumor's aggressiveness. I had a grade II tumor, which tend to grow more quickly and are more likely to spread to other parts of the body. My mind raced. My cancer was invasive and there are only three grades – so my breast cancer was more aggressive than I had previously understood.

> "THE ENCOUNTER EXTENDED A WARM TOUCH IN A WORLD FILLED WITH BARCODES, STERILE INSTRUMENTS, AND STARCHED WHITE COATS."

Michele Mitchell views her slides through a microscope.

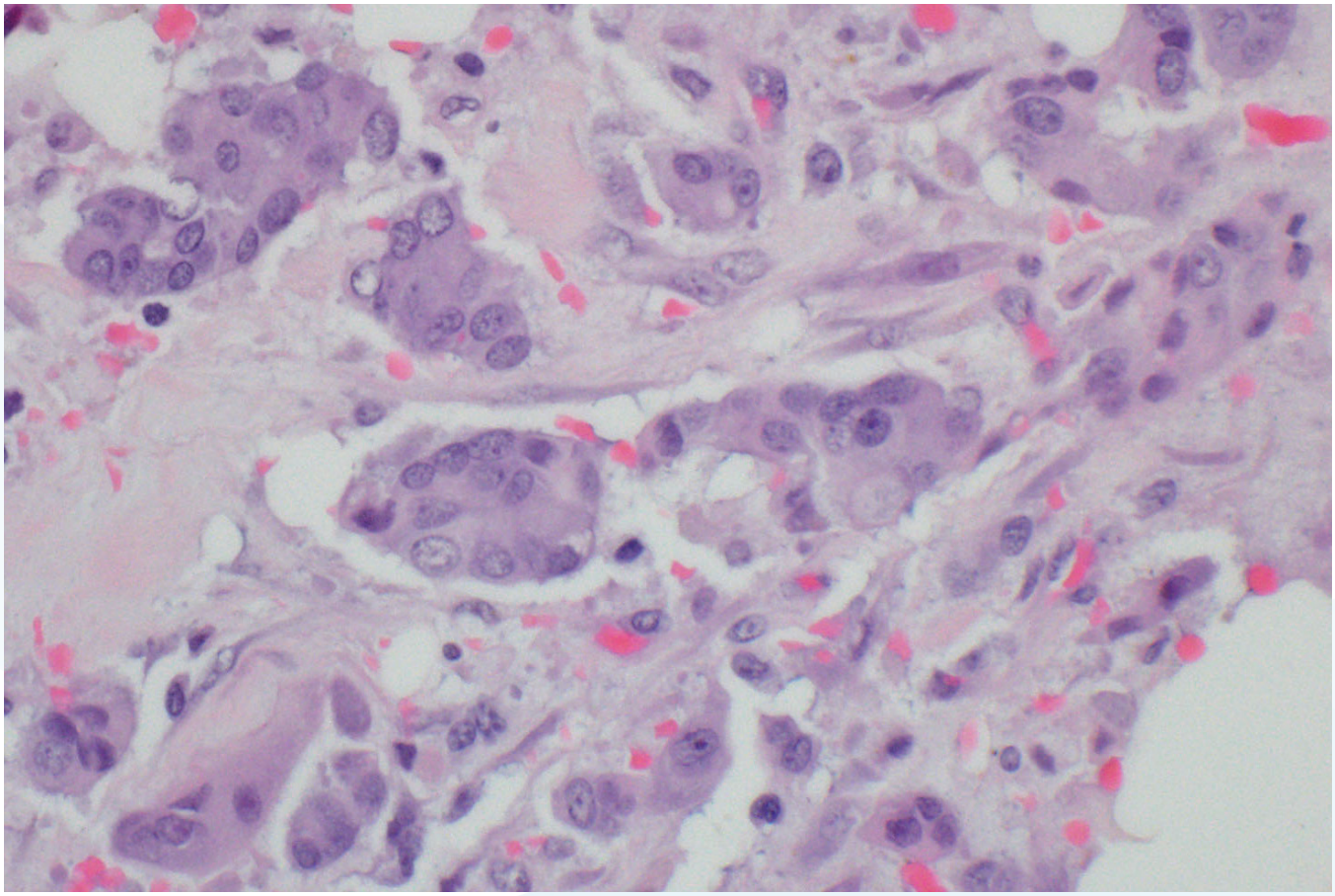
I was clearly upset by this news, so we stopped for a moment so that I could process the information. The sheer "size of the enemy" is what stays with me from that experience. It has been 16 years and I still wonder whether some of those cancer cells are floating around in my body. Although it was not what I expected, I am grateful for the compassionate way the pathologist handled the visit. The encounter extended a warm touch in a world filled with barcodes, sterile instruments, and starched white coats.

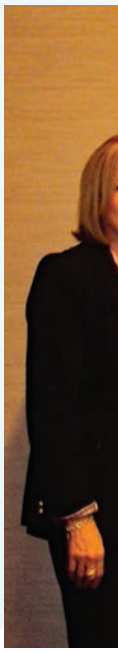
From patient to advocate

I retired from my 25-year career with a large healthcare insurer in 2009. At that point, my desire for patient advocacy work led me straight to the University of Michigan healthcare system. I also serve as an advocate for the American Society for Clinical Pathology and for the American Cancer Society. I am honored and privileged to serve each of these institutions. It feels wonderful to educate and empower patients, move the needle on important issues, and make a real difference in policy, quality, and safety in health care. I view my efforts through the lens of a quote by Ralph Waldo Emerson – "The purpose of life is not to be happy. It is to be useful, to be honorable, to be compassionate, to have it make some difference that you have lived and lived well."

I'm no stranger to advocacy – not just for myself, but for others as well. In 2013, my stepdaughter, Tricia, lost her three-and-a-half-year battle with non-Hodgkin's lymphoma. Tricia had asked for my support on her journey and my help navigating health systems. We tried desperately to get her well – but even experimental treatments failed. She died at the tender age of 23. Next, my parents had open heart surgery 11 days apart. My Dad's lungs never recovered after surgery and he passed away in 2014. My mother's health failed shortly

Clockwise from top left: Michele's cancer; Michele meets with her pathologist; at the 2019 ASCP Annual Meeting; receiving the 2020 Patient Champion Award; posing with another cancer slide.





thereafter. She had pulmonary hypertension and congestive heart failure. We lost Mom in 2019. In 2016, my husband, Bill, had a melanoma recurrence and we discovered that he carries a *MITF* gene mutation that predisposes him to melanoma and renal cancer. In my role as caregiver, I helped family navigate healthcare systems, which can be challenging. My path was made clear; these experiences ignited a fire within me to pursue patient advocacy.

You can see how much pathology and laboratory medicine have touched my life – and how much they touch every patient's life.

Advocacy challenges

I think it is important to understand the history of advocacy in the US healthcare system. The Hospital Consumer Assessment of Healthcare Providers and Systems (HCAHPS) survey program over a decade ago highlighted the importance of high-quality patient- and family-centered care. HCAHPS survey results are used in the Centers for Medicare and Medicaid Services Value-Based Purchasing program and affect hospital reimbursement by up to 25 percent – so hospitals are motivated to achieve. Patient- and family-centered care should involve working with patients and families, rather than just working for them or doing something to them. I have witnessed some progress over the years to move from doing things on behalf of patients towards doing things in conjunction with patients – but, in my opinion, the pace is too slow.

I would love to reframe the role of councils in healthcare systems everywhere from "advisory" to more action-oriented "transformation" teams. In my experience, hospital staff bring issues to patient advocates, who then provide feedback. I would like to see advocates be given a more active role. I believe this is the next step in the evolution of the movement. Advisors can provide systematic feedback on quality and safety concerns by truly partnering with healthcare systems and organizations – moving from bystander to policymaker. With the advent of personalized medicine, AI, and a more educated patient population, I think patient advocates are ready to make real change.

We're in an exciting and transformational time. Patients have never had more access to information about their health, including options for maintaining or improving their condition. Medical records are available online, as are patient forums, blogs, and websites. With health records now fully digitized and available on patient portals, action can be instant. At the same time – in part because of the rising costs to individuals – increasing numbers of patients

Michele Mitchell poses with a histopathology slide.

are investing in their health to stay well, not just get well. Health trackers are now the norm rather than the exception. Savvy patients are beginning to understand how unhealthy behavior can impact their pocketbooks in the long run. When patients become ill, they are increasingly focused on learning more through online communities. Advanced digital communication technologies enable the delivery of chronic care at home. A patient's laptop or mobile device can be a substitute for the doctor's office through apps and virtual visits – a game-changer during the COVID-19 pandemic.

The era of the passive patient is over – and consumers of healthcare will increasingly demand better tools, personalized treatment plans, and multidisciplinary care teams.

A double-edged sword

Patients have a right to their own health information but often need assistance understanding and interpreting it. There is a vast amount of information – and, unfortunately, misinformation – out there. Patients need help to synthesize this information and I think doctors and health systems need to take on an expanded role. Trusted clinicians should provide reputable sites to search, engage in more outreach, and preemptively educate their patients. I love the phrase, "Nothing about me without me." However, patients must also take more responsibility for their own care. They need to help their providers by engaging in the prescribed treatment plan, asking the right questions, and partnering with their providers in shared decision-making.

The 21st Century Cures Act, which was signed into law in 2016 and updated in December 2020, includes provisions for making pathology reports and laboratory results immediately available to patients via electronic portals to ensure timely access to health information. The College of American Pathologists provides some guidance for how to handle publishing test results, including this note on the new rule: "Pathologists should not delay the release of laboratory and pathology results until the ordering clinician's review (1)."

Some pathology practices have responded with a great deal of anxiety; others have risen to the opportunity by rethinking the way they provide results to patients. Some practices have added disclaimers on the patient portal; others have added links to reputable sites on the resources tab so that patients can find trusted information.

> "YOU CAN SEE HOW MUCH PATHOLOGY AND LABORATORY MEDICINE HAVE TOUCHED MY LIFE – AND HOW MUCH THEY TOUCH EVERY PATIENT'S LIFE."

Most cancer patients never meet or interact with the pathologist responsible for evaluating their tissue samples to determine the type and stage of their disease. Yet pathologists can impart knowledge about test results and better prepare the patient to participate in their own care. There is a growing movement in pathology to create opportunities for pathologists and patients to interact in what is referred to as "pathologist–patient consultations" or "pathology educational clinics." I hope that this unique approach to personalized medicine takes off and is offered at many health institutions.

The case for consultations

I think pathologists can offer patients a different perspective on their condition. Showing a newly diagnosed patient their tumor offers them an opportunity to understand how the diagnosis was made and to learn some of the science behind the diagnosis. The pathologist can clarify the diagnostic process, enhance the patient's overall understanding of the disease, and answer any questions – ideally without inducing "information overload." There are trailblazers out there doing this work already. For example, Lija Joseph at Lowell General Hospital, who has been conducting pathologist–patient consultation services for breast cancer patients, recently held a webinar that included a step-by-step masterclass in successful patient interactions.

Speech at the University of Michigan Anatomical Pathology Quality meeting.

Above: University of Michigan pathology booth for Patient Experience Week. Right: At the University of Michigan's 2018 Quality Month.

Even for more experienced patients, the ability to ask questions can help decisions about a course of treatment or a clinical trial. Moreover, a conversation with a pathologist can help them understand how their treatment plan is working and offer them some feeling of control over their disease process. Knowledge is power.

There is also plenty of data on how interactions with patients can help pathologists. A recently published article indicated that 86 percent of pathologists were interested in meeting their patients (2). Pathologists identified several benefits, including increased job satisfaction through meaning and purpose. Some have described these encounters as a reason to get up in the morning and called them "the right thing to do." In addition, it may increase motivation to complete the less interactive parts of their work. Other positives include creating a more multidisciplinary work environment; pathologists have unique expertise and including them in the care team could reduce clinician burden. Pathologists are often referred to as "the doctor's doctor" – but they can be much more than that. A pathologist can also be the patient's doctor and a vital part of their care team.

Supporting patient-centered care

What can you do? Well, you can seek out opportunities to engage with patient advocates in your own work environment. There are labs and institutions doing patient education sessions and starting their own patient and family advisory councils. Some trailblazers in patient education consultations have information available on the Internet – from published papers to step-by-step video guides.

To make sure these clinics are sustainable, I believe you must show some benefit in the quality of care, treatment compliance, and increased patient satisfaction – things that could affect the bottom line; for example, you could follow up with patients via surveys or use the messaging tools in patient portals to communicate with them. The pathology report is an important source of information regarding the diagnosis, treatment, and prognosis, but it can be difficult to understand due to its specialized language. Very few resources are available to help patients read and understand their pathology report.

Personally, I use websites such as mypathologyreport.ca.

TIPS FOR INSTITUTIONS

Lessons from UMich on increasing the patient's role in pathology and laboratory medical care

- Patient advisors have been added to patient safety meetings, in which participants perform root cause analyses and examine lessons learned when things go wrong.
- The team has completed work on a video project to show what pathology is all about. The 20-minute video takes viewers behind the scenes of Michigan Medicine's pathology labs with a former leukemia patient now in remission.
- Patient advisors attend the Department of Pathology Quality Council and participate on quality panels.
- The pathology department has participated in patient experience expos in which members spread the word about the impact of pathology on diagnosis and treatment.
- The group is currently working on developing a pilot patient education consultation program focusing on two disease groups: breast cancer and diabetes.
- We are addressing the Cures Act by adding a disclaimer to the patient portal and reliable resources for patients to access regarding pathology reports and lab results.

Developed in collaboration with patients and family members, such resources can be offered as an alternative to or alongside pathologist–patient consultation programs. Notably, there is an option on the site to ask for additional information; I did so and, within a day or so, I received a response with additional links to vetted information. Adding this kind of service or linking to other reputable sites on a resource tab in patient portals can be helpful; after all, patients are already out there Googling…

Interested in starting a patient communication initiative? Here are my top tips:

- Find a colleague or ask your department chair to support a small pilot program. Having a champion is key to moving patient education consultations forward.
- Social media hashtags like *#visiblepathologist* are good sources of information and contacts.
- Training on how to deliver difficult news is important. I would encourage this type of training for pathologists who want to be involved in patient–pathologist consultations.
- Create a video to explain what pathologists do or to explain the sections of the pathology report and what each one means.
- Perhaps you can add a patient-friendly section to the pathology report itself. If not, something as simple as adding your phone number or email address to the pathology report lets patients know you are available to them – and could be the start of a larger movement.

The shift toward patient education is forward-thinking and, in my opinion, moves the needle on personalized medicine. These steps begin to transform the healthcare system from doing things to or for patients and toward partnering with them instead. My hope is that, someday, pathologists will be an integral part of a patient's multidisciplinary care team.

Behind every test, specimen, or result is an anxious, sick, tired, scared person. They are wondering what you are looking at or for. And they are waiting for crucial answers. What does it mean for their future? How will it change their treatment plan? You are the first one seeing that person's diagnosis, which may be life-altering. It should never be taken for granted.

Finally, to the pathologists and technicians who examined my tumor, stained my slides, and determined that I had clean margins; to the blood draw team who determined whether I could or could not be infused with chemotherapy on a given day; to the countless others who worked on what may have felt like routine tasks at the time, I will be forever grateful to you all. You are the nameless heroes who saved my life.

Michele Mitchell is Patient Adviser and Co-Chair of the University of Michigan Department of Pathology's Patient and Family Advisory Council, Ann Arbor, Michigan, USA.

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A Helping Hand from AI

Using AI to enhance personalized healthcare for patients with prostate cancer

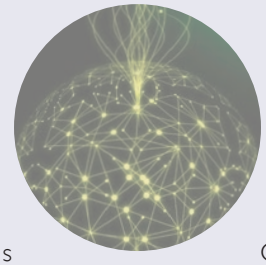
An interview with Chaith Kondragunta

Could you give me an overview of AIRA MATRIX as a company?

AIRA MATRIX started its operations about seven years ago. Although our core operations involve developing artificial intelligence (AI)-based solutions for digital pathology, our beginnings were in preclinical research and development with pharmaceutical companies. Since then, we've expanded our scope of operations to include clinical healthcare diagnostics. In both areas, our primary focus is on AI solutions for cancer care. However, in the drug discovery and development (preclinical) stage, we focus on translational oncology solutions to help bring new drugs to market faster and more affordably. We do that by enhancing the efficiency of preclinical pathology and toxicology workflows. On the healthcare diagnostic side, we develop solutions for the diagnosis, prognosis, and prediction of a few different cancers – ultimately aiming to enable precision diagnostics and personalized healthcare.

What challenges do lab medicine professionals face in diagnosing and grading prostate cancer?

Prostate cancer is one of the more prevalent cancers, so there is a large volume of cases. Longevity is also increasing, meaning that healthcare systems across the globe are seeing an even larger rise in demand for prostate cancer diagnostics. If you dig a little deeper, you'll see that it's not just the volume of cases – underdiagnosis and overdiagnosis are also prevalent. When the cancer is not properly diagnosed at the right time, it can metastasize, which has a real impact on patient mortality. On the other hand, overdiagnosis can lead to morbidity, in which more radical intervention methods or stronger treatments are delivered than are strictly required.



These problems arise for two reasons: i) pathologists are overworked and ii) there is a lot of variability in the diagnosis and stratification of prostate cancer. Two different pathologists might interpret biopsy or patient samples in different ways – a discrepancy that could lead to mortality, morbidity, or even misdiagnosis.

How does AIRA MATRIX assist pathologists and clinicians in stratifying disease?

Stratification plays a large role in understanding where a patient falls on the Gleason grading scale and what intervention is required – but misdiagnosis during stratification may cause the patient to slip through the net or yield suboptimal treatment. For example, assigning a Gleason grade of three versus four can be a difficult decision; three is a "watch and wait" situation, whereas four requires intervention and treatment. As you can imagine, a patient's grade group and ensuing treatment has significant quality-of-life ramifications, so we are looking at how to more finely grade cancers – for example, whether we can say that a cancer is "a three that behaves more like a four" or vice versa. This would allow us to provide more nuanced information to physicians so they can make the right decisions for their patients.

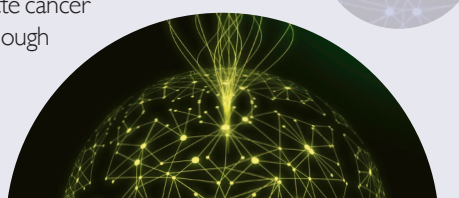
We are also trying to augment MRI-based diagnosis by using knowledge gained from pathology reporting. MRI images are routinely used to assess images of prostate cancer and, though they are much less painful and invasive than a biopsy, they have a lot of accuracy and interpretation errors. Our project takes the gold standard of pathology reporting and translates it to an MRI diagnosis so we can leverage the strengths of each – helping patients by providing less invasive testing methods without compromising accuracy.

On the prognosis and prediction side, we're working on extremely rich datasets with multiple patient cohorts that have been followed for years. This way, we can investigate not just the pathology or radiology modalities, but also other factors that we can consider in our conclusions on disease course or management. This will help us make prognosis predictions much more accurate.

What achievements are you most proud of so far?

What I'm most proud of is our ability to tackle complex problems. We have always viewed AI-based solutions in pathology as more than just a tool to help pathologists quantify their work or provide simple quantification or segmentation – there are plenty of other companies and AI-based techniques doing this. Instead, we have focused on the complex problems pathologists experience because of the sheer amount of information the human eye must process, which makes tasks extremely difficult or time-consuming. For example, one of our products in the toxicology space takes a few minutes to accomplish a task that would take a human pathologist several weeks. As you can imagine, drastically reducing time constraints is a massive achievement for us because we are driving the field forward with AI solutions and helping pathologists achieve better outcomes faster.

Chaith Kondragunta is CEO of AIRA Matrix, Mumbai, India



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Probing Prions. Prion diseases are a terrifying concept – growing aggregations of proteins that are not only misfolded, but can transmit their defective folding to their functional counterparts and cause the rapid death of their host. New research suggests that an axonal rapid endosomal sorting and transport-dependent aggregation mechanism may regulate the formation of these "endoggresomes" – aggregations inside enlarged endomembranes in the axon (1). This pathway may help us better understand and identify prion diseases early – potentially even offering an actionable treatment target in the future.

A Healing Process. Without resolvins, healing from an injury would be a difficult prospect. These molecules act in the resolution of acute inflammatory processes – but how? Recent research uncovers the role of 4S,5S-epoxy-resolvin – a critical intermediate molecule used by the cells of the immune system (2). Whereas neutrophils convert this intermediate to resolvins D3 and D4, macrophages convert it to resolvin D4 and a previously unknown cysteinyl-resolvin isomer. The latter, which exhibits powerful healing properties, may open new doors to therapeutics that promote wound healing.

Copy Numbers and Cognition. Individuals with 22q11.2 deletions exhibit a wide variety of symptoms, with cognitive and developmental delays among the most common. To examine the mechanisms underlying these deficits, researchers studied a mouse model with a heterozygous deletion of 22q11.2-encoded gene *Txb1* (3). Specialized imaging revealed that loss of one copy of *Txb1* led to an overall reduction in myelin and decreased oligodendrocyte production. The mice exhibited slower cognitive speeds, but no loss of accuracy.

Combined Efforts. Respiratory viruses have the world on edge right now. A new diagnostic platform combines CRISPR technology with microfluidics to distinguish between 21 different viruses, including six variants of SARS-CoV-2 (4). Evaluation on over 2,000 patient specimens revealed high concordance with sequence-based detection and classification, potentially offering a new solution for rapid respiratory infection diagnosis.

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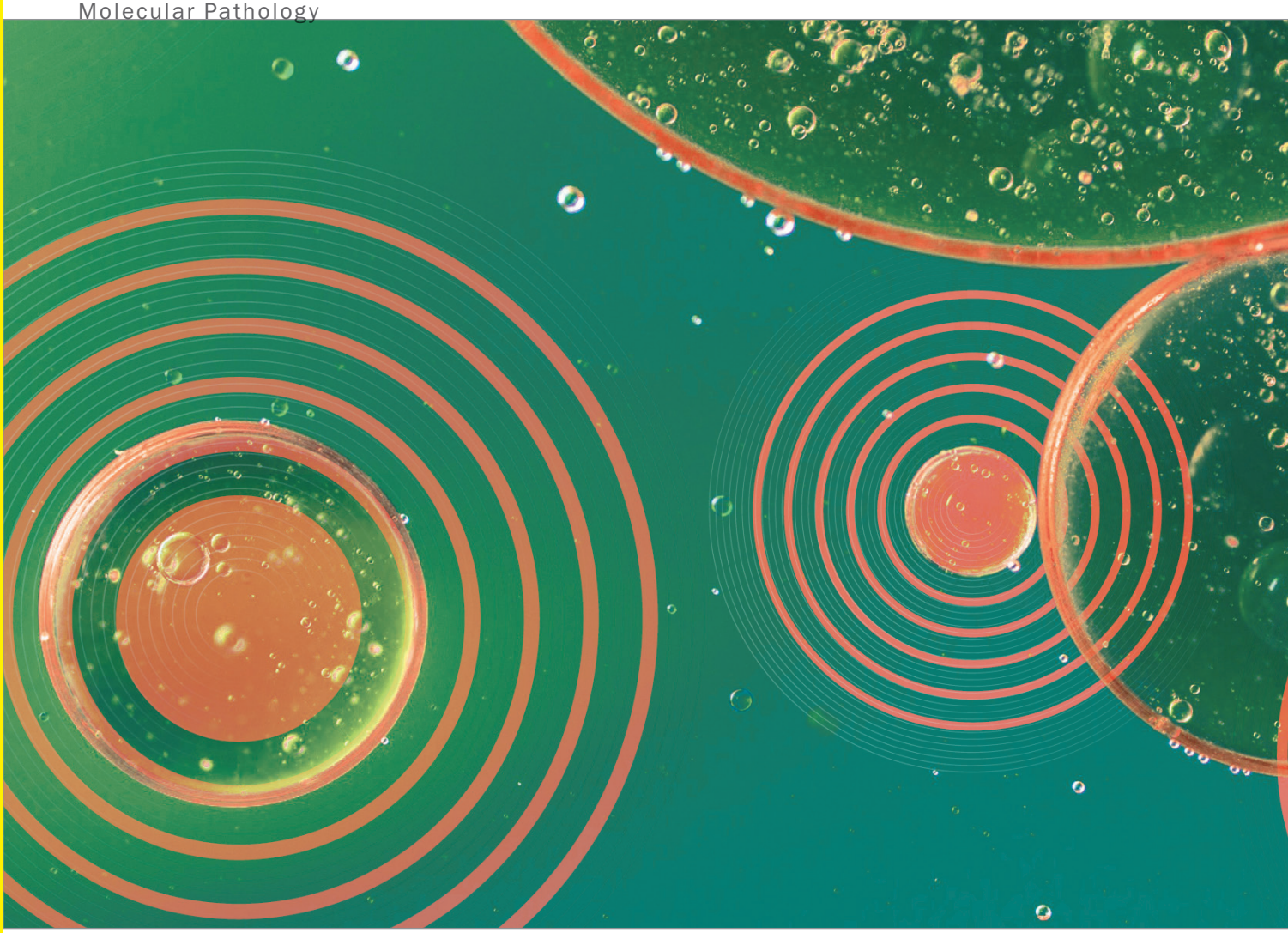
IN OTHER NEWS

Immune specificity insights. *Recent research in* Caenorhabditis elegans *reveals that conserved protein NMUR-1 may regulate innate immune system gene expression in response to different pathogens (5).*

Familiar mutations. *Although the Omicron variant of SARS-CoV-2 is highly mutated relative to other variants, new research shows that most of its mutations have been seen in previous variants – explaining vaccines' continued effectiveness against severe disease and death (6).*

Survival of the fittest. *Why has the SARS-CoV-2 Delta variant proven so infectious even in countries with high vaccination rates? The answer lies in a combination of N-terminal domain antibody escape and receptor binding domain ACE2 affinity (7).*

Metastasis mitigator. *Solute carrier MFSD1 has been shown to regulate tumor migration; loss of the protein in a mouse model led to increased β1 integrin activation and metastasis (8).*



A Spatial Biology Startup Guide – Part 1

Top concerns for ensuring preanalytical quality control

By Michael Surace, Houssein Sater, Carlos Andrea, Jeffrey Chun Tatt Lim, Jaime Rodriguez Canales, Houssein A. Sater, and Joe Yeong

Multiplexed immunofluorescence/immunohistochemistry (mIF/IHC) is a comparatively new tool for investigating the spatial tumor microenvironment. It has high potential in both clinical and translational applications, with its nearest-term applications in cancer immunotherapies – particularly in uncovering biomarkers for more accurately predicting patient response to immunotherapies and in situations involving a limited supply of tissue specimens.

A 2019 systemic review and meta-analysis of studies also showed that mIF/IHC improved prediction of responses to *PD-1/PDL-1* checkpoint blockade immunotherapy in 10 solid tumor types when compared with conventional monoplex IHC analysis (1). Another study, published in early 2021, also demonstrated that mIF/IHC techniques can offer multi-site reproducibility (2).

Here, we discuss users' top considerations when setting up the preanalytical components of mIF/IHC in a histology laboratory

What if pathologists or histologists are uncomfortable with quantification using software?

Visualization of the whole-slide images (WSI), in contrast to a region-of-interest (ROI) demonstration, is one potential way to make pathologists comfortable with software scoring, especially if one can generate a pseudo-IHC WSI. If that can be provided (even without pseudo-IHC), most pathologists and histologists should be able to manually score the mIF/IHC WSI by showing each marker

or combination individually, as with standard digital pathology solutions.

Both commercial and open-source software applications capable of WSI processing and analysis are also available.

Can I use my existing conventional monoplex IHC pipeline for tissue processing, sectioning, and staining?

Tissue processing and sectioning should be undertaken under the same conditions. Remember that the optimization and validation of an mIF/IHC panel are done in the following order: i) conventional monoplex IHC; ii) monoplex IF; and iii) the mIF assay. These stains are performed in consecutive tissue slides.

Staining protocols for converting conventional monoplex IHC to mIF can vary. This was highlighted in the MITRE study, where researchers had to change the secondary detection system to achieve the same signal intensity between the two assays (2).

Can I build an mIF/IHC panel from an existing, validated flow cytometry panel?

Possibly; however, most flow cytometry antibodies are not compatible with IHC, especially IHC-paraffin. This is most likely because the epitope presentation of an antigen in cell suspension could differ from IHC tissue sections.

Fluorochromes are usually conjugated directly to primary antibodies in flow cytometry. Conversely, most IHC and mIF/IHC protocols use indirect labeling methods requiring secondary antibodies for signal amplification. A good signal-to-noise ratio for detection by flow antibodies can be challenging for mIF/IHC, as signals may appear weak or undetectable for less abundant or weakly expressed proteins.

Flow and IHC scientists may have different perspectives on cell phenotype detection. IHC scientists might use only FOXP3 antibody for identification of regulatory T cells, for example, whereas flow scientists usually include lineage markers. Literature reviews and discussions with immunologists and pathologists are recommended before translating flow panels to mIF/IHC.

What are some of the considerations around performing WSI efficiently?

Tissue microarrays (TMA) are the most cost-effective way to perform mIF/IHC. However, even if the TMA was constructed by the pathologist, the morphology and the composition of the TMA tissues will be changed after a few sections. H&E staining is recommended before starting a project to ensure that the TMA is still suitable.

In a relatively resource-unlimited setting, WSI – and even whole-slide analysis – would be the ideal way to mimic the pathological examination. However, one must be careful to differentiate between "whole-slide analysis" and "whole-slide examination." Pathologists do need to examine the whole slide, but do not need to quantitate the whole slide. Even when the focus is on the tumor region, some biomarkers are only scored in the hotspots. Putting the right answer – and the right scientific question – into the right context is the key to successful outcomes.

See an extended version of this article and references online at: tp.txp.to/spatial/biology

Michael Surace is Associate Director of Translational Medicine Oncology at AstraZeneca, Gaithersburg, Maryland, USA.
Houssein Sater is Physician-Scientist in Hematology-Oncology at the Cleveland Clinic's Carol and Robert Weissman Cancer Center, Stuart, Florida, USA.
Carlos Andrea is a pathologist at the University of Navarra, Pamplona, Spain.
*Jeffrey Chun Tatt Lim is Senior Research Officer at the Institute of Molecular and Cell Biology, A*STAR, Singapore.*
Carmen Ballesteros-Merino is a Research Scientist at Earle A. Chiles Research Institute, Providence Cancer Center, Portland, Oregon, USA.
Jaime Rodriguez Canales is Senior Pathologist at AstraZeneca, Gaithersburg, Maryland, USA.
Houssein A. Sater is an immuno-oncologist and physician-scientist in hematology-oncology at the Cleveland Clinic's Carol and Robert Weissman Cancer Center, Stuart, Florida, USA.
*Joe Yeong is Group Leader at the Institute of Molecular and Cell Biology, A*STAR, Singapore.*
With thanks to JEDI – the Council for Multiplex IHC/IF Global Standardization.

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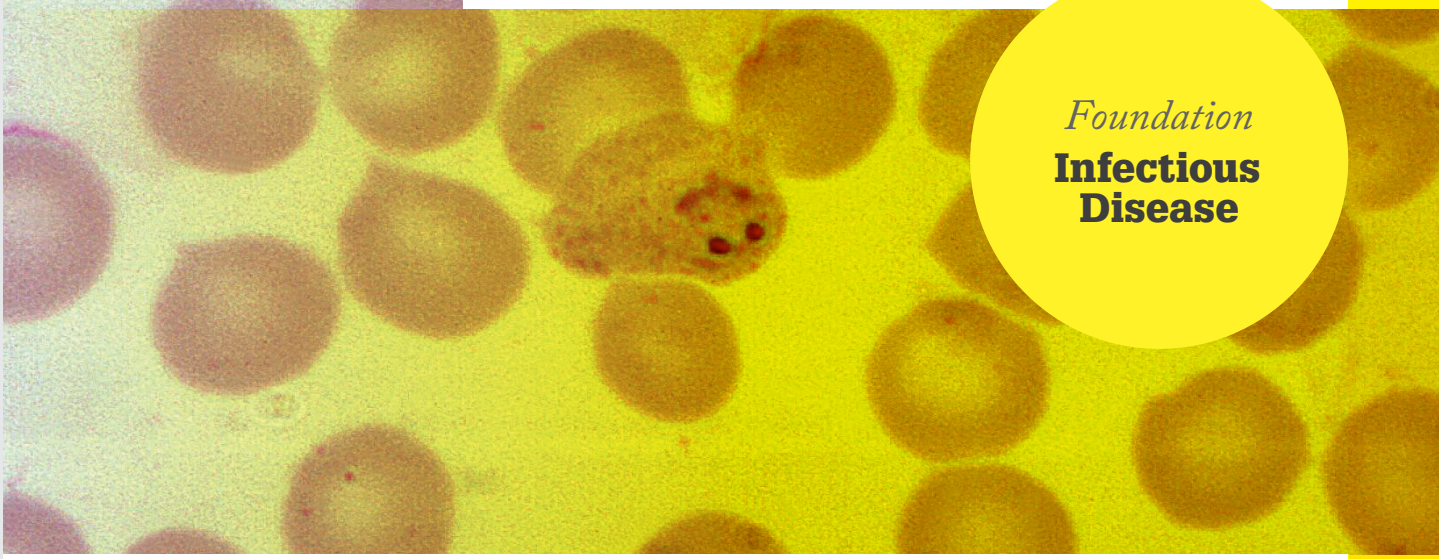

Parasite Predictors

Defining a new way to predict clinical outcomes in malaria patients

The World Health Organization estimated 241 million malaria cases and 627,000 deaths from malaria worldwide in 2020 alone – respective increases of 14 million and 69,000 from 2019. Levels of *Plasmodium* parasites in the blood are often used as a measure of disease severity – but patients can suffer from poor clinical outcomes even in the presence of low peripheral parasitemia.

To find out how, researchers from the University of Campinas investigated the relationship between peripheral parasitemia and total parasite biomass and host response in *Plasmodium vivax* malaria (1). Their analysis revealed two patient groups (Vivax-low and Vivax-high) based on differences in total parasite biomass, but not peripheral parasitemia. Vivax-high patients showed significant differences in hematological parameters, glycocalyx breakdown, endothelial cell activation, and cytokine levels regulating different hematopoiesis pathways, and displayed more severe thrombocytopenia and lymphopenia than Vivax-low patients, who were more closely aligned with healthy donors.

"When we separated some of the patient plasma samples to stimulate endothelial cells, we observed strong modulation of the cellular monolayer without direct or indirect interaction with the parasite for endothelial dysfunction," said co-principal investigator Fabio Trindade Maranhão Costa when talking to Agência FAPESP about the research (2).

A strong association between total parasite biomass and markers of endothelial cell activation, thrombocytopenia, and lymphopenia severity was found when patients' signatures were combined. The findings demonstrate that combining host parameters and total parasite biomass could better predict infection outside the bloodstream than peripheral parasitemia.

Based on their findings, the authors suggest that "changes in clinical parameters and biomarkers detected in the plasma of *P. vivax* patients are the result of both systemic host responses and local infection in tissue reservoirs such as bone marrow and spleen (1)." Costa adds, "Biomass, rather than parasitemia, is associated with several problems. This is extremely novel and hasn't been investigated in depth until now. Our findings highlight the importance of parasite biomass in the bone marrow and spleen. It's clear that these two organs play a major role in vivax malaria complications (2)."

With *P. falciparum* and *P. vivax* the two most common causes of malaria, the research has significant implications for unraveling the two. "Every step we take in our research confirms that *P. vivax* is different from *P. falciparum*," Costa told Agência FAPESP (2). "From afar, they may seem the same, but when you look more closely you detect the differences. This is important for the development of more effective treatment, specific controls, and even a vaccine."

"Combining host parameters and total parasite biomass could better predict infection outside the bloodstream than peripheral parasitemia."

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Sacrificing Safety for Speed?

Wide adaptation of antigen testing could increase the risk of exposure to infectious SARS-CoV-2 samples

By Tian Yu

Nearly two years into the COVID-19 pandemic, rapid antigen tests are finally gaining traction in the US. There is a clear demand for rapid turnaround in repeated testing to slow the spread of SARS-CoV-2. Though antigen tests have been branded as inferior to PCR tests since the pandemic began (largely due to their lower sensitivity), we are finally beginning to recognize the significant advantages of receiving a diagnosis in minutes rather than days – and the positive ramifications this has on people's everyday lives. By the end of 2021, the White House spent US$3 billion on rapid antigen testing manufacturing. Following the example of countries that have shown evidence of the beneficial impacts of community testing – such as a substantial reduction in COVID-19 hospitalizations in the UK – the Biden administration also plans to give out a total of one billion free home test kits to individuals.

The lateral flow-based antigen testing is "decentralized" owing to its ease of use and lack of dependency on additional instruments. It offers disease control and prevention opportunities for travel, work, schools, congregate housing, and public gatherings such as concerts and conferences. There is at least one rapid antigen testing station in each major airport, mobile testing sites can be spotted in company parking lots, and school nurses are trained to perform rapid tests. During a recent international trip, I packed a home COVID-19 test in my luggage – allowing me to test myself in my hotel room and obtain the negative result required for re-entry without having to locate a testing station abroad.

As someone who has received training on the management of infectious pathogens, I appreciate the convenience and timeliness of rapid antigen tests, but there are some elements that I find worrisome – and that might result in a significantly increased infection risk.

A major concern with COVID-19 is that it can be transmitted through the air. To prevent this, PCR testing labs have implemented several safety procedures for processing samples – including the use of inactivating transport media, a heat inactivation step, and the use of biosafety cabinets for sample processing to create an air barrier between specimen and operator. These precautions have been built into each lab's workflow to prevent contamination and protect operators from highly transmissive viruses. But most antigen tests don't inactivate the virus and specialized protective laboratory equipment is unavailable in most rapid testing settings.

In addition, antigen tests – unlike PCR testing, which takes place in a controlled environment – are conducted in an open-face format comparable to pregnancy checks. This implies that test operators are frequently exposed to aerosolized, highly infectious SARS-CoV-2 samples, because those who use antigen tests could be symptomatic with high viral titer. What's more, test operators may not have extensive experience dealing with pathogens and infectious diseases; they might be school nurses or airport employees. If staff members do not have expertise in handling high-volume testing and properly cleaning and maintaining equipment, the risks of transmission and cross-contamination are much higher. To handle high-volume antigen tests appropriately, additional training and implementation of risk-based standard operating procedures are sorely needed.

Another issue with at-home COVID-19 testing is waste management. My self-administered COVID-19 test took me roughly 20 minutes to complete – but I was stuck with the used test card for the next two hours, determined to find the right way to dispose of what should be considered potentially infectious waste. Because there was no guidance on the test insert about proper disposal, I looked to the Centers for Disease Control, which recommends discarding the card in a biohazardous waste container – not something I could easily find in my hotel room. I decided to double-bag my used test kits and toss them in the regular trash after reading multiple articles with conflicting information (and was only comfortable doing so because of my negative result). The absence of instruction on how to properly dispose of used COVID-19 tests poses a significant and avoidable hazard for those who may encounter potentially infectious waste, such as trash collection and hospitality staff. Test producers and the authorities must collaborate to offer training on the proper disposal of used home tests.

To conclude, antigen tests present unique safety challenges. Because of the emergence of highly transmissible variants such as Omicron, it is important to consider all stakeholders and implement procedures to reduce the risk of exposure as antigen test use increases. This includes training on proper handling techniques, cleaning equipment after use (including disinfecting surfaces), disposal guidance, and more. Furthermore, before conducting any tests, it is critical to use transport media that prevents viral particles from being transmitted, which could further minimize the threat.

Tian Yu is Chief Scientific Officer of Truckee Applied Genomics, Nevada, USA.

Tian Yu

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(PANDA) Challenge Accepted

Challenging the world to develop artificial intelligence for prostate cancer grading

Over 10,600 digitized prostate biopsies; 1,290 developers; 65 countries; and just one goal: to design an algorithm that could automatically assign a Gleason grade group to a biopsy sample. A fun challenge for developers and digital pathology enthusiasts alike, this is the aim of the PANDA (Prostate cANcer graDe Assessment using the Gleason grading system) challenge, set by Wouter Bulten and colleagues from various institutions (1).

Why crowdsource artificial intelligence (AI) this way? The team wanted to take the next step toward automating Gleason grading for prostate cancer – and the challenge was the perfect setup. To help developers in their quest, the researchers released all training data from two large studies on automated Gleason grading, along with slide-level labels and label masks. Though no method was off limits, teams had to follow some instructions to make sure biopsies could be loaded correctly during the evaluation stage. What made the PANDA challenge unique was that teams were asked to submit their algorithms; test data was kept hidden from participants so that cheating wasn't an option and results could be translated to other datasets.

Final entries into this largest known histopathology competition were validated on a private set and were given a time limit of six hours to analyze 1,000 biopsies. In a blog post on his personal website, lead author Wouter Bulten gave insight into the selection process from there. "After the competition ended, we selected 15 teams to join for extensive independent validation of their algorithms on new data. The selection was based on the score on the final leaderboard, method description, and scientific contribution. The latter criteria were used to ensure we had a good representation of algorithms for the analysis (2)."

Bulten and his team then reproduced these algorithms and tested them on external validation sets from Europe and the US – yielding agreements of 0.862 and 0.868 with expert uropathologists. In his post, Bulten highlights how global challenges like this can benefit the development of AI tools. "Challenges are often a powerful way of crowdsourcing new AI innovations. The PANDA challenge was no exception; due to the scale of the competition, after 10 days, one of the algorithms was already at the level of the average pathologist. In the remainder of the challenge, many teams caught up and improved further. This speed in development was also driven by extensive sharing of tips and tricks through the challenge forums (2)."

"After 10 days, one of the algorithms was already at the level of the average pathologist."

Will we see more of these crowdsourcing development challenges? Hopefully – not only do they sound like a great way to engage a talented pool of developers in pathology, but they also promote interdisciplinary working between laboratorians and technologists to achieve a common goal.

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The IT Crowd?

The pathologist's guide to IT considerations for digitization

By Coleman Stavish

Here's a trick question: how much are pathologists expected to know about IT?

Your immediate answer is probably along the lines of "not much." After all, pathologists have primarily carried out their commitment to excellent patient care with the microscope for decades. Now, though, the rise of digital pathology is putting pathologists in a position where they need to understand the basics. Digital pathology is, in fact, technology that your laboratory will likely soon implement to realize clinical and economic gains. Although you can rest assured that your IT team will serve as trusted advisors in this effort, you – as the user – have the opportunity to collaborate closely with your technical colleagues to drive alignment, accelerate timelines, and ensure the project goes smoothly.

Just as you would begin your digital transformation by building a business case and identifying uses, you should also take the time to understand the key IT considerations that will affect your transition from microscope to image. With even a little understanding, you can be empowered to shape your laboratory's digital future.

Performing at scale

One of the most important decisions you'll make in the digitization journey is choosing your platform. This software sits at the center of your day-to-day operations, powering everything from image viewing to sharing and collaboration.

When evaluating platforms, you'll likely be drawn to features and functionality at first. And that's natural; you'll want to understand how it will enhance your routine work. Your peers in IT, on the other hand, will probably prioritize scalability – and for good reason. Scalability has everything to do with how the solution will grow with your organization. If a platform isn't scalable, it's worth ruling out from the get-go.

How will your IT team assess scalability? They will ensure that the platform can support all your pathology images, which have massive file sizes, as well as your users and sites – both today and tomorrow. They will also assess user management, looking for robust roles and permissions to provide everyone with the right amount of access no matter the number of users. Scalability also encompasses security and compliance to address HIPAA and protected health information requirements.

Performance, a closely linked concept, is one that you'll also want to grasp. When some platforms scale to support multiple sites, it comes at the expense of other important factors, such as image quality and load times. These solutions do not perform at scale – a key consideration if you want to implement digital pathology across an entire institution or organization.

Open to the future

There's one final component of scalability so essential that it merits a discussion all its own, and that's interoperability. "Interoperability" refers to the exchange of information – and, because it has made headlines in healthcare for years, it might be somewhat familiar.

With respect to digital pathology, interoperability comes into play when thinking about scaling the hardware and software ecosystem needed to power your operations – including your digital pathology platform, scanners, laboratory information system, and image analysis applications. If data cannot pass between these solutions, your team will be forced to waste precious time manually uploading scanned images and jumping from screen to screen.

To help guide your conversations with IT, it's useful to understand how laboratories address the need for interoperability. Because the digital pathology platform sits at the center of day-to-day work, many organizations ensure that their platform is open in nature and integrates with any complementary hardware or software solution. This way, images automatically appear in the platform and pathologists can see all relevant case details and analysis results when making a diagnosis. An open platform also provides investment protection so that you can seamlessly deploy and scale new technologies, such as artificial intelligence, as your needs evolve. Alternatively, some organizations opt for a closed system whereby a single vendor provides both scanner and platform. Although it may seem easier to get up and running with a closed system (because you rely on just one vendor for the two most critical components of your digital pathology ecosystem), these systems offer less flexibility when it comes to integrating other solutions.

Unclouding infrastructure selection

Infrastructure, which relates to where you house your applications and data, is an especially important IT consideration for digital pathology. Pathology images are massive – two to 10 times larger than the average radiology image. And that means they can be expensive to store and

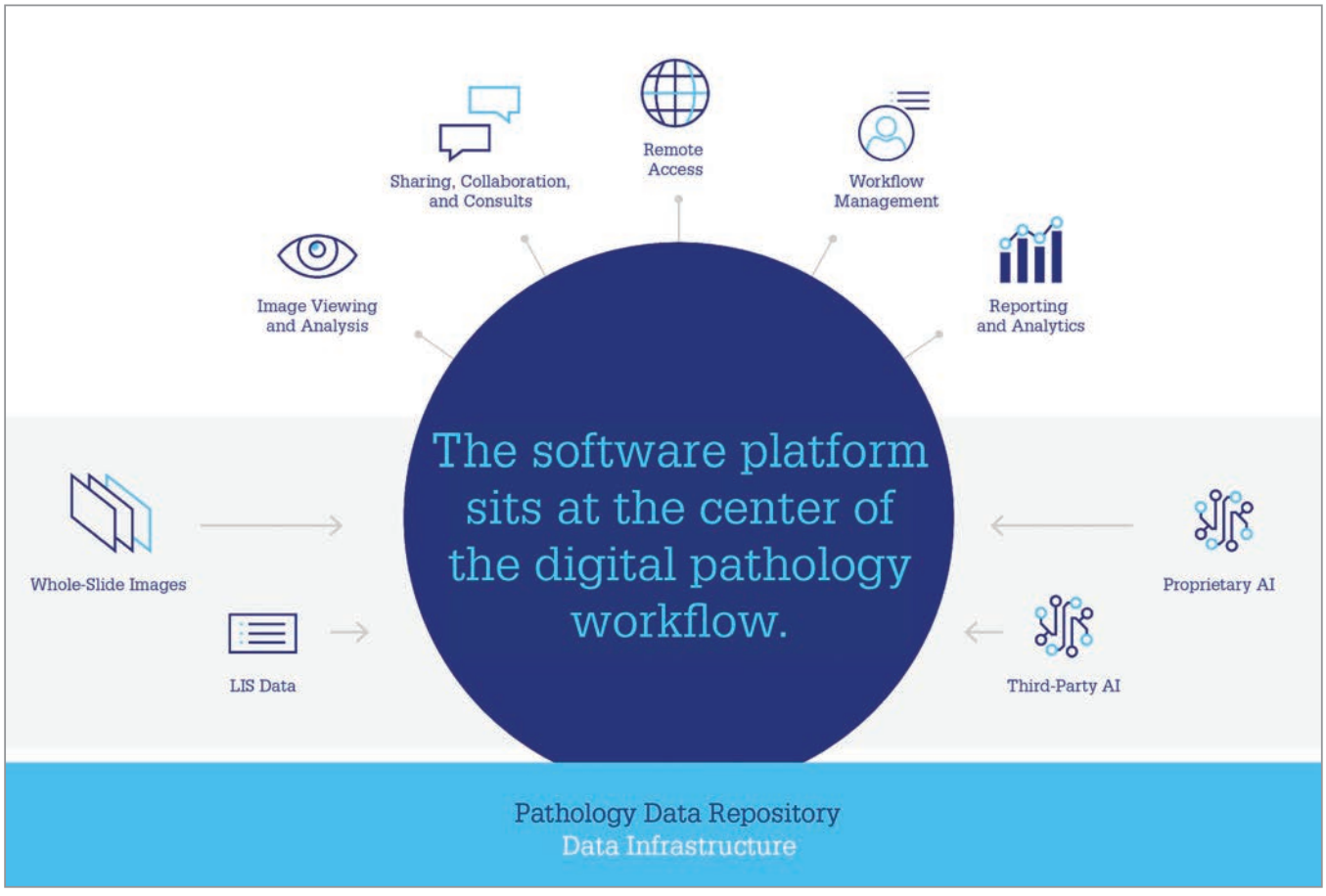

Figure 1: The digital pathology workflow centers on the software platform that enables it.

slow to access if the right infrastructure isn't in place. Although your IT team will almost certainly have organization-wide policies that guide infrastructure selection, you should know that, at the highest level, there are two different options: on-premises and cloud.

With an on-premises model, all data lives within your organization on servers managed by your IT team. For this reason, on-premises infrastructure typically delivers better performance for image viewing. It provides your IT team with more control, which can be ideal given the need to keep sensitive patient information secure. The main drawback is that on-premises infrastructure comes with a bigger upfront capital investment and requires more resources to maintain.

Data stored in the cloud is hosted in an off-site location. This location can be public, shared among organizations with data hidden, or private. Public clouds are managed by well-known providers, so they present less work for your IT team and offer instant scalability. And, because resources are shared, they can be more affordable. Private clouds, on the other hand, can be managed by third parties or by your IT team. Like on-premises infrastructure, they give you more control, but come at a higher cost.

Because there are pros and cons to each of these options, some organizations choose to go with a hybrid model where they mix infrastructure to best suit their needs. These organizations might keep some data on-premises for quick access and send archival data to the cloud where it can reside at a lower cost.

The rapid acceleration of digital pathology adoption means that every pathologist is quickly turning into an information technologist. By establishing a basic understanding of the key considerations you'll need in this new role, you can collaborate closely with your IT team to grow your knowledge and increasingly ensure that your laboratory is prepared to capitalize on the benefits that lie ahead.

Coleman Stavish is Chief Technology Officer at Proscia, Philadelphia, Pennsylvania, USA.

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Track and Trace

Can tracking medical events, rather than patients, help us tackle diagnostic error?

By Sidney Smith

Diagnostic errors are a significant type of healthcare-associated harm, reported to affect one in 20 outpatient adults (1,2) and generate US$34 billion in malpractice payments annually in the US (3). A common cause of diagnostic error is failure to respond to medical data in an appropriate manner, often referred to as failing to "close the loop." With the exception of a few randomized controlled trials, the evidence base for interventions that close the loop for diagnostic tests is limited – and existing studies have not assessed the clinical impact of those interventions (4).

Our current electronic medical record (EMR) system is designed to store medical data linked to a patient's name and date of birth – just like paper charts before the digital age. Medicine's continued reliance on this method of data storage reflects its universal bias in assuming that medical information must be tracked at the patient level. It also makes reliably closing the loop much more challenging, raising the risk of diagnostic error (4).

Could our 50 years of EMR development experience and the relatively recent expansion of advanced logistics companies like Amazon, Google, and FedEx challenge our basic assumptions about tracking medical information? Solving the challenge of closed treatment loops requires us to reorient the way we track medical data. Let us first look at how EMRs store and track medical data today.

Successes… and failures

The purpose of the EMR is to document patient care and store medical files.

"Event-based medical tracking adopts the most advanced communication platforms, used by the most successful communication industries throughout the world, for use in healthcare."

Records are saved in electronic files linked to patients' unique identifying information, such as their date of birth, social security number, unique medical record number, or address. Attaching the patient's unique identifying information to medical events, such as a lab or pathology report, enables the EMR software to file information in the patient's chart.

These EMR files are stored as PDFs using a common EMR software language called Health Language 7 (HL7). All EMRs use HL7 software – but no two file the patient's medical information in the same way, which means that they cannot easily send files between vendors. This failure is referred to as lack of interoperability.

In the EMR software, each patient has a unique file with subfiles for labs, imaging, pathology results, and physicians' notes. Today, patients have access to their files through patient portals for every physician and hospital where they have received treatment – thanks to EMR. And that's not its only benefit; consider quick, shared access to patient records, the automatic return of lab and imaging results, the ability for multiple users to use charts simultaneously, electronic prescribing, integrated physician dispensing, checking of drug interactions and medication allergies, file recovery after disasters, spellchecking, improved legibility…

These benefits are incontrovertible – but, nonetheless, several of EMR's most important goals are not being achieved: interoperability; collaborative quality care; effective communication; and dynamic, patient-centric medical records. Why has our current EMR software failed to meet these goals – and what steps can we take to achieve them?

Aiming for interoperability

A seemingly simple solution to attaining interoperability is the creation of a single large electronic storage system, or health information exchange (HIE) that would provide every patient with a single portal to which every physician and health system would send information.

As a result of the Health Information Technology for Economic and Clinical Health Act of 2009, large HIEs are being created – but resistance from EMR vendors and large healthcare systems has made it challenging. Medical data is a commodity and a competitive advantage for EMR companies. Easily sharing medical information between EMR vendors is not in their financial interest. Many vendors have been accused of "information-blocking," or intentionally interfering with the flow of information between systems (5,6). Health systems may also coerce providers to use specific EMR vendors rather than making it possible to collaborate across different vendors. In addition, hospitals and health systems share patient health information either selectively or inconsistently. Their apparent motivation is improving their revenue and enhancing their market dominance by controlling patient referrals and having exclusive access to patient data (6).

It is likely that the risk of fines imposed by the Office of the National Coordinator for Health Information Technology will reduce this resistance and HIEs will eventually become a reality. Unfortunately, just like the HL7 EMR software, HIEs track medical

data at the patient level and will therefore fail to achieve EMR's ultimate goals. So if neither EMR software vendors nor HIEs can achieve those goals, what can?

A borrowed solution

To meet medicine's full potential in terms of patient safety, quality, and efficiency, we need to track medical data differently. Rather than tracking a patient with a medical event, such as a biopsy or imaging report, we should track medical events and link them to the patient, a process referred to as medical event tracking (MET).

Consider that every transaction-based industry in the country – including shipping companies, airlines, retailers, and banks – assigns each transactional event a unique "confirmation" number to identify, track, and manage all activity related to that event. The same chain-of-custody approach can be employed in tracking medical events. However, rather than tracking a physical object, the confirmation number can link all communication and documentation between care providers, laboratory personnel, and the patient. Alerts, notes, and patient communication can be incorporated into this solution – effectively closing the treatment loop.

Transactional event tracking software infrastructure creates a digital space for the care continuum to interact, sharing information, quality metrics outcomes, and common medical data storage. MET can also enable direct patient engagement. Linking tracking numbers for each patient's care team interaction creates the first linked care continuum.

Unique to MET is the concept of medical data life cycles (MDLC). Each medical event has a definable lifespan. For example, a benign skin biopsy has a relatively short MDLC and associated event documentation. The associated event data includes tracking the physical location of the specimen to the lab, communicating the report to the physician, and finally notifying the patient of the benign diagnosis.

In contrast, a skin biopsy demonstrating a melanoma has a MDLC that lasts the lifetime of the patient. This event would include the same initial linked data as the benign biopsy, but would also include tracking numbers for special stains, genetic studies, pharmacological treatments, and future skin examinations. The initial tracking number serves as the reference key to which all subsequent linked events are digitally attached.

Forward-thinking processes

An additional critical step in the MET process enables a physician to recommend future events, communicate instructions to the care team, and create time metrics to make sure care is delivered in a timely manner. For example, when a diagnosis of melanoma is made, the pathologist links a recommendation of excision by attaching a code to the tracking number. This recommendation code links a series of time metrics for calling the patient, scheduling the excision, and excising the melanoma. The entire care team, including the pathologist, physician, and patient, is notified if the appropriate steps are not taken in a specific timeframe. The ability for an individual physician to link future events with quality controls in this way did not exist in medicine before MET. Using MET with pathology reports means that no specimen is lost, every pathology report is received by the physician, every patient is notified, every cancer is treated, and future care is coordinated.

Another significant advance with MET is the creation of a "living PDF file" that eliminates "chart flipping" or the need to move from a pathology report to another section of the chart to determine whether or not a patient received treatment. Through embedded tracking numbers in PDF pathology reports, future linked medical events are retrospectively added to linked PDF files. By hovering over the pathology report, care providers can see the full sequence of events linked to the report. This information is "sent back in time" to prior reports so that any pathology report describes all subsequent related future events.

The first commercialized MET platform was created in 2013. The

technical advance enabling its development was the insertion of software between the EMR and the lab information software (LIS) located in the application program interface (API). Using this bridge between the EMR and LIS, the MET software creates a unique tracking number shared by the practice, pathologist, patient, courier, medical malpractice company, and insurance company. Using the EMR's computerized physician order entry system for ordering a biopsy, the tracking platform creates a unique tracking number and a radiofrequency identification device (RFID) label for the specimen bottle. The patient (via app), the physician, and the pathologist are simultaneously linked to the entire data life cycle of the event. Every stakeholder tracks the physical location of the specimen from the office to the lab with all parties receiving real-time notifications about all specimen location transitions.

Today, MET is used to coordinate cancer care – but it will soon be used to coordinate the entire care team interaction, integrate genetic testing and pharmaceutical therapy, track patient outcomes, integrate patient mobile devices, and enable expanded research.

Moving to MET

Adopting integrated MET across the care continuum addresses interoperability issues, creates shared quality metrics, addresses communication deficiencies, and creates a dynamic, patient-centric medical record.

Creating a shared taxonomy for assessing data quality addresses

"Using MET with pathology reports means that no specimen is lost, every pathology report is received by the physician, every patient is notified, every cancer is treated, and future care is coordinated."

the five dimensions of EMR data quality: completeness, correctness, concordance, currently, and plausibility (7). These features allow high-quality data to be stored and presented in a usable manner, providing reliable, accurate, and actionable information. Uniquely, this approach eliminates the highly variable correctness and completeness results observed with current HL7 EMR software.

The MET system standardizes the quality metric database, eliminates inconsistency across data elements, provides real-time information and communication, allows data segmentation, tracks completed tasks, stores information prospectively, integrates data retrospectively through embedded PDF tracking numbers, and unifies the data storage between care partners. The system generates clinical quality measures through defined data life cycle communication and performance metrics of the care team, thus documenting care transitions and outcomes. Additionally, MET allows practices and communities to accurately measure performance, identify care delivery and workflow issues, make needed corrections – and even enable efficient transition to value-based payments.

With open MET technology, users and developers can create customized templates that integrate into their clinical workflows and maximize data completeness, creating an efficient structured data entry system (8). They can also adjust templates to physician preference based on encounter-specific variables, such as diagnosis, complaint, or other findings, to create structured data narratives.

Because MET provides unique API software insertions between systems, costly EMR upgrades are unnecessary; there is no additional cost for extraction software or services, system reconfiguration, or developing or purchasing reporting and analytics software. MET adoption has little impact on physician and staff workflow, thus minimizing the time and expense of staff training. In addition, the data quality review and resolution process takes up little staff time.

With the creation of high-quality, real-time data, MET enables primary and secondary uses of data and supports the development of a learning healthcare system. Real-time data can drive quality improvement, performance reporting and benchmarking, and clinical decision support; create a patient engagement digital space; foster payment reform and pay-for-performance; support health services research; and develop the next generation of patient-centric medical records that move beyond HIEs.

In short, event-based medical tracking adopts the most advanced communication platforms, used by the most successful communication industries throughout the world, for use in healthcare. MET enables medicine to achieve the goals of interoperability, shared quality metrics, better communication, and creation of a new dynamic, patient-centric medical record. It integrates efficiently, effectively, and economically into existing EMR vendor systems to impact the entire care continuum. Most importantly, MET allows practices and communities to accurately measure performance, identify care delivery and workflow issues, make needed corrections to deliver the highest quality, evidence-based care, and enables the movement to value-based care.

Sidney Smith is a practicing dermatologist and CEO of PathologyTracker.com, Dalton, Georgia, USA.

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Digitization – By the Lab, For the Lab

Thoughtful software design and implementation can smooth the transition to digital pathology

For Fujifilm, a global leader in digital imaging in healthcare, the move to pathology is a natural one. Its first step into the field of digital pathology is a partnership with Inspirata, whose pathologist-designed *Dynamyx* software Fujifilm now distributes. "*Dynamyx* software has three elements: a fully integrated workflow tool, an evidence tray that collects all the digital interactions pathologists have with the case, and an image utilization tool," explains Tim Wing, Fujifilm's Head of Digital Pathology. The software also has an open interface to any scanner or laboratory information management system (LIMS), as well as an open Application Program Interface (API).

Particularly noteworthy is the fact that *Dynamyx* software serves the clinician, rather than the research lab. "It can connect and archive to anything it needs to – and both first- and second-read image analysis tools can be embedded in the workflow, including automatic flags on cases that contain suspicious material." And the software's usefulness doesn't end there. "It also has a digital management tool for the laboratory, specifically designed by biomedical scientists, that allows them to quality control, scan, and evaluate slides, all within the histology workstation." It's clear that the innovative *Dynamyx* software prioritizes the needs and interests of the clinical laboratory team.

Becoming One with Digital Pathology

Ashley Ballard, Senior Biomedical Scientist at Royal Bournemouth Hospital, Bournemouth, UK

Tell us about One Dorset…

One Dorset Pathology is a three-hospital network that aims to improve productivity, quality, and turnaround times while also reducing costs. We have taken our first steps towards this goal with the recent implementation of a new shared LIMS. The main benefit of digitization within the network will be the ability to share histology workloads. We face an increasing workload and a reduced pool of pathologists – so we hope that digitizing will make case sharing easier, smoothing workloads. We also hope that this will release productivity and quality improvements across the network, leading to improved patient outcomes.

What led you to choose Fujifilm as your digital solution?

Fujifilm offered the best package in terms of the scanner compatibility, IMS, and storage solutions. We hope to implement a cloud storage solution, so we needed a supplier who could support us with this. It also helped that we had previously run a successful digital pathology trial with Fujifilm.

What advice do you have for others seeking to digitize?

Get full engagement from staff at all levels – and start as soon as possible.

Making the Move

Rahul Deb, Consultant Histopathologist and Breast MDT Lead, Royal Derby Hospital, Derby, UK

How do you use digital pathology in your lab?

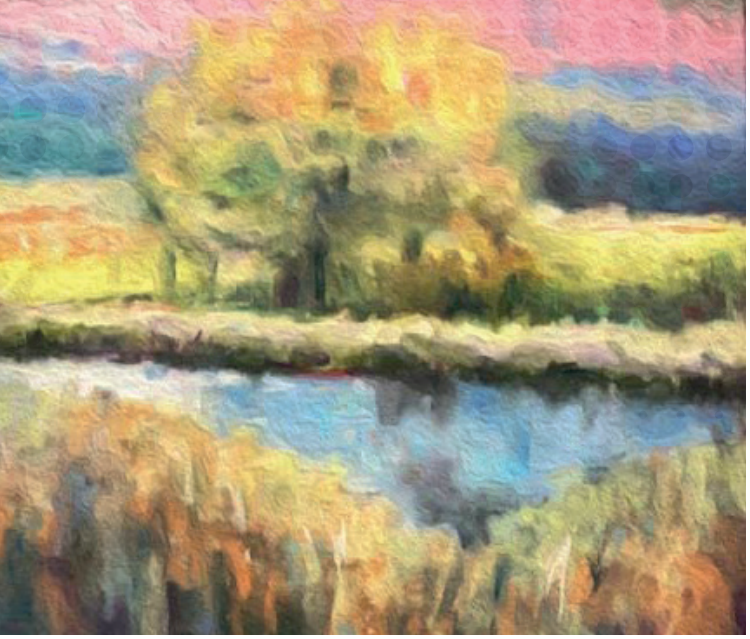
Several processes in our laboratory are already digitized. This includes slide and paraffin block barcoding and digital dictation. We also use an automated pro forma reporting system for most cancer cases where a minimum dataset pro forma is required. As a result, we can authorize our cases as soon as we have examined them under the microscope, rather than waiting for reports to be typed. The next logical step for us is to move to digital images – and our aim is to get as close to 100 percent digitization as possible.

What led you to choose Fujifilm as your digital solution?

In our tender, we asked for an end-to-end digital pathology solution. Fujifilm's offering met most of our department's requirements and was also financially competitive. The *Dynamyx* software is vendor-neutral and will allow us to remain relevant as our needs and equipment change in the future. Introducing digital pathology will pose many challenges, but Fujifilm are proactive and are happy to work with us to overcome them.

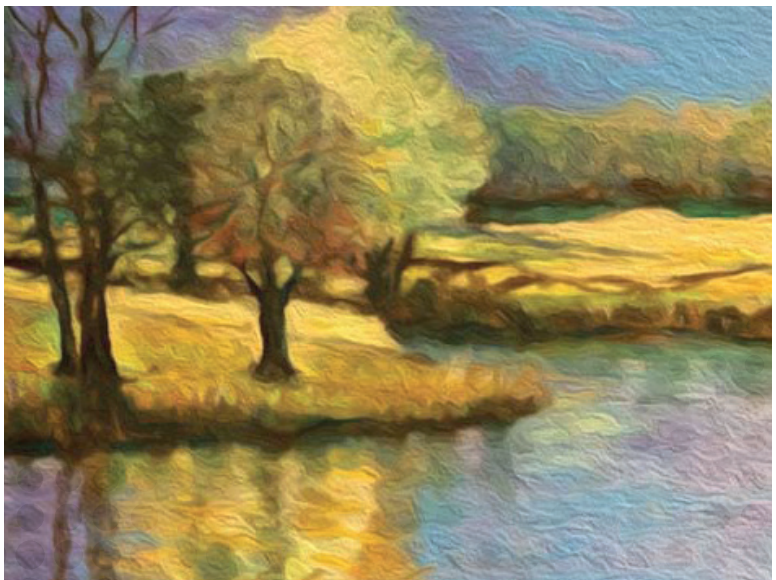
What does the future hold for pathology?

Cellular pathology is at an exciting crossroads. Digitization of slide images is not just replacing the microscope with a screen; it has the power to transform the entire laboratory workflow – increasing speed and throughput and reducing waste. It will also allow AI and machine learning to be used in ways we have never seen before. Sending cases away for second opinions will take minutes rather than weeks. Overall, I think digitizing pathology will be the most transformative thing we do in our lifetimes.



Painting a Picture of Pathology

Sitting Down With… Jan Silverman, Professor of Pathology and Laboratory Medicine at the University of North Carolina School of Medicine, Chapel Hill, North Carolina, USA



What first drew you to pathology as a specialty – and how did you end up in cytopathology?

Like many medical students, I was undecided and entertained a variety of different specialties as potential future careers. However, I did a summer externship in pathology – and, at that point, I was hooked. I was an art major at the High School of Music and Art in New York and that experience deeply affected my views on the importance of images in making diagnoses that could influence patient care. I knew then that pathology was my calling. I was fortunate to do my residency and fellowship at the Medical College of Virginia in Richmond and was greatly influenced by Jack Frable, who was a senior faculty member and director of cytopathology at that time. Jack was one the pioneers of fine-needle aspiration (FNA) cytology in the United States – and I quickly realized what a powerful impact this revolutionary, minimally invasive procedure had in establishing rapid diagnoses that aid clinicians and expedite clinical care.

How did you become an expert in FNA cytology?

After my residency and fellowship, I was recruited to the department of pathology at the Medical College of Virginia in Richmond, Virginia, followed by a brief time in private practice in San Antonio, Texas. Although I thoroughly enjoyed being involved in every aspect of pathology, I missed the academic environment – research, teaching, mentoring residents and fellows…

I came back to academic pathology to practice at East Carolina University School of Medicine in Greenville, North Carolina. I was recruited to be the Director of Cytology and to establish a contemporary FNA cytology program. I was extremely excited to join a relatively new medical school and pathology department and to have the opportunity to grow with the program. That motivated me to develop my expertise in this evolving discipline.

What would you like other pathologists to know about FNA cytology?

I believe that being competent at FNA cytology should be based on first being well-grounded as a surgical pathologist. In a way, it's like being bilingual in surgical pathology and cytology and being able to translate back and forth between the two disciplines. Within limits, we make the same diagnoses as in surgical pathology – but we do more with less. Currently, in this era of targeted therapies, we are often asked to be the first responders in establishing a diagnosis and directing appropriate treatment. I believe that the application of immunohistochemistry and molecular diagnostics in cytology, including FNA cytology, will only increase in the future.

You are also known as an educator in cytopathology. What are your priorities as a pathology educator – and what tips do you have for other educators?

One of the great joys of my life is the opportunity to be a teacher and mentor to residents and fellows. I believe that a good educator should instill the joy of lifelong learning in their students, be accessible and truly interested in the students, and – hopefully – serve as a role model. One of my goals as an educator is to have my students become my teachers. I have been fortunate to have wonderful residents and fellows at Allegheny General Hospital in Pittsburgh and currently at the University of North Carolina in Chapel Hill – and I am constantly astonished, but not surprised, at how bright and motivated they are. I learn from them every day.

I recommend that every educator make their teaching pertinent and practical so that it becomes relevant to the student. When lecturing, you are essentially telling a story, and I approached each lecture with that in mind. Start with a good introduction, have a strong middle, and bring your presentation to a satisfying conclusion. I also tell my residents and fellows to observe other speakers at meetings, learn what works and what does not, and incorporate that learning into their presentations.

You are active not just as a pathologist, but also as a fine artist. Can you tell us a little about your art?

Art is an important part of my life. Even when I am not painting, I am constantly looking at images, searching for patterns around me in my daily life, and framing visuals in my mind as if I were painting. I have gravitated to pastel painting and do primarily landscapes and seascapes. I have been mostly influenced by the impressionists and paint in an impressionistic style. My art background has greatly influenced how I practice pathology as well as how I teach – emphasizing the search for patterns in both making diagnoses and teaching pathology. I even have a presentation that I have given nationally and internationally entitled "The Search for Common Patterns in Art and Pathology."

How do you balance your work, teaching, art, and personal life?

Finding balance in one's life can be difficult and there are times in my life when it has been a challenge. I try to live a balanced life, but it requires much discipline in managing my professional and personal time.

The one key message I have for my peers and colleagues is to make every moment count and find joy in your life. I have been fortunate to have been able to combine my art and pathology, enhancing my joy in both. I also have a loving wife, Lisa, two sons, Patrick and Lachlan, and two dogs, Vinny and Rosie, all of whom I adore and all of whom bring joy to my life.

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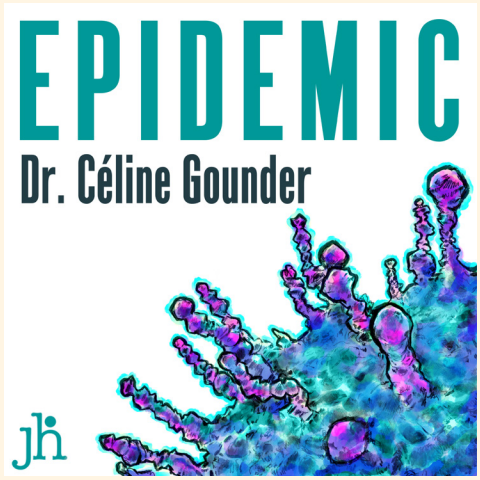

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