NOVEMBER 2020 # 70

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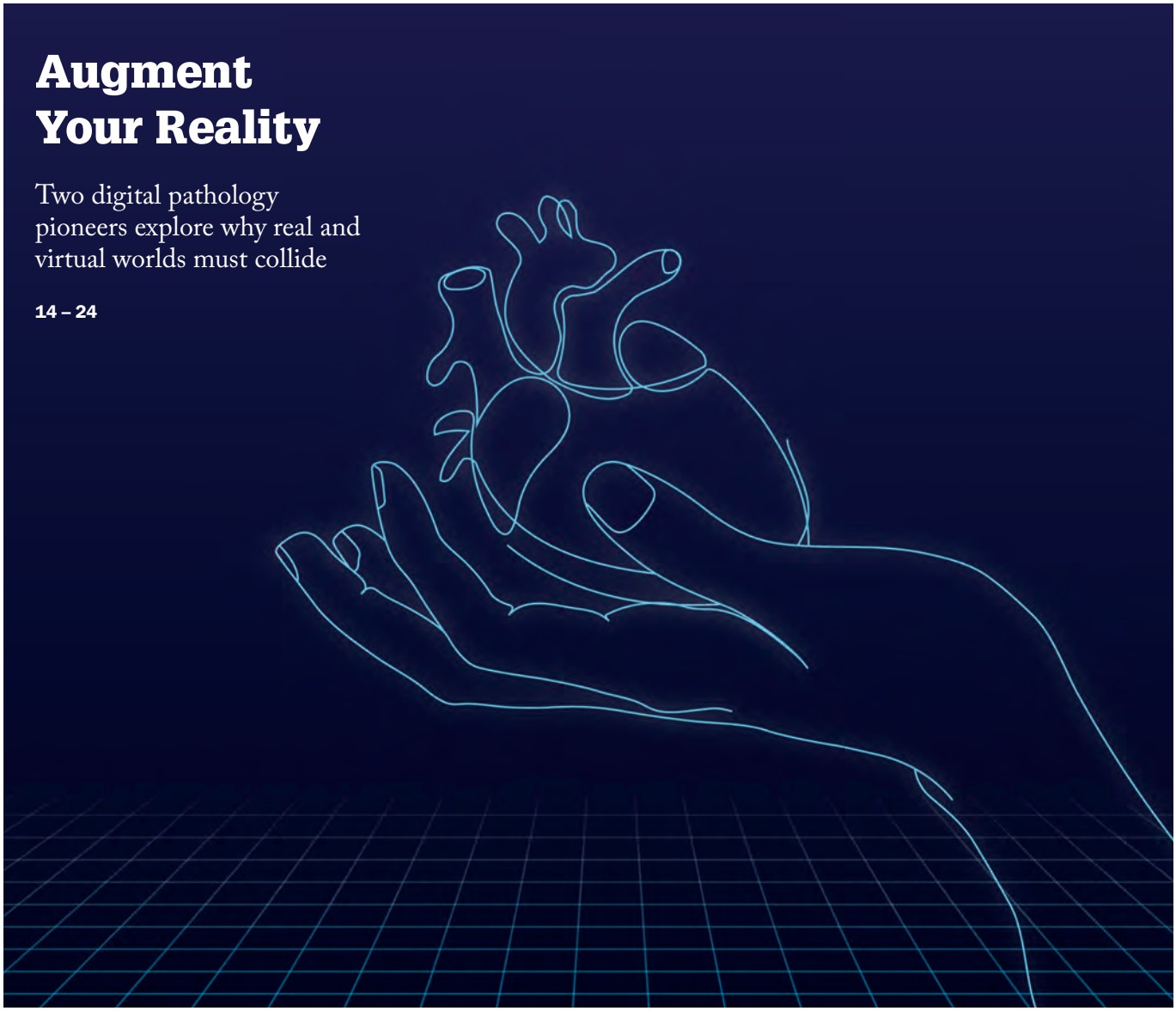

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Do You Believe in Science?

For many laypeople, the answer is increasingly uncertain – and that may be difficult to fix

More than ever these days, we're seeing a lot of talk about… talk. In a worldwide public health crisis, almost as important as its management is how we communicate that management – and the public is growing increasingly distrustful of experts and their advice (1). The situation is only worsened by administrations whose statements and policies seem directly counter to what those experts are saying: contradictory public addresses, leaders who visibly censor scientists, media whose news reporting bears little resemblance to the truth, policies that prevent households from meeting (but are perfectly happy with gyms, bars, and restaurants)… It's unsurprising at this point that people prefer to make their own decisions.

Unfortunately, those choices generally do more harm than good – and not just to the decision-makers themselves. COVID-19 conspiracy theories are making it difficult to convince the public to take simple protective actions, such as social distancing, mask-wearing, and testing when needed (2). Many are wary of accepting a vaccine once developed; more radically, others prefer to design and administer their own, rather than trust one offered by "Big Science" (3). A quick online search for "public distrust of experts" shows that this is not a regional problem – the results come from around the world. Headlines ask, "To defer or rebel during COVID-19?" or "What if they make a coronavirus vaccine and nobody takes it?" One publication, though, puts the responsibility squarely on those experts themselves: "Scientists must battle the disinformation pandemic" (4).

With only so many hours in a day – and a pandemic to fight – is it fair to place the burden of proof on the experts themselves? And, fair or otherwise, what can scientists and medical professionals do to fight back against an onslaught of misinformation and disinformation? Let us know how you're tackling the problem (edit@thepathologist.com) and we'll share your advice with others facing the same issues.

Michael Schubert
Editor

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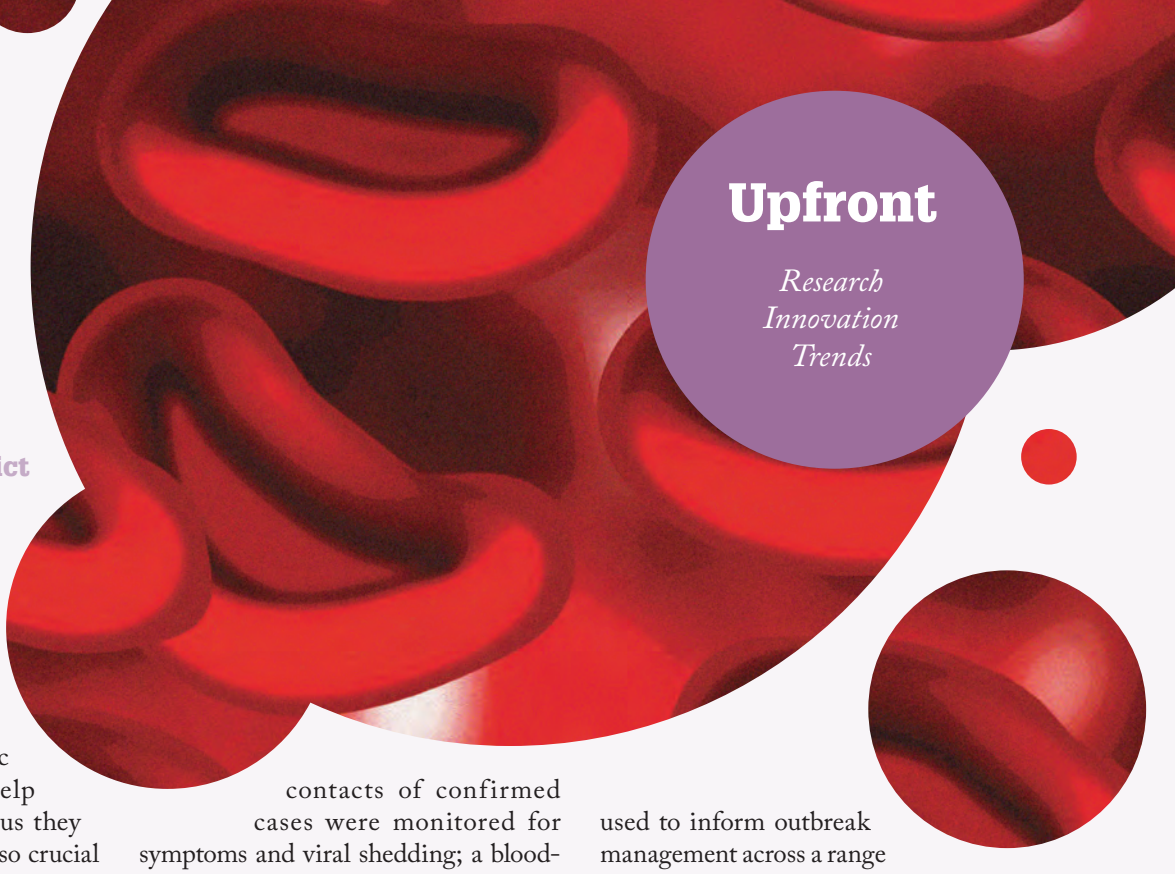
the Pathologist

ISSUE 70 - NOVEMBER 2020

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

General enquiries
www.texerepublishing.com | info@thepathologist.com
+44 (0) 1565 745 200 | sales@texerepublishing.com

Distribution: The Pathologist (ISSN 2055-8228), is published 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

Ahead of the Curve

Genomic markers predict viral infection up to three days before symptoms appear

Even before COVID-19 took over the world, researchers from Duke Health were investigating biomarkers to identify presymptomatic respiratory viruses and help control their spread (1) – focus they did not realize would become so crucial so quickly. After all, acute viral infections are the most common reason for primary care visits in high-income countries. And, after COVID-19, viral outbreaks will continue to threaten public health worldwide. Despite this need, we face logistical barriers to detecting infection early, such as availability of tools and the need for a priori knowledge of the pathogen in question.

Over five years, the Duke Health team recruited and monitored 1,465 students for symptoms of respiratory infection. 264 index cases were identified, with RT-PCR confirming presence of viral infection in 57 percent of cases and detecting nine different viruses in total. Close contacts of confirmed cases were monitored for symptoms and viral shedding; a blood-based 36-gene RT-PCR assay measured transcriptomic responses.

The assay accurately predicted infection up to three days before peak illness, when symptoms were minimal or absent and before viral shedding was detectable. The assay was 99 percent accurate for predicting illness from influenza, 95 percent accurate for adenovirus, and 93 percent accurate for the cold-causing coronavirus strain.

"We can use the body's natural immune response signals to detect a viral infection with a high degree of accuracy, even at a time when people have been exposed to the pathogen but don't yet feel sick," said Micah McClain, lead author of the study (2).

Transcriptional biomarkers could be used to inform outbreak management across a range of viral causes and stages of disease. Now, the team is looking at the effectiveness of these markers in detecting SARS-CoV-2. "Our data show that these biomarkers of viral infection are present and detectable before clinical disease develops and thus could form the basis of novel approaches to early identification and management of emerging viral outbreaks and pandemics," said McClain.

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INFOGRAPHIC

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Early Esophageal Insights

Can aneuploidy and driver gene mutations in Barrett's esophagus predict progression to cancer?

The study

- 88 patients
- 777 endoscopy samples
- 15 years of surveillance

Risk of progression

High 20x more likely to progress

Moderate Average risk of progression

Low 10x less likely to progress

QUICK HITS

A whistle-stop roundup of the latest research in pathology and laboratory medicine

At a Glance

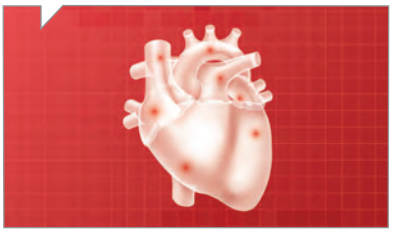
The results are now in from the Association for Molecular Pathology's SARS-CoV-2 diagnostic testing survey (1). New recommendations include ensuring that regulatory requirements are neither duplicative nor burdensome and supporting the clinical lab workforce as essential to the pandemic response.

Matters of the Heart

A single-cell atlas of the human heart has been published, documenting the complex nature of the healthy heart and the different cell types and genes expressed (2). It will provide a healthy reference heart for future research into targeted treatments for heart disease.

A First for mFMD

Researchers have found a recurring genetic variant associated with multifocal fibromuscular dysplasia (mFMD) (3). The *COL5A1* variant c. 1540G>A – also associated with classical Ehlers Danlos Syndrome – meets the criteria for pathogenicity, a first for mFMD.



Breaking Down Barriers

Not an expert in bioinformatics or programming languages? Not to worry – DrBioRight has got you covered (4). The new artificial intelligence-driven program enables biomedical researchers to analyze large datasets without the need for specialized expertise through its user-friendly, natural-language interface.

Pipeline Predictor

Scientists have developed a computational pipeline to predict the treatment responses of different tumors based on the co-occurrence of alterations in cancer driver genes (5). In testing, the model was able to predict therapy outcomes in 12 of 14 cases – higher than that of approved biomarkers.

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More than Meets the Eye

Neurodegeneration marker found in blood, CSF – and now the eye

They say the eye is the window to the soul, but could it also show neurodegenerative disease? Neurofilament light chain (NfL) is being investigated as a potential biomarker of neurodegeneration after it was found in cerebrospinal fluid and blood – but researchers at Boston Medical Center have also detected the protein in the vitreous humor.

Collecting eye fluid samples from ophthalmic surgery patients, they investigated the presence and association of NfL with known biomarkers of neurodegenerative disease. NfL was positively associated with t-tau, amyloid beta, and select inflammatory and vascular proteins in the vitreous humor. It was not associated with existing eye conditions, suggesting it is not influenced by eye disease.

Although further research is needed to validate whether ophthalmic NfL is a definitive indicator of neurodegeneration, the authors hope their findings will help detect disease before irreversible atrophy begins.

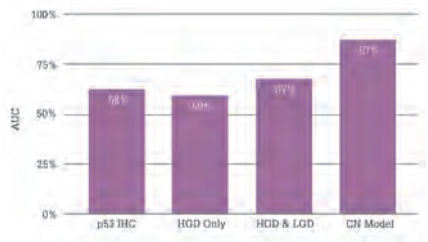
Reference

1. *SML Subramanian et al., Alz Res Ther, 12, 1 (2020). PMID: 32943089.*

Predicting progression in high-risk patients

Percent of patients classified as high-risk before progression.

Test sensitivity



Sensitivity of different approaches to progression prediction.

Reference

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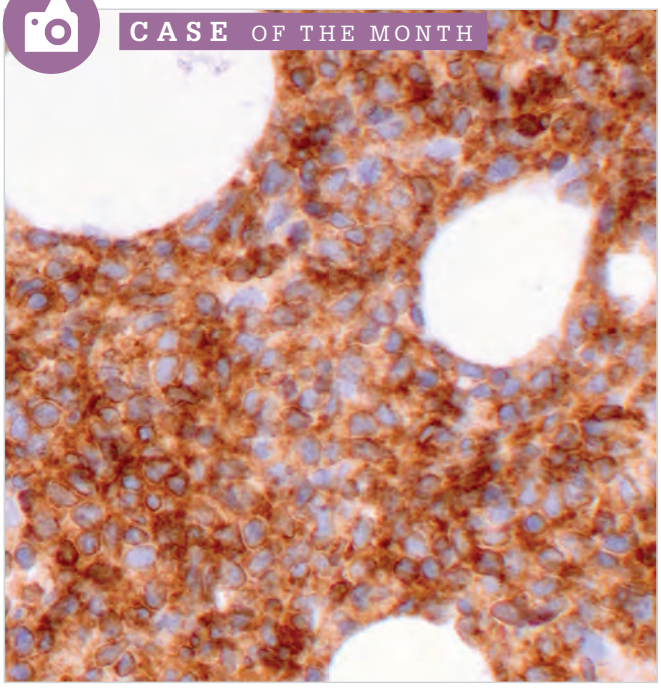
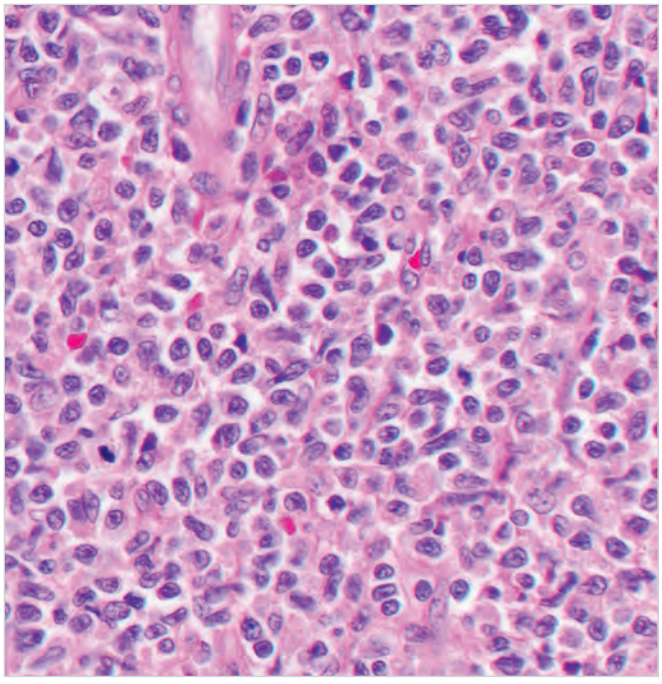
CASE OF THE MONTH





A 71-year-old man presented with a 2x2 cm chest wall mass, which was completely excised. The diagnosis was blastic plasmacytoid dendritic cell neoplasm (BPDCN).

Which of the following immunophenotypic markers is typically negative in BPDCN?

a) *CD56*
b) *CD123*
c) *CD3*
d) *CD4*
e) *CD45RA*

Answer to last issue's Case of the Month…

b) *Doxycycline-induced gastric injury*

The antibiotic doxycycline has been reported to cause gastric mucosal injury. The histologic findings of doxycycline-induced gastric injury are unique and include characteristic vascular changes. Disruption and degeneration of the superficial capillaries manifest as a ring of deeply eosinophilic granular material that often separates from the surrounding tissue, creating a so-called "halo effect. Microthrombi are present in some of the capillaries and can be highlighted with a CD61 immunostain. Other typical findings with doxycycline-induced gastric injury include reactive epithelial changes and superficial mucosal necrosis with active inflammation.

Submitted by Shula A Schechter, Lecturer, University of Michigan, Ann Arbor, Michigan, USA.

Further Reading

1. *AR Shih et al., Am J Surg Pathol, 41, 374 (2017). PMID: 28009607.*
2. *SY Xiao et al., Am J Surg Pathol, 37, 259 (2013). PMID: 23060354.*
3. *M Gorospe, O Fadare, Adv Anat Pathol, 14, 224 (2007). PMID: 17452819.*

To register your guess, please go to http://tp.txp.to/01120/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.

In advanced ovarian cancer,

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

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

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

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

Learn more at **testforHRD.com**

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

References: 1. Frey MK et al. *Gynecol Oncol Res Pract.* 2017;4:4. **2.** Pennington KP et al. *Clin Cancer Res.* 2013;20(3):764-775. **3.** Konstantinopoulos PA et al. *Cancer Discov.* 2015;5(11):1137-1154. **4.** Ledermann JA et al. *Eur J Cancer.* 2016;60:49-58. **5.** Watkins JA et al. *Breast Cancer Res.* 2014;16(3):211. **6.** Cheema PK et al. *J Oncol Pract.* 2017;13(2):e130-e138. **7.** Hoskins PJ et al. *CA Cancer J Clin.* 2017;67(6):493-506. **8.** Sundin T. *Med Lab Manag.* 2019;8(11):6.

Precision Medicine & Nurse Education

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In My View

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

Doing Our Part to Do No Harm

The laboratory medicine community must play its part in the pursuit of a healthier world

By Lara Richer, Anatomical Pathology Resident (PGY-5) at McGill University Faculty of Medicine, Montreal, Quebec, Canada

A few months ago, when I decided to write about the environmental crisis, I could not have imagined the state of the world as it is today. It seems almost inappropriate to be talking about issues other than COVID-19 in these surreal and devastating times – but, as our routine testing volumes temporarily decrease, it does allow for a period of reflection.

Although I have been enamored with pathology since starting my residency, I am simultaneously dismayed at the amount of waste that we produce on a daily basis. Sadly, we are part of a much greater problem. I learned this year that, if healthcare were a country, it would be the fifth-largest polluter in the world (1). Depressing? Yes. The sector responsible for keeping us healthy is a massive contributor to illness around the world. From vector-borne diseases to respiratory illnesses and food and water insecurity, climate change is expected to have a significant impact on human health in the coming years (2). As healthcare professionals, we must advocate for a healthier world for those we serve.

It is convenient to say that health care is privileged – that our waste is unavoidable to maintain quality standards in labs and to ensure the safety of healthcare professionals and patients alike. Or one might invoke the rhetoric that climate change policy should begin in a top-down fashion from the governmental level. If the COVID-19 pandemic has a silver lining, I believe it's that we've been shown what a profound impact one individual can have. The resilience, creativity, and resourcefulness of my colleagues and neighbors have given me hope in this time of crisis.

So what can we do to help limit the environmental impact of our profession? The answer to that question is nothing new. It centers on the three Rs: reduce, reuse, and recycle. I would add one more step to the beginning – something like "recognize" (to keep the alliteration going) – to remind us to be conscious of our actions and identify areas with potential for improvement. Being more aware of our energy consumption, for example, will become increasingly important as we transition towards digital pathology and start implementing machine learning algorithms into our practice. Many organizations offer ideas from which to draw inspiration for beginning this process. A nice list of resources has been compiled by the Canadian Association of Pathologists (3).

Perhaps the most important R of all is "reduce." Some reductions you could think about implementing include choosing digital publications over print (I recently changed my subscription to The Pathologist!), streamlining your LIS system to limit reliance on printed documents, turning off computers at the end of the day to save energy, and reconsidering travel to meetings – especially now that we're all practically experts at the art of meeting digitally!

Reuse is a tricky category. If you walk through your frozen section or grossing room, do you see any single-use items? Could any of your margin brushes, paper towels, specimen containers, or other items be replaced with a more sustainable option – or appropriately washed for reuse without compromising quality? Could you negotiate with vendors to have them reclaim and reuse the packaging that comes with your purchases?

Recycling is the last resort and the most expensive intervention, but up-front costs can be amortized over time or mitigated through funding. For example, we found out that our lab alone uses hundreds of thousands of

plastic gloves in a year, so we partnered with other labs in our network and applied for funding from our associated university to institute a glove recycling program. Recycling solvents, done in other labs, may lead to financial gains in the long term. There are many more examples of labs proudly going carbon-neutral, many of whom have posted their "how-to" advice on the Internet.

It remains to be seen whether our experiences during the COVID-19 pandemic will lead to an inflection point in how we treat the environment. I believe that, as healthcare professionals, we have a responsibility to contribute to the health and wellbeing of our patients – not only through the quality of our diagnoses, but also by ensuring that the practices involved in making those diagnoses are in their best interests as well.

Please see references online at: tp.txp.to/hcppe

An Inseparable Team

The emerging and essential role of the pathologists' assistant in interventional pathology

By Karen Villar Zarra, Maria del Mar Olmo Fernandez, Santiago Nieto Llanos (Hospital Universitario del Henares, Madrid, Spain), Hector Enrique Torres Rivas, Luis Manuel Fernandez Fernandez (Hospital Universitario Central de Asturias, Spain), and Carla Macleod Beltran (CBM Pathology, Washington, DC, USA)

For a long time, pathologists' assistants (PAs) have worked silently and diligently (and often unrecognized) in hospitals across the world. Their work represents an important link in the chain of duties required of a good pathology service. PAs in our institutions perform gross examinations, including complete description, mapping, evaluation/inking of margins, and sectioning of surgical pathology specimens, as well as processing all cytology samples. In addition, they are always ready to learn new techniques that give added value to their profession.

At the moment, our institutions are focused on a new professional activity for pathologists: interventional pathology techniques. These activities are important because they improve diagnostic and economic efficiency (1,2,3), shortening the time to diagnosis for the patient. Interventional pathologists do not limit themselves to waiting behind the microscope for samples, but perform the procedures to obtain cells, ensure sufficient representative samples, and optimize management of the material obtained (4). And because interventional pathologists make real-time decisions, it's the PA's intimate knowledge of the requirements for each potential procedure that allow optimal sample management. And, if another sample is required, it's the PA who prepares for complementary techniques, such as ultrasound-guided core needle biopsy, and assists the pathologist in performing them.

While the pathologist conducts ultrasound-guided puncture sampling procedures, the PA maintains the interface between the skin and the probe with repeated applications of quickly evaporating solutions, such as chlorhexidine (because gel interfaces may result in artifacts or obscure cells needed for cytological evaluation). The PA also knows what type of fine needle will be chosen according to the tissue and the depth of the lesion; they assist in the aspiration, prepare direct smears as needed, and immediately assess the adequacy of the sample, if the pathologist is not available.

Indeed the PA is integral to the entire process – from obtaining each patient's informed consent, to managing the ultrasound, to including patient data in the ultrasound imaging consultation, to changing probes, taking pictures, freezing images, and measuring and applying color Doppler to areas of interest.

PAs are also trained to handle common pathology laboratory techniques and prepare for rapid staining so that the pathologist can perform rapid on-site evaluation of samples or pursue ancillary testing if needed.

In this new interventional scenario, the pathologist–PA team must work well together to ensure optimal flow of the interventional pathology consultation and, ultimately, accurate and complete diagnosis. Good coordination between pathologist and PA is achieved through training – and after performing a few procedures. From that point on, the synchronization of tasks should be practically seamless. And that's why, at our institutions, we consider PAs the "right hand" of interventional pathologists. Without their training, assistance, and motivation, we would be less fluid and efficient.

Most pathologists already know how fundamental PAs are to their daily work and to the smooth operation of the laboratory. And this reality is only intensified in interventional pathology, where the PA's work is indispensable to efficient procedures, optimal sample use, and – most important of all – the best possible outcome for the patient.

Please see references online at: tp.txp.to/tppt

Digitize to Overcome

The pandemic has spurred pathology's digitization; now is the tech's time to shine

By Monika Lamba Saini, Pathologist at HistoGeneX, Antwerp, Belgium

The pandemic has had a deleterious effect on health care systems worldwide. The influx of patients with COVID-19 overwhelmed not only clinical, but also diagnostic facilities. Laboratories were particularly badly affected – and the paucity of pathologists became all too clear. Without sufficient personnel, how can we continue to cope with the demands of not just our usual workload, but a pandemic as well? I believe the answer lies in digitization.

Image digitization technology has progressed in the last decade, and it's time for pathology to benefit. Whole-slide imaging (WSI) scanners can now produce scans with excellent resolution that pathologists can manipulate just as they would a glass slide. And it's not just useful for research and education, but also for diagnostic surgical practice (1). Many countries have recently stepped up efforts to integrate digital pathology systems into routine hospital workflows to enable efficient remote second opinions and consultations (2), keeping people safe as we tackle COVID-19.

The pandemic also precipitated a change in the regulatory climate. In March 2020, the College of American Pathologists won a waiver from Centers for Medicare and Medicaid Services regarding remote pathology work (3). A month later, the FDA issued guidelines for the remote reviewing and reporting of pathology slides (4). This guidance has helped boost the practice of digital pathology for primary diagnosis; now, pathologists can access slides and perform remote consultations from their homes. As patients return to hospitals for everything from elective surgeries to clinical trials, our ability to work remotely becomes increasingly important for coping with our growing caseload while keeping ourselves and our families safe.

"[Digital pathology] helps to make the science of pathology more robust, addresses our discipline's workforce shortage, and helps us to grow, collaborate, and share."

Although COVID-19 prevention has spurred these changes, their benefits go far beyond pandemic safety. Digital pathology adoption helps with remote consultations and second opinions – not just in developed countries under lockdown, but also in resource-restricted settings. With technologies that reduce the cost of WSI, digital pathology can help small, independent laboratories in these settings share their cases seamlessly across laboratories and countries. Better storage facilities in the form of cloud computing aid easy retrieval, assist in review during clinicopathologic consultations and meetings, and provide an excellent teaching resource. And, having worked with digital pathology for the last three years, I can vouch for its ergonomic benefits!

To improve diagnostic accuracy, WSI can be combined with image processing techniques. The introduction of algorithmic intelligence provides pathologists with tools that can assist their decision-making process. When applied to WSI, artificial intelligence helps assimilate clinical, genomic, and pathologic data for diagnosis and prognosis, helping to reduce inter-observer variability and enhance reproducibility – and ultimately leading to better clinical outcomes.

Digital pathology's time has come. It has helped pathologists work remotely during the pandemic, but it will continue to be an important tool in the post-pandemic era. It helps to make the science of pathology more robust, addresses our discipline's workforce shortage, and helps us to grow, collaborate, and share. And, as every pathologist knows, sharing makes a great pathologist!

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Expanding Our Horizons

Digital pathology: a tool to meet the needs of patients worldwide

By E. Blair Holladay

The technology used in pathology and laboratory medicine has changed exponentially over the past two decades – and it shows no sign of slowing down soon. With the rise of personalized medicine, the importance of the outcomes of our work – not just running tests as ordered – increases, and these changes become not only needed, but expected. As pathologists and medical laboratory scientists, we are the cornerstone of healthcare, and not to embrace advances that provide better insight into patient needs ultimately means doing a disservice to the patients we serve.

In recent years, digital pathology has emerged as an essential component of how we practice. By incorporating digital pathology into our processes, efficiency has increased and our views have expanded (in some cases literally, when whole-slide imaging comes into play). Digital pathology lets us move our work beyond our own laboratories and healthcare organizations. It allows us to reach more patients – both in our own backyard and on the other side of the world.

In 2015, digital pathology allowed us the opportunity to reduce the suffering and death that so often follows a cancer diagnosis. ASCP expanded the reach of patient care by launching Partners for Cancer Diagnosis and Treatment in Africa. This ASCP-led coalition brought much needed leapfrog technology to sub-Saharan Africa, where in-continent pathologists and medical laboratory scientists could now connect with colleagues in America for rapid diagnosis. The ability to impact so many lives through digital technology is something we at ASCP have both appreciated and embraced since that launch – and something we are committed to continuing.

"In recent years, digital pathology has emerged as an essential component of how we practice."

Even throughout the COVID-19 pandemic, we have been able to care for patients in resource-limited countries, thanks in large part to digital pathology. Recent equipment donations from our members to laboratories in Zambia (1), for example, have enabled pathologists there to get second opinions from local and international subspecialists, which the country lacks. The direct access to renal, neuro-, and dermatopathologists using digital technologies has helped improve patient care despite the global crisis.

As pathologists and medical laboratory scientists, embracing advances that make us better is not a choice – it is a must. If we want to progress in research and in our profession, developments like digital pathology will help us get there. If we want to make a difference in and improve patient care, it is this forward motion that will save lives.

Reference

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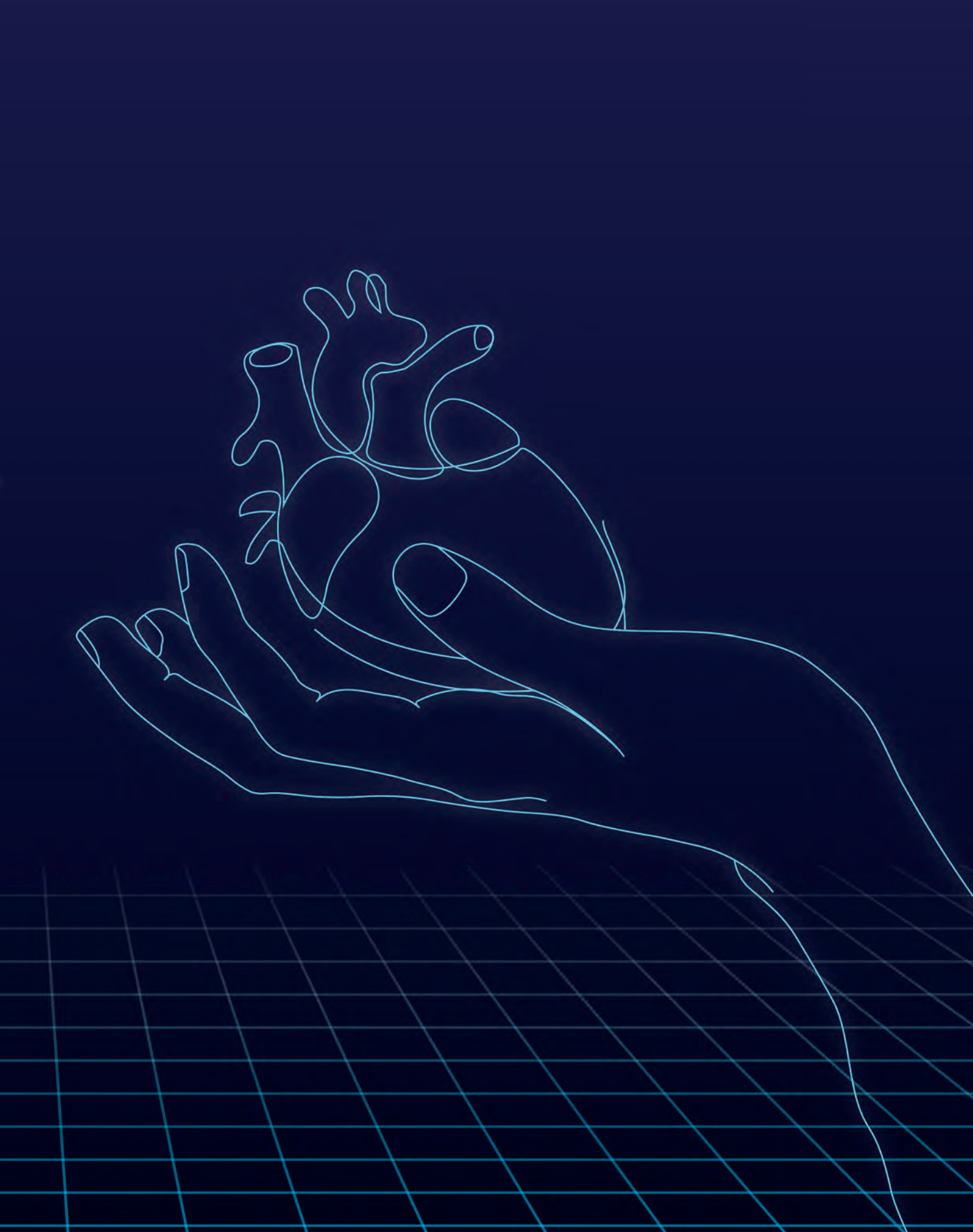
AUGMENT YOUR REALITY

How AR technology can add a new dimension to pathology

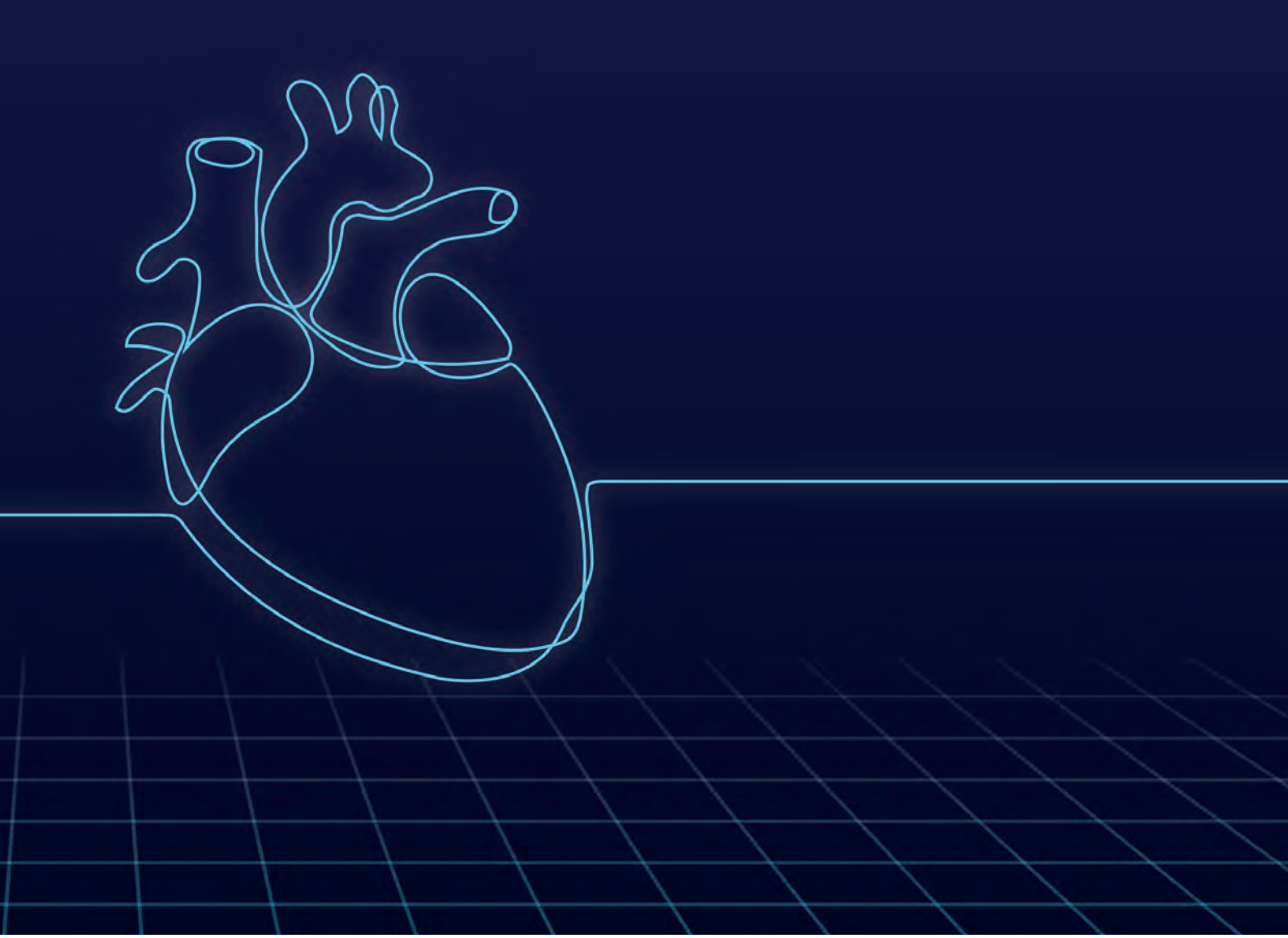
By Liron Pantanowitz and Swati Satturwar



"I have always been intrigued to find out if there was a better way to practice pathology," says Liron Pantanowitz, Director and A. James French Professor of Anatomic Pathology at the University of Michigan. "Most recently, I have been extremely impressed with the capability of augmented reality (AR) microscopy." Having tested the technology, he reports, "It was awesome and delivered just as expected, bringing AR right to my microscope. There are so many use cases for augmented and virtual reality in pathology – I am just getting started."

Swati Satturwar, Genitourinary Pathology Fellow at the University of Pittsburgh Medical Center, says that digital pathology was limited to tumor board presentations during her residency – but when she took up her cytopathology fellowship position, she began using it on a daily basis. Eventually, she took on a research project using AR microscopy (ARM) with real-time image analysis for Ki-67 quantification in cell block material of neuroendocrine tumors. The project involved comparing conventional manual counting methods to novel AI-based methods using digital image analysis and ARM. "I am excited to work on more projects exploring the potential of these technologies to complement pathologists," Satturwar says. "I am also excited that UPMC is going to adopt Ibex AI algorithms for prostate biopsies. As a GU fellow, I will have the opportunity to be a part of this adoption of novel, AI-based diagnostics in routine clinical practice."

"WHAT I LOVE MOST IS THAT, ONCE A SLIDEIS DIGITIZED, IT OPENS UP A WORLD OF POSSIBILITIES. THE APPLICATIONS WITH A DIGITAL IMAGE ARE ENDLESS."



POWERFUL PROMISE

Of course, AR and VR aren't new technologies. "I'm not much of a video gaming person," says Pantanowitz, "but I tried AR/VR briefly for gaming and had some fun. Of course, my kids love it. At one stage, I couldn't get them to stop playing!" Augmented reality has also taken him to museums and far-flung locations such as Machu Picchu. "Most recently, I nearly bought a house after just taking a 3D virtual tour!" he says. "It was almost as good as a real walkthrough of the property."

Satturwar prefers to use the technology for social purposes. "I use AR while taking fun photos with my smartphone – for instance, to add a variety of stickers," she says. VR is reserved for video games, from bowling to roller coasters.

In the lab, though, the tech takes on a more serious tone. "I am a huge proponent of digital pathology," explains Pantanowitz. "What I love most about it is that, once a slide is digitized, it opens up a world of possibilities. The applications with a digital image are endless." The biggest obstacle to pathology's digital transition has been the need to acquire the image first. Photographing slides is cumbersome and doesn't give you access to the entire slide, whereas scanning the glass slide is time-consuming and requires expensive hardware and software. "With ARM this inertia is removed. All you need to do is attach an AR device to your microscope and voila – you are ready to go. That's what inspired me."

Originally, Satturwar didn't know ARM technology existed. "In the first month of my cytopathology fellowship, Liron Pantanowitz asked me if I would like to participate in a research project using ARM. He showed me a video of the technology. I was amazed by its potential and said yes right away."

The ARM Satturwar uses is an Olympus microscope with an Augmentiqs AR device attached between the microscope's objectives and eyepiece unit and an inbuilt camera to capture high-quality images. The images can be viewed through the microscope's binocular lens or displayed on the monitor of an attached computer. It can overlay additional information (whether computer-generated data or the pathologist's manual annotations) onto the original microscopic field of view (FOV) in real time, without having to first digitize a glass slide.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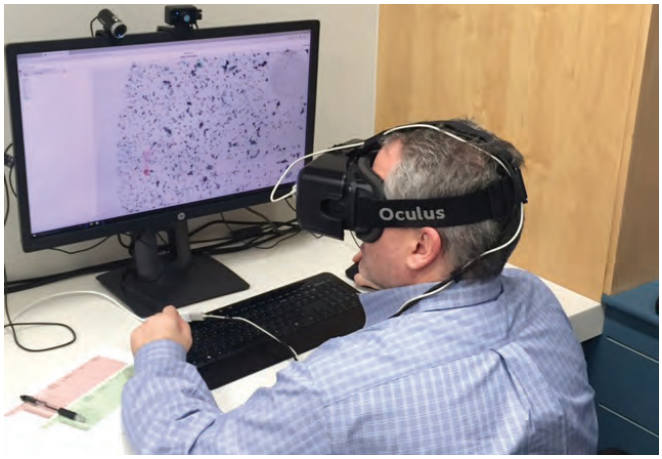

ARM even enables real-time image analysis on the glass slides. How? By integrating AI algorithms to generate a composite FOV that can be used for advanced data collection without altering the traditional manual pathology workflow or the optical quality of the microscope. This modified "smart microscope" can be used for a variety of diagnostic purposes, including:

- simple measurements (e.g., size and depth of tumor or lymph node metastasis)
- immunohistochemical stain quantification (e.g., Ki-67 proliferation index)
- diagnosing non-neoplastic diseases (e.g., myopathy and non-alcoholic steatohepatitis)
- cancer diagnosis (by integrating AI such as deep machine learning algorithms)

The high-quality digital images the microscope produces can be used for telepathology, tumor board presentations, frozen section peer reviews, teaching, and research.

PROS AND CONS

Augmented reality – and ARM in particular – has a lot to offer in the lab. Its benefits include:

- AR devices can be attached to any conventional light microscope to convert it into a "smart microscope."
- Real-time image analysis on glass slides by avoiding the time-consuming process of digitizing glass slides prior to image analysis. This decreases the disruption to routine workflow in a busy pathology practice.
- Minimal technical skills required to operate ARM, unlike whole-slide scanners that require special technical expertise.
- More affordable than a conventional whole-slide scanner.
- Not associated with simulator sickness, which is known to occur with wearable AR/VR devices.

But though AR and VR look like promising tools for pathology, the technology has a long way to go before it's ready for routine clinical use. Some existing devices lack sufficient image resolution for medical-grade work; others carry privacy concerns when sharing protected health information over the Internet. "Of course, the instant you turn a device into a 'medical instrument,' everything suddenly becomes more complicated," says Pantanowitz, citing challenges from liability to regulations to vendor support.

Satturwar agrees. On her list of things that need to be addressed before integrating ARM into routine pathology workflow are large-scale studies validating its uses; increased awareness of ARM among trainees, practicing pathologists, and researchers; and the development of affordable, yet sophisticated, deep learning algorithms for pathology diagnostics.

But which is better – AR or VR? Is it preferable to combine reality with computer-generated information and superimpose a digital image onto a view of the real world or to provide a completely computer-generated environment that merely simulates a real experience?

"ARM IS MORE LIKELY TO BE ADOPTED BY USERS BECAUSE IT INTEGRATES INTO THE EXISTING MICROSCOPE AND DOES NOT REQUIRE ANY WEARABLE ACCESSORIES."

Pantanowitz sees benefits and shortcomings to both. "VR is definitely more immersive – but, for pathology work, it's just not practical and can cause issues such as motion sickness," he says. "AR, on the other hand, is more practical, additive, and offers more possibilities (1)." Expanding on AR's user-friendliness, Satturwar adds, "ARM is more likely to be adopted by users because it integrates into the existing microscope and does not require any wearable accessories."


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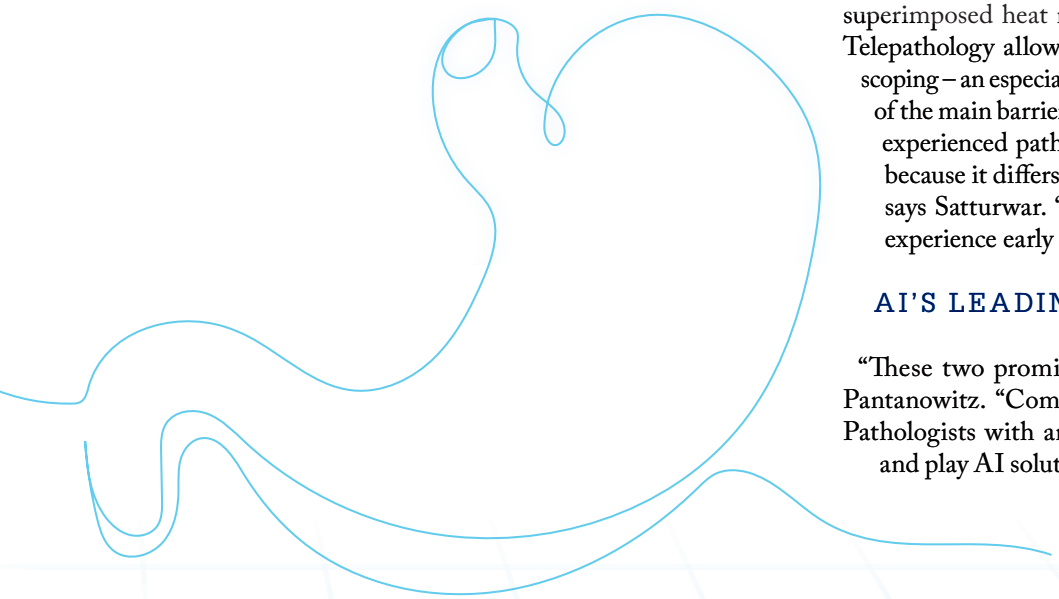
AR technology offers the potential of greater accuracy, efficiency, and reproducibility for simple morphometric measurements or stain quantification. And, coupled with AI algorithms, it can enhance lab workflow and decrease turnaround time by automating multiple diagnostic steps.

THE LEARNING CURVE

"AR is ideally suited for education," says Pantanowitz. "It offers learning that is more engaging, fun, helps explain abstract concepts, and can reach more people. This is becoming big business."

Because AR devices can be attached to multi-headed microscopes, educators can use ARM to annotate important pathology features, such as mitotic figures. Some devices even have a stage-tracking facility that students can use to follow the educator's exact movements in reviewing the slide – helping them learn to navigate difficult cases. Satturwar says, "ARM can save time and improve trainees' educational experiences by integrating different features, such as more accurate measurements and automated stain quantification." Manual counting of Ki-67 or H-score for breast biomarkers is time-consuming and shows interobserver variability – whereas ARM can make the process faster and more accurate so that trainees can focus their time on difficult cases.

Here again, AI can be a hero. Real-time integration of AI – for instance, deep learning algorithms – lets multiple users see the same FOV with superimposed heat maps for tasks such as cancer detection. Telepathology allows screen-sharing or even remote double-scoping – an especially helpful feature during a pandemic. "One of the main barriers to adoption of the newer technologies by experienced pathologists is a reluctance to try new things because it differs from what they learned during training," says Satturwar. "If residents and fellows get this learning experience early on, it will increase adoption."



AI'S LEADING ROLE

"These two promising technologies are synergistic," says Pantanowitz. "Combined, they deliver a win-win solution." Pathologists with an AR/VR platform can essentially plug and play AI solutions designed to assist them – something Satturwar, Pantanowitz, and colleagues tried to great effect in a study on Ki-67 scoring in neuroendocrine tumors (2). Satturwar says, "The

MOVING INTO THE AR/VR SPACE

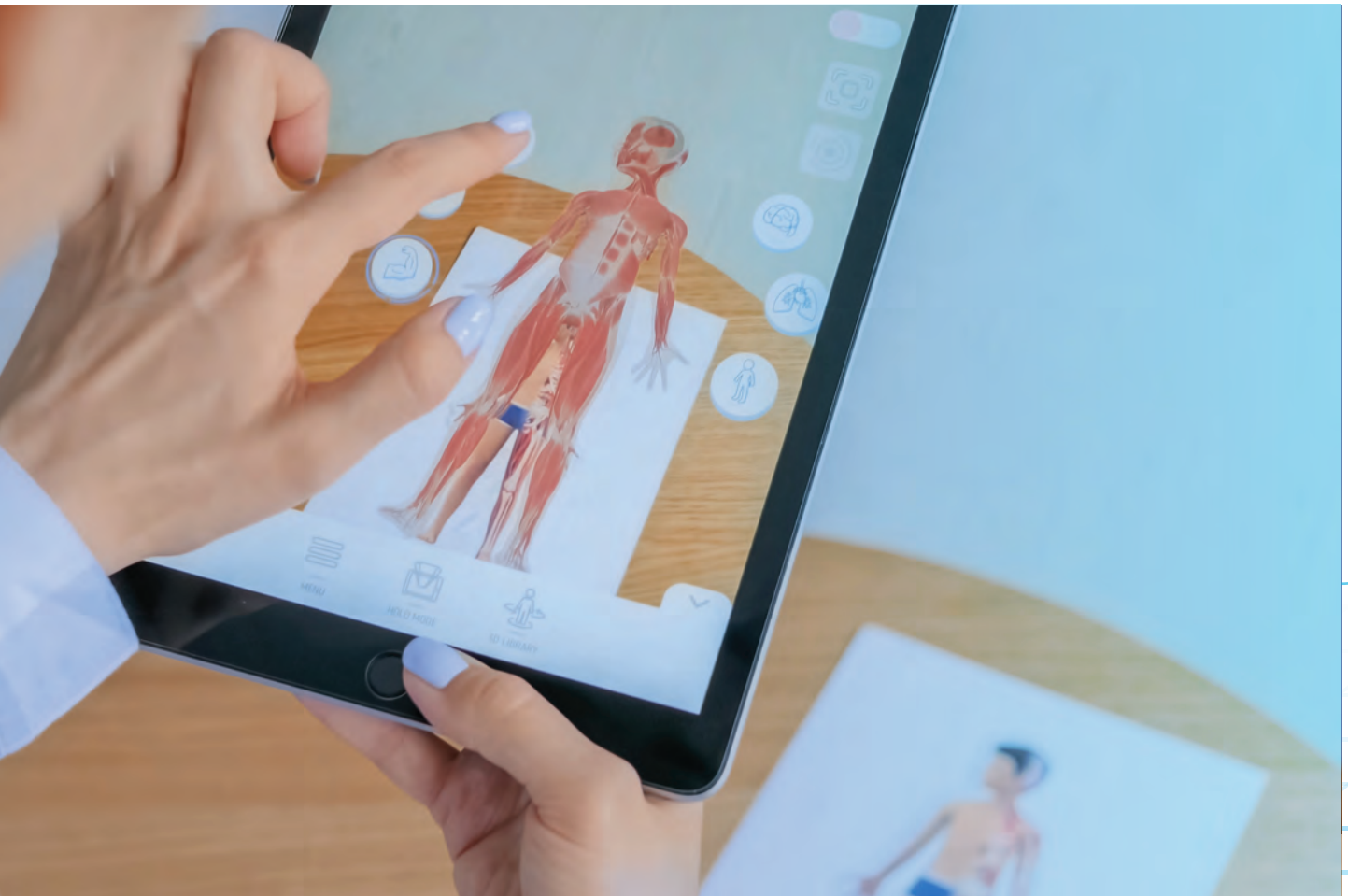
Resources needed

- IT infrastructure to support AR (high-speed Internet, servers, and secure data storage and transmission)
- Equipment maintenance (from trained IT personnel)
- Training (demonstrations and practice sessions for end users)
- Capital budget for purchasing AR devices and AI algorithms

Regulatory and policy considerations

- Validation studies and/or FDA approval prior to routine clinical implementation
- New current procedural codes for appropriate reimbursement
- Laboratory-specific policies for implementation and use, including quality assurance

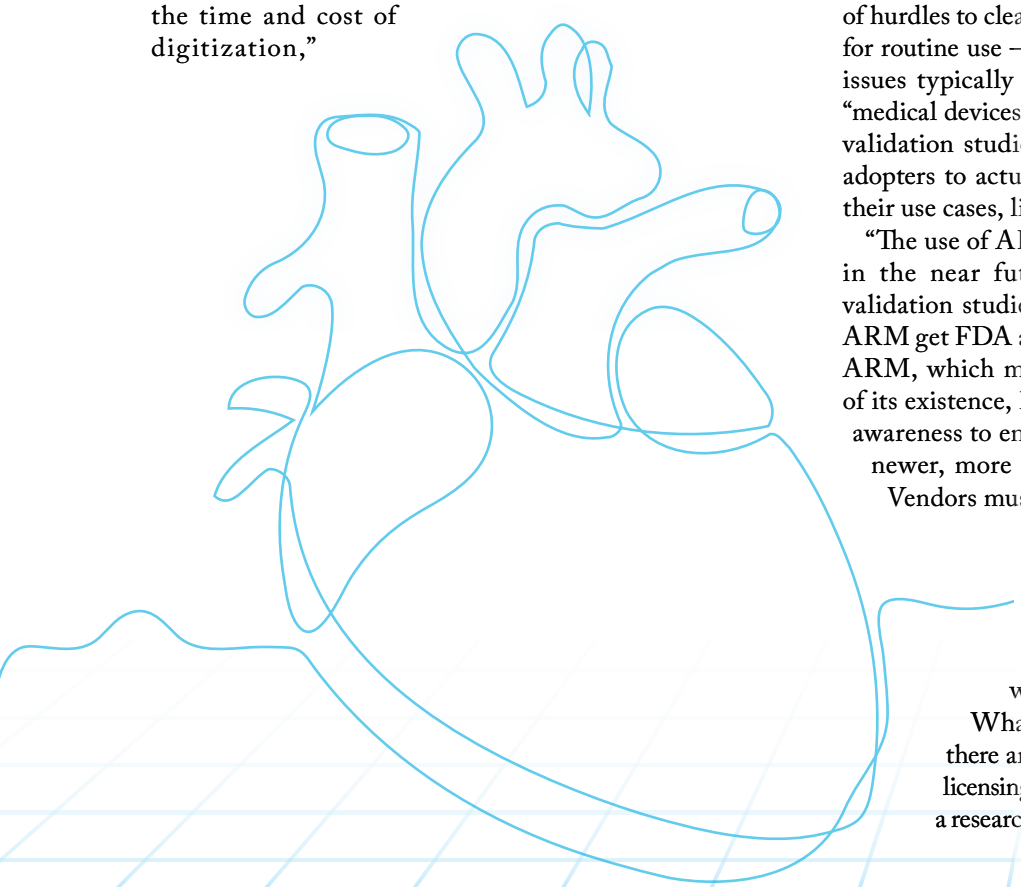
Credit: Zyabich / Shutterstock.com



study allowed us to rapidly quantitate a Ki-67 index without prior digitization of glass slides and demonstrated near-perfect agreement with the printed image manual count method." She also points out that newer, more robust deep learning algorithms with convolutional neural networks have outperformed pathologists in some studies using whole-slide imaging modalities (3) – and that the same may eventually be true of AR coupled with AI/deep learning algorithms.

AI is revolutionizing the way pathology is practiced today. Because of the COVID-19 pandemic, the Centers for Medicare & Medicaid Services (CMS) in the USA have approved remote sign-out using digital pathology. But that's only the first step; pathologists need enough training and confidence in digital pathology to take advantage of it – and there can be not only technical, but also financial barriers to a full digital transition. "AR/VR tools will give us a platform to do what we already do every day, but better," says Pantanowitz. "They can give more precise, accurate, and standardized results and scores with the help of simple image analysis or more sophisticated AI. They can even offer users the ability to work remotely – a big deal now due to the pandemic."

"ARM presents a cost-effective model that allows seamless integration of AI algorithms without digitizing the glass slides, thereby eliminating the time and cost of digitization,"



says Satturwar. "AR also allows focus adjustment, which is essential during the review of unique cytology preparations." The technology's benefits are not limited to state-of-the-art labs, though; AR could eliminate disparities between remote and resource-poor health care facilities and their more affluent counterparts.

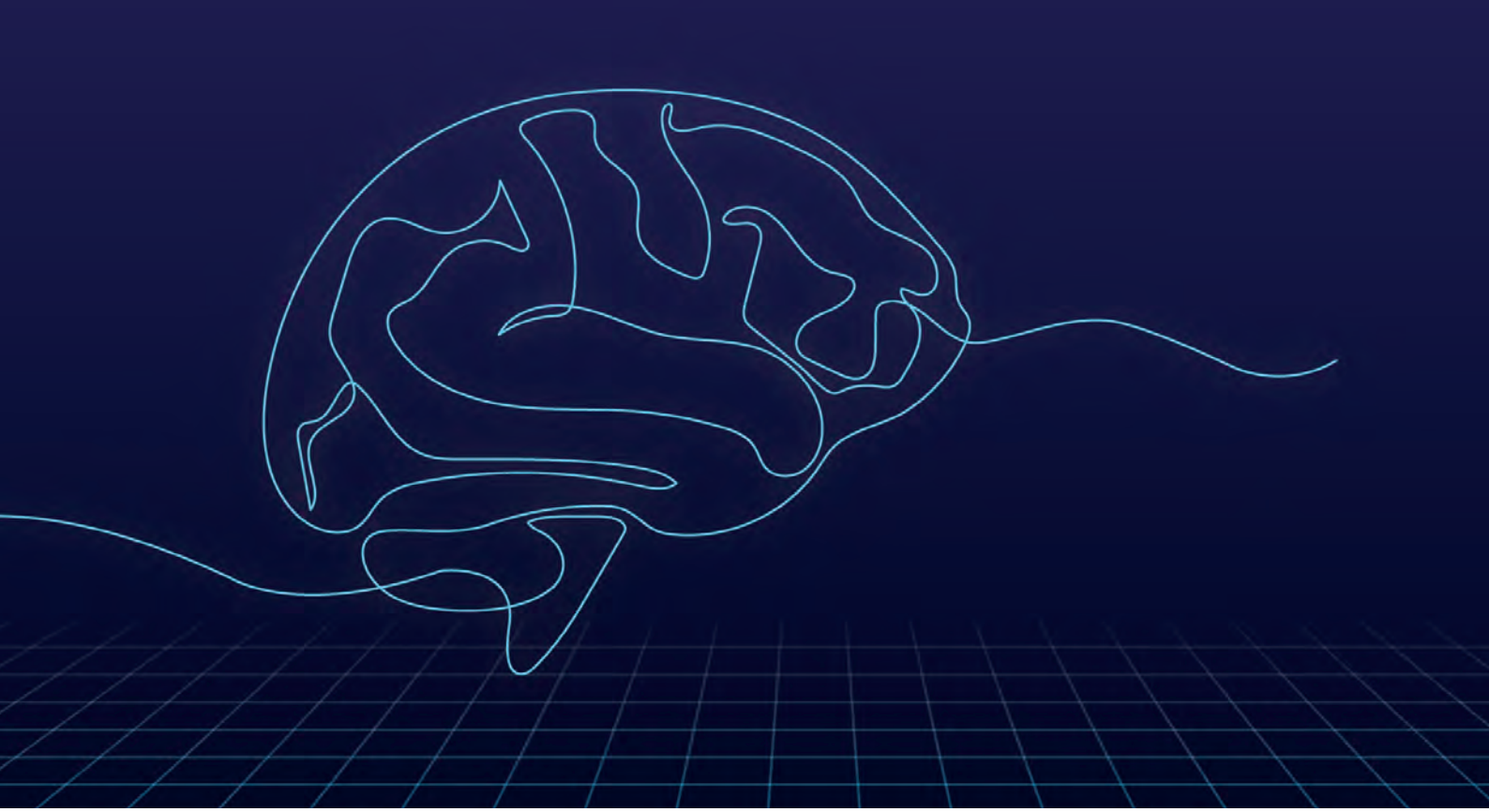
"ARM PRESENTS A COST-EFFECTIVE MODEL THAT ALLOWS SEAMLESS INTEGRATION OF AI ALGORITHMS WITHOUT DIGITIZING THE GLASS SLIDES."

AN AUGMENTED ROUTINE

How soon might we see AR in the lab? There are still a number of hurdles to clear before the technology can be implemented for routine use – including i) appropriately dealing with the issues typically needed to convert these instruments into "medical devices" (such as regulatory approval), ii) published validation studies to get pathologist buy-in, and iii) early adopters to actually deploy these systems and demonstrate their use cases, limitations, and return on investment.

"The use of AR in routine pathology workflow is possible in the near future," says Satturwar, "after large-scale validation studies confirm its utility and technologies like ARM get FDA approval." At the moment, few vendors offer ARM, which means that many laboratorians are unaware of its existence, let alone its promise. "We need widespread awareness to encourage practicing pathologists to adapt to newer, more accurate, and more efficient technologies. Vendors must also develop affordable AI algorithms for common diagnostic specimens according to laboratories' needs." Even after these things are in place, though, she cautions that labs must develop policies regarding the use of AR to enhance the existing workflow before bringing it into routine use.

What of regulatory concerns? At the moment, there are no standardized guidelines on validation or licensing requirements for AR/VR. "It's one thing to do a research study to demonstrate clinical feasibility," says



Pantanowitz. "It's a totally different ball game when you want to start using technology for routine patient care in clinical practice. Within this clinical context, there are regulations that apply to the manufacturer (such as FDA approval) and those that apply to the lab (such as compliance with accreditation needs or establishing a QA program)." Satturwar also recommends that labs conduct their own validation studies before fully adopting the technology. Nonetheless, her excitement remains untempered. "With the integration of AR coupled with AI into routine pathology, the future is bright."

AR and VR technologies aren't meant to replace traditional pathology – or the pathologist. Instead, they should be adopted as a complement or enhancement to manual pathology workflow. Satturwar warns that labs need not only a quality assurance system for all AR- or AI-assisted diagnostics, but also a full understanding of the tools' limitations. For instance, AI algorithms are trained for diagnosing certain diseases – which means they may miss co-existing pathologies for which they are not trained. Of course, cost is always a concern. "Look for a vendor who can provide affordable AI according to the needs of a given laboratory," she advises – a task that may become easier as appropriate billing codes for computer-aided diagnosis are established.

Pantanowitz adds, "There is always the risk of trying out new technology just because it is novel. I would advise pathologists to avoid the 'shiny object syndrome.' However, if there is a good niche application (for instance, to enhance training/education, perform better path-rad correlation, or provide a platform for easy image analysis) that justifies use of the technology, then go for it!"

But despite these cautions, Satturwar and Pantanowitz believe the clinical laboratory is ready for augmentation – perhaps even before entertaining thoughts of a full digital transition. "Although converting to complete digital workflow is optimal, there are certain challenges," says Satturwar. "AR technology that offers similar applications without prior digitization of slides is a more affordable and cost-effective route to adopting novel technologies into routine pathology workflow."

The final word? Pantanowitz sums it up in an apt paraphrasing of Darwinian theory: "It is not the strongest of the species that survives, nor the most intelligent. It is the one that is most adaptable to change."

Liron Pantanowitz is A. James French Professor of Anatomic Pathology and Director of Anatomic Pathology at the University of Michigan, Ann Arbor, Michigan, USA.

Swati Satturwar is Genitourinary Pathology Fellow at the University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, USA.

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2. *SP Satturwar et al., "Ki-67 proliferation index in neuroendocrine tumors: Can augmented reality microscopy with image analysis improve scoring?" Cancer Cytopathol, 128, 535 (2020). PMID: 32401429.*
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Precision Oncology's Greatest Tool?

The power of in-house genomic profiling is felt by both patient and pathologist

An interview with Rui Manuel Reis

Tell us about your background in oncology…

I've worked in cancer genetics since 1996. I started out studying microsatellite instability, then moved to molecular pathology for my PhD. In 2010, I moved to Barretos Cancer Hospital, where I coordinated the implementation of the molecular diagnostics laboratory. It's one of the largest cancer hospitals in Brazil and, because we only attend to the Brazilian public health system, treatment is free of charge. We do something that is unique in Brazil – deliver state-of-the-art diagnostics and treatment to people who cannot afford private healthcare. And is something we are incredibly proud of.

What are the benefits of precision oncology – and how does genomic profiling play a role?

Put simply, precision oncology allows us to determine the best approach for each individual cancer patient. Genomic profiling is a crucial tool to guide treatment decisions and select a drug that targets each tumor's particular molecular profile. We mainly use next-generation sequencing because we can evaluate both DNA and RNA alterations, such as gene mutations and fusions. We plan to increase the number of genes reported by tumor type and evolve into a liquid biopsy approach, as well as expand into the use of gene expression signatures.

What is your opinion on in-house testing versus centralization?

We perform in-house testing as it allows us to control the whole workflow – from tissue selection and sample manipulation to generating reports for our clinicians – and we believe that ensures our patients receive a higher standard of care.

In Brazil, most tests are expensive – particularly in centralized labs. But when we test in-house, we can choose the best, most cost-effective method for our needs, giving all patients access to the information that will guide treatment decisions.

Also, it is important to preserve the sample material because it might be required for future tests. Because we have complete control over the tissue block, we can use only what is necessary for our chosen assay. Many centralized labs don't take the same approach – they use large panels to avoid repetition and often exhaust the sample.

In-house testing also avoids the delays that centralized labs face – the turnaround time is much shorter. This difference is even greater in countries like Brazil, where couriers have to travel long distances.

Finally, because we are a teaching hospital, we can also provide a better training foundation for our interns; not only do our current patients benefit from in-house testing, but our future patients will as well.

How does in-house testing help you address Brazil's new general data protection regulations?

Genetic data is now categorized as sensitive data. If you want to perform a test, you must obtain written consent from the patient – but we already do that when they are admitted. Sending samples abroad to centralized labs adds a layer of complexity because the patient needs to sign another form specific to the lab receiving their samples. Again, having the in-house lab accelerates this process and provides a faster result for the patient.

How does it affect your collaboration with clinicians?

In-house testing allows us to have conversations about the results with our clinicians during multidisciplinary tumor boards. This helps them better understand the findings, ask questions, and plan the best treatment for each patient, which ultimately leads to better care and outcomes.

What are your thoughts on pharmaceutical companies' paying for samples to be tested in centralized labs?

I think the problem lies in the size of the panels these labs use. Although broad-spectrum diagnostics may be a great tool in future, there are still only a few drugs available to us that have clear benefits for patients. In my opinion, it's not ethical to perform a test that generates results that are not actionable; that only gives patients false hope. That's why, at my hospital, we only perform tests that guide real treatment options.

Rui Manuel Reis is Coordinator of the Molecular Oncology Research Center, Barretos Cancer Hospital, Barretos, São Paulo, Brazil.

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Research advances
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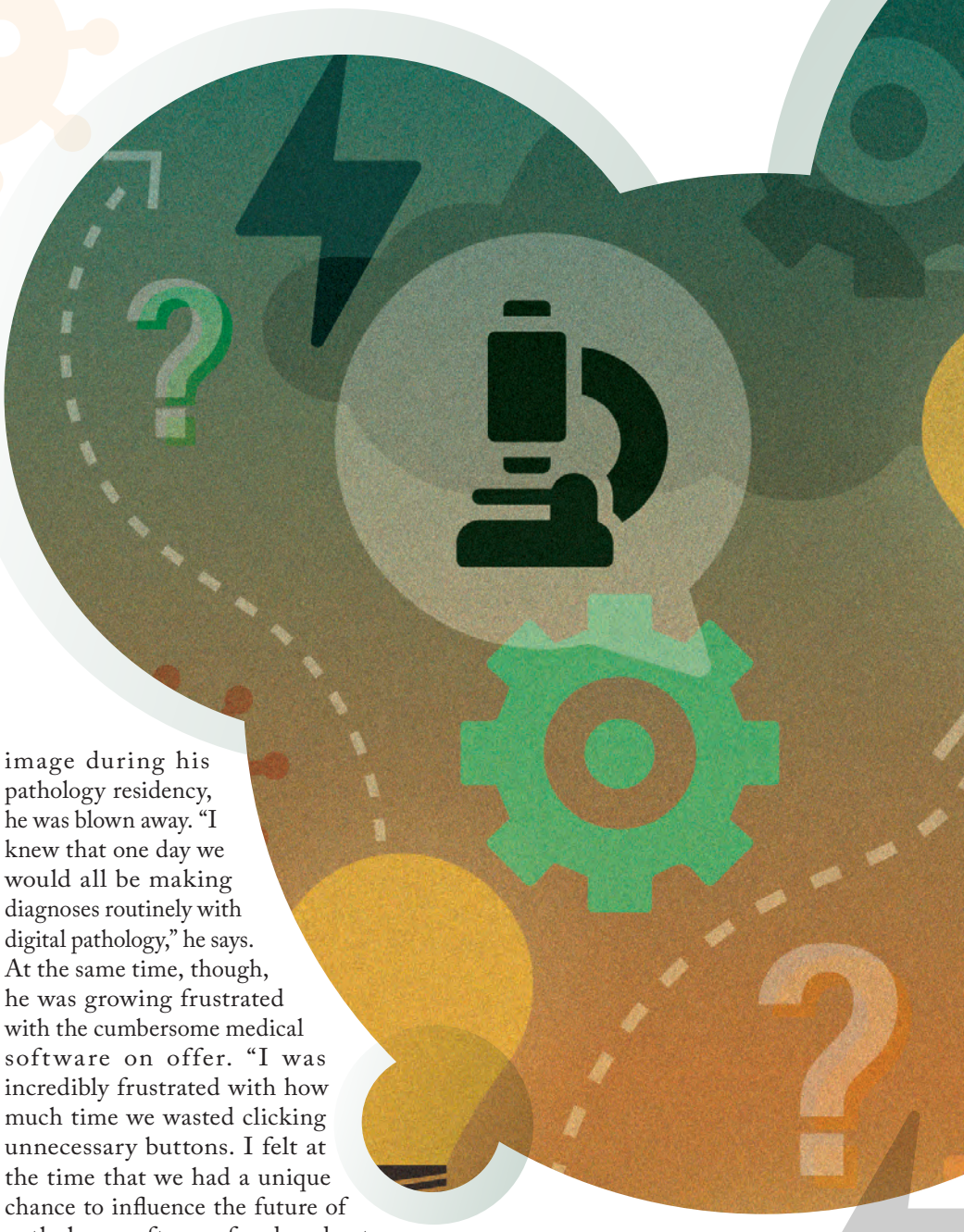
28–30
A Digital Destiny
Although some doubters remain, the value of digital pathology is increasingly being recognized around the world, especially in this post-pandemic era. Digital enthusiasts Jonhan Ho and Sylvain Mailhot review the current state of play and how digital adoption can be encouraged.

31–35
A Vascular Victory?
For decades, researchers have proposed attaching tumor vasculature to treat a wide variety of solid tumor types with minimal risk to the patient – but the effects of antiangiogenic therapies are often transient and the resulting hypoxia can increase tumor invasiveness and metastatic potential. Could lower-dose treatment to induce vascular normalization offer a solution?

A Digital Perspective

The present and future of digital pathology

By Michael Schubert and Luke Turner



Digital pathology is, by now, indisputably the future of the field. Although some are still reluctant to accept its place in the lab – and despite its slow adoption in many institutions – the digital slide image is slowly replacing the glass slide on the microscope's stage. The flexibility, accuracy, and potential to deploy ever-improving informatics and image analysis tools make digital pathology an attractive option. But significant hurdles remain nonetheless – the initial expense, disrupted workflows, and altered infrastructure required for implementation prevent many labs from accessing digital pathology's full potential.

However, the onset of the COVID-19 crisis at the start of 2020 only served to highlight some of the key benefits of digital systems. Those institutions with digital pathology enabled their pathologists to better manage workloads and diagnose from the comfort – and safety – of their own home. Regulatory issues can hamper digital adoption – but, as we adapt to the practical consequences of the pandemic, medical and regulatory communities are increasingly analyzing ways to combine slide digitization and the benefits of remote diagnosis. To learn more about the current state of play and where things are headed, we spoke to Jonhan Ho and Sylvain Mailhot, two pathologists with digital experience.

Time for change

When Jonhan Ho first saw a whole-slide image during his pathology residency, he was blown away. "I knew that one day we would all be making diagnoses routinely with digital pathology," he says. At the same time, though, he was growing frustrated with the cumbersome medical software on offer. "I was incredibly frustrated with how much time we wasted clicking unnecessary buttons. I felt at the time that we had a unique chance to influence the future of pathology software for decades to come." One vision for the future led to imperfect pathology workflows forced by bad software; the other to happy and inspired pathologists at work – and Ho wanted to do everything in his power to make the latter a reality.

With the rise of the pandemic, his aspirations were timely. "COVID-19 has really hastened the need for remote learning, and we have shifted all of our teaching to whole-slide images," Ho explains. But, as education becomes increasingly democratized, he noticed a glaring absence – a platform for doctors, especially pathologists, to share their knowledge. To solve that problem, Ho created KiKo – an acronym for "knowledge in, knowledge out." There, pathologists share collections of whole-slide image cases paired with videos and other forms of content. And KiKo is taking off. Recently, the platform hosted its first global digital dermatopathology grand rounds, in which dermatopathologists worldwide shared cases and traded their best tips and tricks.

"Digital pathology empowers the pathologist," says Ho. "We are no longer chained to the location of the histology lab. On top of that, digital

pathology opens up a whole new set of informatics and image analysis tools that we are just now starting to create." He cautions, however, that not all digital pathology software offers a good user experience – and that it's important to impress upon vendors the importance of having dedicated user experience designers on their team.

But is now the right time for a move to digital? Ho thinks so. "Hospital systems will save money with digital pathology by decreasing errors and dynamically distributing workloads," he says. "I am hopeful that, because the pandemic has highlighted the need, regulatory agencies will be more willing to allow pathologists to adopt digital pathology."

Ho's Top Tip: **"Garbage in = garbage out. To get good, clean images, the histology lab must put out good, clean slides."**

Demonstrating digital desirability

After Sylvain Mailhot first experienced digital slides during the Laval University virtual slide telepathology project, he realized its unlimited potential and was sure that the field would be fully digital within five years. Why? "You have immediate access to colleagues anywhere on the planet. You can transfer them the files and quickly obtain a second opinion," explains Mailhot. "It can also be difficult to physically locate slides when required, so being able to access them immediately on a digital system saves a lot of time." Mailhot also believes that digital pathology is more ergonomic than the traditional setup, with digital slide viewers offering a more comfortable working experience than sitting hunched over a microscope.

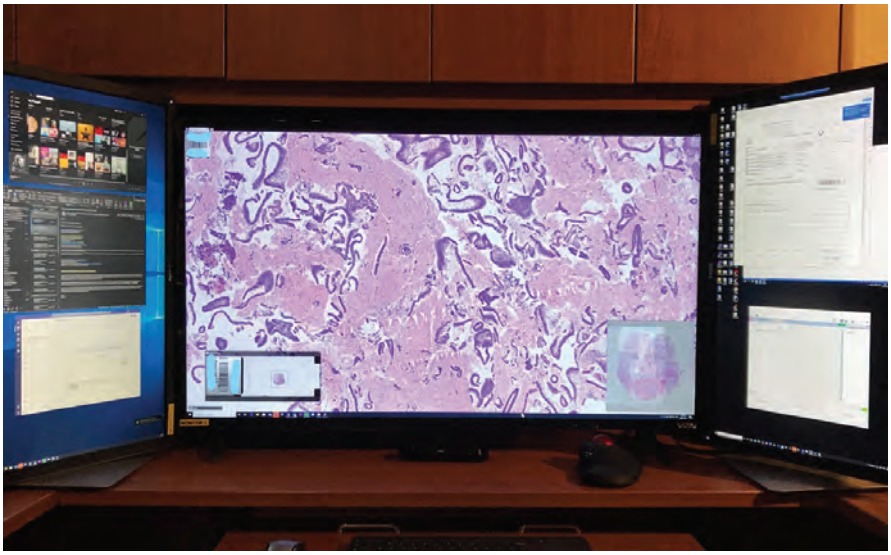
But why has digital pathology not been embraced fully across the field as Mailhot anticipated a decade ago? "Based on my experience working with digital slides and discussions with others across Canada and the US, the major obstacle to digital pathology is the resistance of the pathologist," he says. Mailhot believes that, for digital adoption to succeed, the number of pathologists who are interested in, and enthusiastic about, digital pathology must reach a critical threshold. He acknowledges that there can be stumbling blocks when it comes to digital implementation – but none are impossible to overcome. "There is a lag between the production of the slides and the digital image when scanning your own slides, so it's important to devise a system for prioritizing important slides," Mailhot explains. "There will also be times when you are disappointed with the quality of the digital image, which is why we manually pre-scan all slides to detect any out-of-focus areas."

It's partly thanks to digital pathology that Mailhot's lab has successfully adapted to the challenges of COVID-19. With no on-site work permitted during lockdown, the ability to diagnose cases digitally meant that pathologists could operate from the safety of their homes. Mailhot also highlights the workflow benefits in the event of illness. "If one pathologist cannot work, I can immediately resend the slides to a different pathologist on the system. Before, I would have had to go into their office to physically retrieve and redistribute the slides."

"Digital pathology empowers the pathologist. We are no longer chained to the location of the histology lab."

Given the current rate of adoption, how does Mailhot propose to convince the doubters that digital pathology is the way forward? "Some pathologists have the misconception that digital slides will never look as good as glass under a microscope – and that they take more time to navigate. To prove that this isn't the case, it's important to show these people digital slides on a high-quality screen using an advanced system to demonstrate image quality and ease of use." Once people are on board, Mailhot believes the second step to successful implementation is to work closely with the IT department. It's not only a question of having a great image, he says, but also of having sufficient

The digital pathology workroom.



The pathologist's workstation.

storage and network facilities to support a seamless digital system.

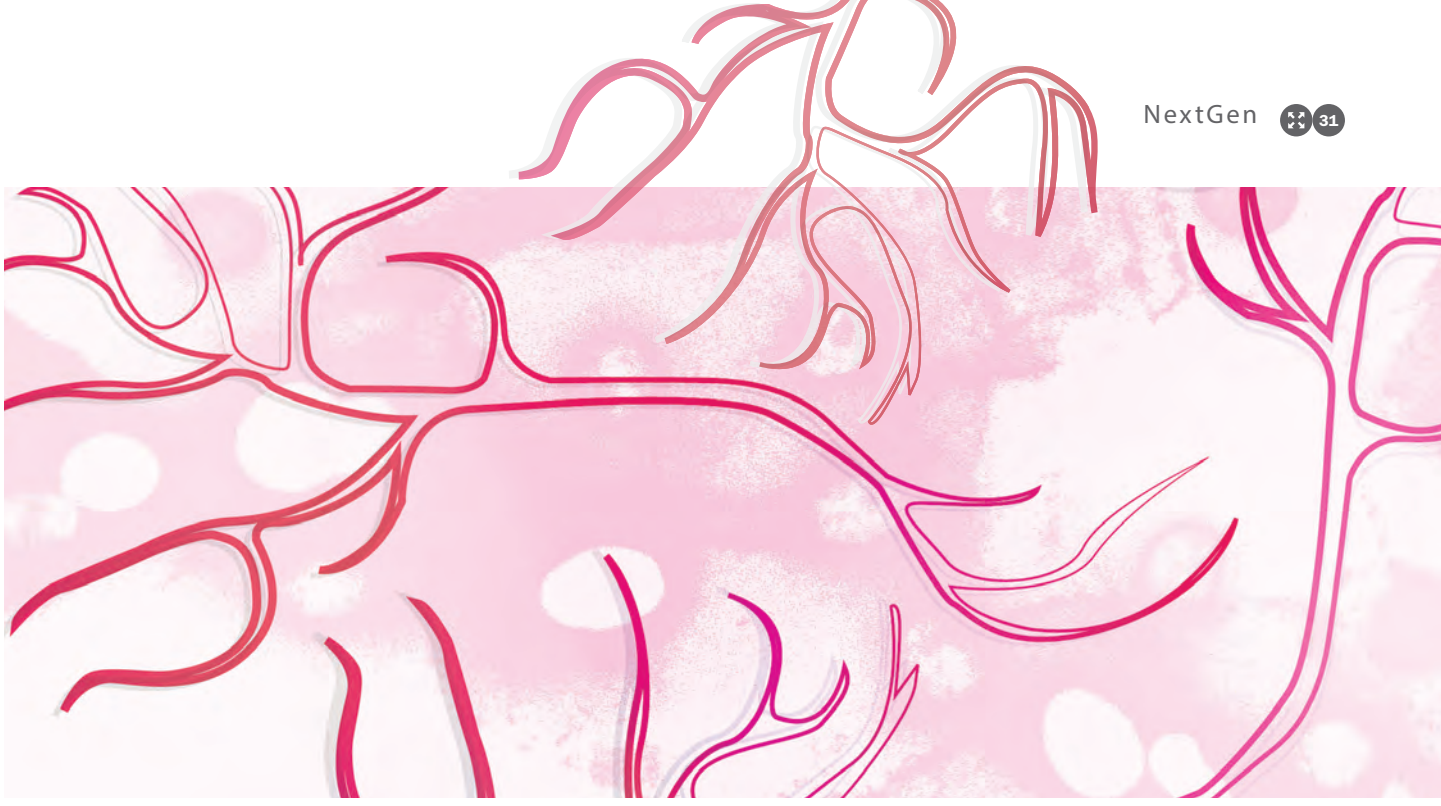
Although the transition to routine digital diagnosis can be costly for institutions at the outset, Mailhot believes that the long-term savings make it worthwhile. Consolidating digital slide production to one site, distributing slides digitally, and improving slide organization will all save money and time in the long run. "Looking further into the future, I think that sophisticated artificial intelligence (AI) tools will force laboratories to go digital," says Mailhot. "Once the early promise of AI is realized, pre-screening slides into categories will save both time and money."

After scanning slides and diagnosing them digitally for many years, Mailhot believes that institutions like his have a key role to play. "Labs that have already made the transition will build up experience and expert knowledge – and they need to make sure they pass it on to others to increase digital pathology's value and to help with the transition."

Mailhot's Top Tip: **"I think people have misconceptions about digital pathology. I would advise everyone to try it. Look at slides using a high-quality screen, computer, and scanner, and I think you'll love it!"**

Jonhan Ho is Assistant Professor of Dermatology and Pathology and Director of the Dermatopathology Unit at the University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, USA.

Sylvain Mailhot is Medical Director at PathAssistant Laboratory, Moncton, New Brunswick, Canada.



A Vascular Victory?

Antiangiogenic cancer treatment still holds promise – if we dig deeper into vascular normalization

By Adil Menon

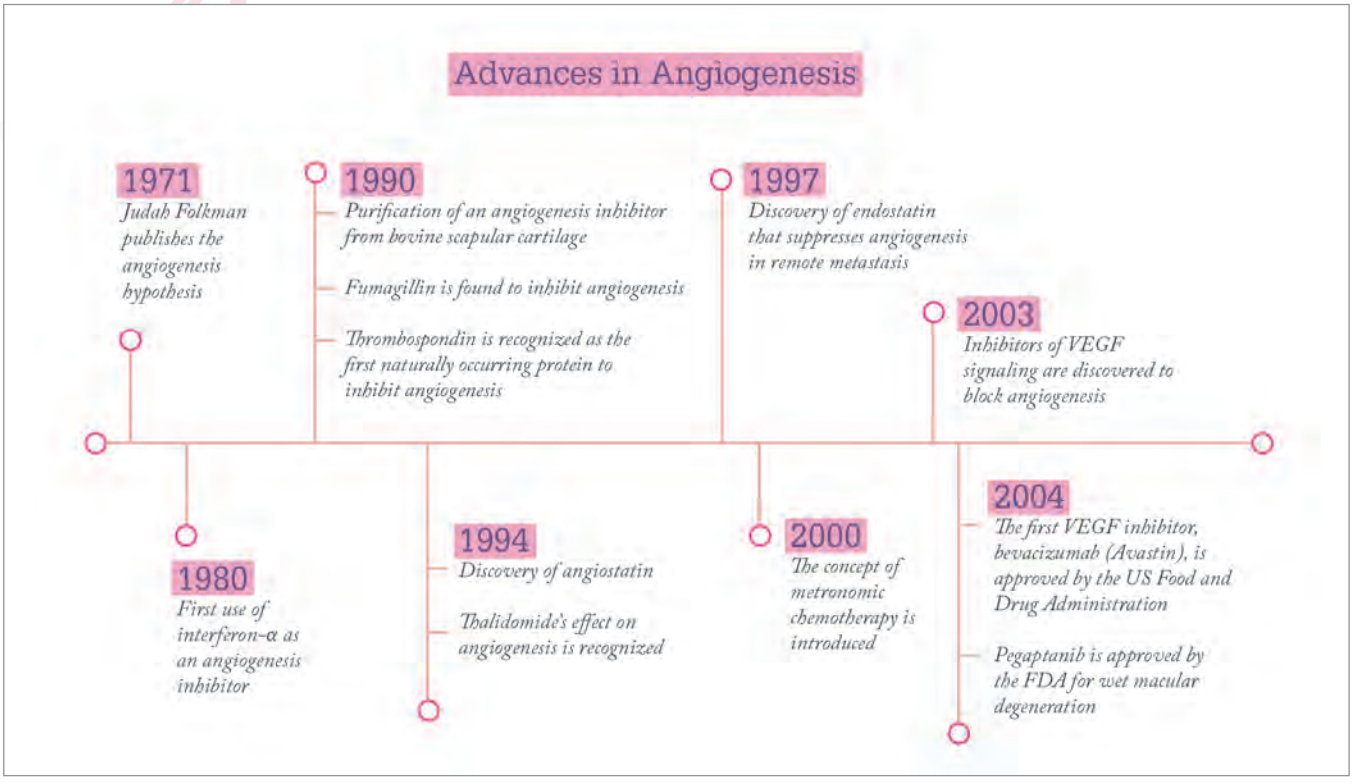
The importance of vasculature for the growth and development of solid tumors has been well established for close to a century. Nonetheless, it was only following Judah Folkman's 1971 discovery of tumor angiogenic factor that researchers began to explore the therapeutic potential of antiangiogenic strategies (1). Folkman and his colleagues coined the term "antiangiogenesis" and believed that, when this strategy could be clinically achieved, it would be "a powerful adjunct to present methods of cancer therapy." They theorized that metastases might not arise from a non-vascularized tumor and that such tumors were more vulnerable to chemotherapy and cell-mediated immunologic attack.

Early promise?

The field of angiogenesis progressed (see "Advances in Angiogenesis") until, in 2004, its theoretical promise became testable with the development of bevacizumab (Avastin), an antibody targeting vascular endothelial growth factor (VEGF) (2). Initially, antiangiogenic agents appeared to deliver on their potential; in the absence of neovascularization, tumors neither grew beyond 2 mm nor underwent metastasis (3). The treatments demonstrated efficacy in many cancer types, including breast, colon, renal, and ovarian – and, in early studies, researchers found no major toxicities (3). In contrast, traditional chemotherapy was characterized by lack of specificity, potential for severe side effects, variable dosing regimens, and development of treatment resistance. As a result, antiangiogenic agents gained appeal and a large number were designed, tested, and made available for clinical use (see Table 1).

As the use of antiangiogenic compounds increased, though, the aura of invincibility began to give way. Cardiovascular side effects – hypertension, conduction abnormalities, QT prolongation, left ventricular systolic dysfunction (LVSD), and even heart failure – were noted, along with risks of bleeding, thrombotic events, proteinuria, leukopenia, lymphopenia, and hyperthyroidism (3). However, the most discouraging clinical observation was the recurrence of more aggressive tumors following a course of antiangiogenic treatment. Research has demonstrated that antiangiogenic drugs can accelerate metastatic tumor growth and decrease overall survival in mice receiving short-term therapy in various metastasis assays (4). Acceleration of metastasis was also seen in mice receiving sunitinib prior to intravenous implantation of tumor cells, suggesting possible "metastatic conditioning" in multiple organs. Similar findings with additional VEGF receptor tyrosine kinase inhibitors suggest a class-specific effect for such agents. In fact, Marta Pàez-Ribes and colleagues found that angiogenesis inhibitors targeting the VEGF pathway demonstrate antitumor effects in mouse models of pancreatic neuroendocrine carcinoma and glioblastoma, but concomitantly elicit tumor adaptation and progression to stages of greater malignancy, with heightened invasiveness and, in some cases, increased lymphatic and distant metastasis (5).

A decade after the advent of these agents, the concept of an ideal antiangiogenic that destroys tumor vessels without harming normal vessels remains elusive. Although it is conceivable that higher doses of currently available antiangiogenic agents could yield complete tumor regression, such doses are



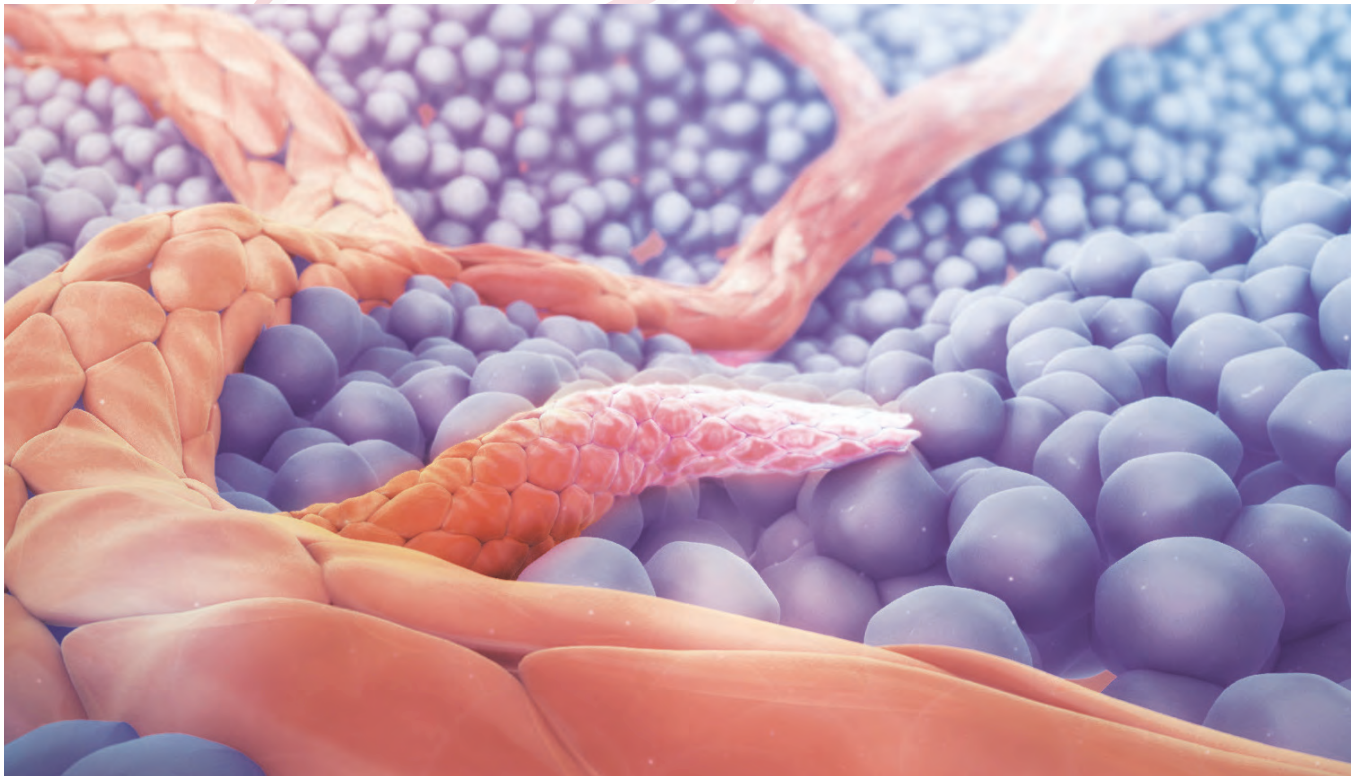
likely to adversely affect the vasculature of normal tissues. Excessive vascular regression is counterproductive because it compromises the tissue delivery of drugs and oxygen (6) – and antiangiogenic therapy is associated with an increased risk of arterial thromboembolic events that could be more pronounced with increased doses (7). Lastly, researchers now believe that supratherapeutic doses or scheduling of antiangiogenic agents might lower tumor oxygenation and drug delivery – antagonizing, rather than augmenting, the response to radiotherapy or chemotherapy. This delicate balance between normalization and excessive vascular regression emphasizes the need for careful prescribing of antiangiogenic agents.

A new approach: vascular normalization

To avoid the pro-metastatic and other deleterious impacts of antiangiogenic therapy while enhancing the efficacy of combination therapy, antiangiogenic compounds can be used at low dosage to induce vascular normalization (8). Two murine breast cancer models have empirically demonstrated that lower doses of anti-VEGF receptor 2 (VEGFR2) antibody induce breast tumor vascular normalization (9), including a more homogeneous distribution of perfused tumor vessels, an increase in pericyte vascular coverage (PVC), and a decrease in hypoxia.

The potential benefits of vascular normalization as a treatment strategy have been experimentally demonstrated. Tumor vasculature is more complex, dilated, tortuous, hyperpermeable, and disorganized than normal blood vessels. These complex, leaky vessels represent a limiting factor for the efficacy of combination therapy – but normalizing doses of an anti-VEGFR2 antibody helps reverse this phenotype in favor of a more homogeneous distribution of functional tumor vessels.

Not only that, but lower doses are superior to high doses in polarizing tumor-associated macrophages from an immune-inhibitory M2-like phenotype toward an immune-stimulatory M1-like phenotype, as well as in facilitating CD4+ and CD8+ T-cell tumor infiltration (10). Based on this mechanism, lower-dose anti-VEGFR2 therapy, with T cell activation induced by a whole cancer cell vaccine, may increase anti-cancer efficacy in a CD8+ T cell-dependent manner in both immune-tolerant and immunogenic murine breast cancer models (10). Recently published animal studies using elegant genetic models have also shown that normalizing tumor vasculature can improve anti-tumor immunity. In a spontaneous pancreatic insulinoma mouse model, RGS5 deficiency normalized tumor vessels, increasing PVC and perfusion, which in turn led to increased delivery of adoptively transferred T cells and improved survival (11). In a more recent study, overexpression of the histidine-rich



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glycoprotein (HRG) induced a normalized vessel phenotype in solid tumors, evidenced by increased PVC, greater perfusion, and reduced hypoxia (12). Together, these findings show a mechanistic link between vessel normalization and enhanced immune cell infiltration and function.

The clinical challenge

Despite enormous theoretical and experimental support for vascular normalization, effectively achieving it in the clinic remains complex and daunting. Perhaps the clearest hurdle is the need to achieve a delicate balance between normalization and excessive vascular regression. Such a precise approach requires careful selection of the dose and administration schedule for antiangiogenic agents (9). Tumors are also highly heterogeneous, so each one requires that we target different proangiogenic factors at different times to induce vascular normalization – and the optimum dose varies by patient and by disease status, so generalizing is impossible. A reliable biomarker would serve a central role in helping to choose a "vascular-normalizing" or "pruning" dose – but identifying such predictive biomarkers remains difficult; after all, we must first elucidate the mechanism of action, which is poorly understood for currently approved antiangiogenic agents

Another challenge in developing effective biomarkers is establishing adequate criteria for response – especially problematic for antiangiogenic agents, which target the stroma. The standard lesion size evaluation may not optimally assess treatment response, particularly in monotherapy with agents such as sunitinib or sorafenib. Anti-VEGF therapy has primarily cytostatic effects, might prune and normalize the tumor vasculature, and can have substantial systemic effects (such as modulation of circulating proangiogenic and proinflammatory cells and cytokines). These effects might stabilize, rather than shrink, the tumor.

The schedule of drug administration matters, too. Different types of immunotherapies – for example, whole tumor cell vaccine, dendritic cell vaccine, and adoptive T cell transfer – take different amounts of time to boost anticancer immunity, so we must optimize the schedules of antiangiogenic treatments to achieve the best possible anticancer efficacy.

A further complexity is the existence of a "normalization window" – that is, a period during which the addition of radiation therapy yields the best therapeutic outcome. This window appears short-lived (about six days) and is characterized by an increase in tumor

Name	Nature of agent	Mechanism of action	FDA approval
Bevacizumab	Monoclonal antibody	VEGF and VEGFR	2004 (as first-line treatment for metastatic colon cancer)
			2006 (as first-line treatment with chemotherapy for non-small cell lung cancer)
			2009 (with interferon for renal cell carcinoma)
			2014 (for platinum-resistant ovarian cancer)
Regorafenib	Tyrosine kinase inhibitor	Dual-targeted VEGFR2 -TIE2 tyrosine kinase inhibition	2013 (for metastatic colorectal cancer)
Ramucirumab	Monoclonal antibody	VEGFR	2014 (for gastric and gastroesophageal cancer)
			2014 (for non-small cell lung cancer)
			2015 (for metastatic colorectal cancer)
Sorafenib	Tyrosine kinase inhibitor	VEGFR2, VEGFR3, PDGFRβ, FGFR1, KIT, and RAF	2005 (for renal cell cancer)
			2007 (as first-line treatment for hepatocellular cancer)
			2013 (for differentiated thyroid cancer)
Sunitinib	Tyrosine kinase inhibitor	VEGFRs, PDGFRs, FLT3, KIT, and RET	2006 (for renal cell cancer)
			2011 (for pancreatic neuroendocrine tumor)
Axitinib	Tyrosine kinase inhibitor	VEGFRs	2012 (as second-line treatment for renal cell cancer)
Pazopanib	Tyrosine kinase inhibitor	VEGFRs, PDGFRs, and KIT	2009 (as monotherapy for renal cell cancer)
			2012 (as monotherapy for soft tissue sarcoma)
Vandetanib	Tyrosine kinase inhibitor	VEGFRs, EGFR, and RET	2012 (for unresectable medullary carcinoma of the thyroid)
Lenvatinib	Multiple kinase inhibitor	VEGFR1, VEGFR2, and VEGFR3 kinase	2015 (for recurrent or metastatic thyroid cancer)
Aflibercept	Recombinant fusion protein	VEGF1 and VEGF2	2012 (as second-line treatment for colorectal cancer)

Table 1. Antiangiogenic agents currently approved by the US Food and Drug Administration.
EGFR, epidermal growth factor receptor; FGFR1, fibroblast growth factor receptor 1; FLT3, fms-related tyrosine kinase 3; mTORC1, mTOR complex 1; PDGFR, platelet-derived growth factor receptor; PLGF, placental growth factor; VEGF, vascular endothelial growth factor; VEGFR, VEGF receptor.

oxygenation, which in turn increases the concentration of reactive oxygen species created by the radiation to enhance its efficacy. During the normalization window, VEGFR2 blockade was found to increase PVC in a human brain tumor grown in mice (8).

In short, we face three major challenges in translating therapies based on the vascular normalization model to the clinic.

- Determining which antiangiogenic therapies lead to vascular normalization.
- Identifying suitable surrogate markers of changes in the structure and function of the tumor vasculature – and developing imaging technology to determine the timing of the normalization window during antiangiogenesis therapy.
- Filling the gaps in our understanding of the molecular and cellular mechanisms of the vascular normalization process.

These challenges will take time to overcome – but, in doing so, I hope we will develop novel approaches to enhance cancer treatment efficacy.

Blood as a biomarker?

As noted, to evaluate vascular normalization as a therapeutic tool, we need a biomarker. An ideal biomarker should be reliable, easy to measure, cost-effective, and allow the clinician to both select and follow the patient's response to therapeutic intervention. The ability to identify tumor-specific changes rapidly after treatment may also allow tailoring of therapy to the patients most likely to benefit – and early discontinuation of ineffective treatment in others. Currently, no such marker exists. But without it, could we evaluate vascular normalization by measuring the actual flow of blood to the tumor and surrounding organ? The answer is yes; we can use a PET-CT scanning device for molecular imaging – something we've done in animal models. With a flow tracer like 15O-labeled water, it is possible to measure blood flow in an organ like the liver or breast in humans as well as in model organisms (13).

I theorized the following experimental model to evaluate vascular normalization. Using a murine breast cancer model, it should be possible to measure the degree of flow in the breast with tumor and compare it with the blood flow in the contralateral breast. Due to the hyperemia induced by the tumor, I expect this ratio to be greater than 1. After proof-of-concept in a small population of experimental models, the experiment will move to its next stage. One cohort of animals with breast cancer, treated with standard chemotherapy and fixed dosages of an antiangiogenesis agent, will serve as our control. In the experimental arm, we will use standard chemotherapy, but will adjust the dosage of antiangiogenic treatment based on blood flow imaging data acquired by serial PET scanning. The goal is to normalize the blood flow between the affected and non-affected breasts using blood flow imaging as our surrogate marker for achieving vascular normalization. With serial CT scanning, it should be possible to evaluate the treatment's impact on tumor size, metastasis, and longevity. This will also be a valuable opportunity to evaluate promising biomarkers by assaying them against tumor vascularity. If our experiments succeed, we will have a way of testing the vascular normalization hypothesis – and evaluating how well antiangiogenic treatments work for patients.

Vascular normalization represents a novel way to use antiangiogenic therapies at lower dosages, simultaneously reducing side effects and improving the efficacy of adjuvant therapies. Because of the relatively small opportunity window and the need for careful dosage regulation to balance normalization and inhibition, this approach is difficult to translate to the clinic – but its potential in cancer and a variety of other medical conditions warrants further study. With the development of a more effective biomarker and a standard experimental procedure, we may be able to move vascular normalization from the bench to our patients' bedsides.

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Flu Season in the Time of COVID-19

It's time for a syndromic approach to respiratory pathogen testing – and the BioFire® Respiratory 2.1 (RP2.1) Panel (EUA) can help

An interview with Amanda Harrington

Between the usual respiratory disease season and the COVID-19 pandemic, we can expect more than 20 different pathogens to circulate in the northern hemisphere over the coming months. Combating these diseases and protecting our patients will require creative thinking, focused effort, and a sensitive, specific testing strategy based on proven technology. One approach is to utilize the FDA Emergency Use Authorized BioFire Respiratory 2.1 (RP2.1) Panel (EUA). It is an available test that offers rapid turnaround times, an efficient workflow, and the potential to detect not only SARS-CoV-2, but also co-infections. To learn more about this tool, we spoke with Amanda Harrington, Associate Professor of Pathology and Laboratory Medicine and Director of the Clinical Microbiology Laboratory at Loyola University Medical Center in Illinois.

How has the pandemic changed your work?

As a clinical microbiologist, I've worked in hospital laboratory medicine for more than a decade. Over the course of the pandemic, I've served as Director of Microbiology at Loyola University Medical Center, which is part of a three-hospital system of Loyola Medicine. Outside of point-of-care testing, our laboratory performs a majority of the COVID testing for our hospital system. My colleagues and I have been neck-deep in this virus – and its effects – ever since it began.

There are no routine days anymore, and the pace of our work has escalated significantly. We've had to focus on COVID-19 testing here in the laboratory and, for better or for worse, we've been doing a lot more logistics and supply chain management than is typical for clinical microbiology. We're trying to make sure we have the right collection devices and test kits available at all times. Do we ever need to validate an alternate collection device or other testing component, like a different swab? It seems like almost daily – and that hasn't changed since the onset of the pandemic.

Although our COVID-19 testing is operational, it has impacted areas of the laboratory one might not expect. We need alternative strategies not only for COVID-19, but also for routine testing. A lot goes on behind the scenes to keep clinical diagnostics running, and it's all in response to COVID-19.

How has COVID-19 testing changed since the start of the pandemic?

Fortunately, new tools have come to market and more are on the way. Some aspects of the supply chain have stabilized; for example, we have more access to swabs than we did before. We've started to evaluate other specimen sources. What has yet to change is the overall fragmentation of the supply chain, so we're never sure which test is available. It's a daily challenge.

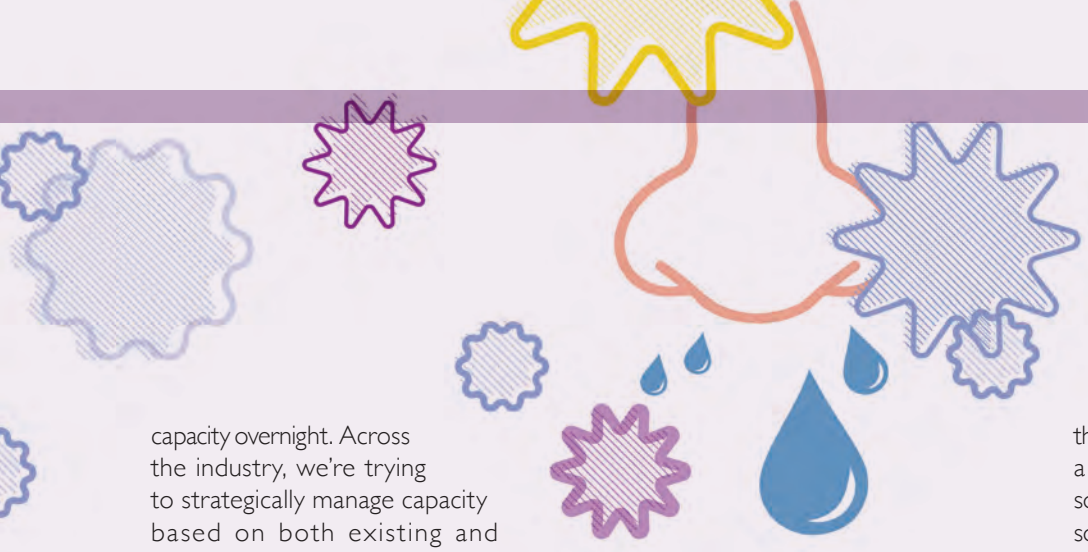
As a result, almost every lab I know has diversified its testing strategy. Offering more than one option is the biggest key to surviving, so many run four to eight different COVID-19 tests. When they can't get supplies for one, they quickly pivot to another or adapt their strategy to compensate.

Initially, we were testing only symptomatic patients. Now, we're beginning to test different populations for surgical procedures as more people return to hospitals for care. The demand for testing has increased – and, now that our students are going back to schools and universities, it will likely increase again.

How do you see the collaboration between labs and vendors playing out?

I applaud our commercial vendors because not every laboratory can produce in-house tests. Many, including ours, rely on industry partnerships and industry-developed tests. The tests that have come to market recently are fantastic.

We have good relationships with our industry partners, so they keep us informed about where they think they're going. Every vendor I've spoken with is doing their best to increase manufacturing capacity. It's difficult because you can't just throw up a building and double your manufacturing



capacity overnight. Across the industry, we're trying to strategically manage capacity based on both existing and expected needs.

When did you begin using the BioFire Respiratory 2.1 Panel (EUA) for COVID-19 testing – and how has it helped you overcome the challenges you've faced?

The BioFire panel is different than many other tests because it's a full, syndromic panel with random access and rapid turnaround. We validated the panel and started using it almost as soon as it was available. We use it in two ways — for situations where a rapid COVID-19 test is needed and for immunocompromised patients. For urgent situations, the fact that I can get test results in just over an hour is a benefit. This test also helps with patient placement in the hospital and care management for our transplant and pediatric groups, who are some of our most vulnerable patients in our hospital. Having a syndromic approach for those patients is a valuable tool, and having COVID-19 on that panel is key.

Over the summer, we were fortunate to have to focus only on single-target testing strategies. But, as the seasonal risk of respiratory disease goes up, we are looking to take advantage of the benefits of a respiratory panel. Without it, we won't know if patients are presenting with symptoms of influenza, metapneumovirus, COVID-19, or some combination of communicable respiratory diseases we confront every year in the colder months. Having one comprehensive diagnostic test to provide those answers is very efficient.

Could you provide more detail on the accuracy, turnaround times, and workflow of the panel?

The short turnaround time and the fact that it's not a batch-based test makes the workflow efficient. Test results are rapid. In terms of accuracy, the panel has performed very well in laboratory comparisons with our other COVID-19 tests – and equally so when testing for other respiratory viruses.

Another feature we take advantage of in our laboratory is that our instrument interfaces directly with our laboratory information system. It saves time and effort because the results transfer seamlessly (eliminating delays from entry). It's very easy to set up and the automatic transfer simplifies our workflow.

Why is it so important to detect co-infections?

That's a significant issue for specific patient populations and one example is our pediatric group. They group their patients into cohorts based on the presence of different viruses to prevent co-infections. We're not sure what co-infection will look like in the USA. Studies from China and elsewhere – including one from Chicago at the onset of the pandemic – have indicated variable prevalence, but we don't know how that will play out as we move through respiratory illness season. The BioFire panel helps us detect sources of potential co-infection, and that's something we're concerned about right now as respiratory season approaches. One of our Master's program medical laboratory scientists will be looking at this as her capstone project this flu season, so we'll see what the data show.

In a traditional flu season, we do see co-infections, but it's impossible to say what this year's respiratory illness season will be like. We've been watching the data out of Australia and haven't seen a lot of flu circulating. Is that the result of social determinants like mask-wearing and social distancing? Will those interventions suppress the circulation of other respiratory viruses or will we see a more traditional respiratory season again? Without the kind of data this panel provides, we really cannot predict that. As an additional benefit, BioFire aggregates submitted data to show what's circulating across the regions; that will be really interesting.

How exactly will the panel be used through the winter flu season?

In past flu seasons, we've offered the BioFire Respiratory Panel to our emergency department and to our hospitalized patients. This year, based on demand due to COVID-19, we're restricting it to our intensive care patients, our pediatric population, and our immunosuppressed population. We have to be strategic about utilization so we can keep up with demand throughout the season.

COVID-19 has taught me that predicting the future is impossible and you need the right tools. All we can do is assemble our tools and a game plan – and then three or four backup plans. This virus has forced us to think outside the box, to be more adaptable, and to use all of our tools, sometimes in unconventional ways. We're happy to have access to BioFire's panel as one of the tools to help diagnose COVID-19 and other respiratory illnesses, because such tools allow us flexibility and provide information that is necessary to help us improve patient care – and that's why we're here.

Dr. Harrington's statements are not an endorsement of BioFire products. She was not compensated for participating in this interview.

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40–44
Laying a #Path2Path
A group of pathologists, fellows, and residents discuss how they built a social media initiative to bring medical students into pathology – and how such efforts can help the discipline succeed.

Laying a #Path2Path

Leading medical students to pathology

By Dana Razzano, Yonah C. Ziemba, Christina A. Arnold, Xiaoyin "Sara" Jiang, Adam L. Booth, Kaitlin Sundling, Valerie A. Fitzhugh, Nicole D. Riddle, Kamran Mirza, Jerad M. Gardner, Amy Deeken, Maren Fuller, Kalpana Reddy, and Daniela Hermelin

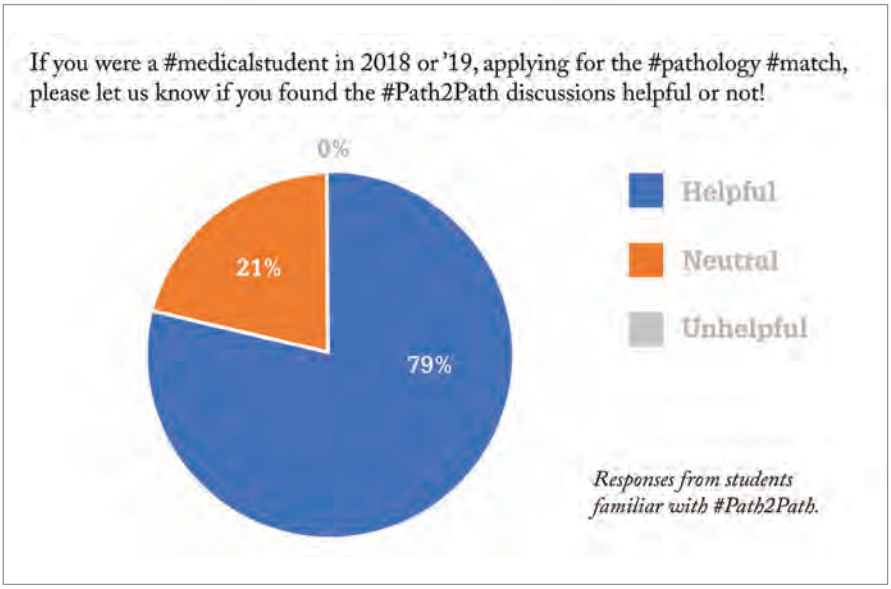

Figure 1. Results from a Twitter survey gauging the helpfulness of the first three #Path2Path Twitter chats.

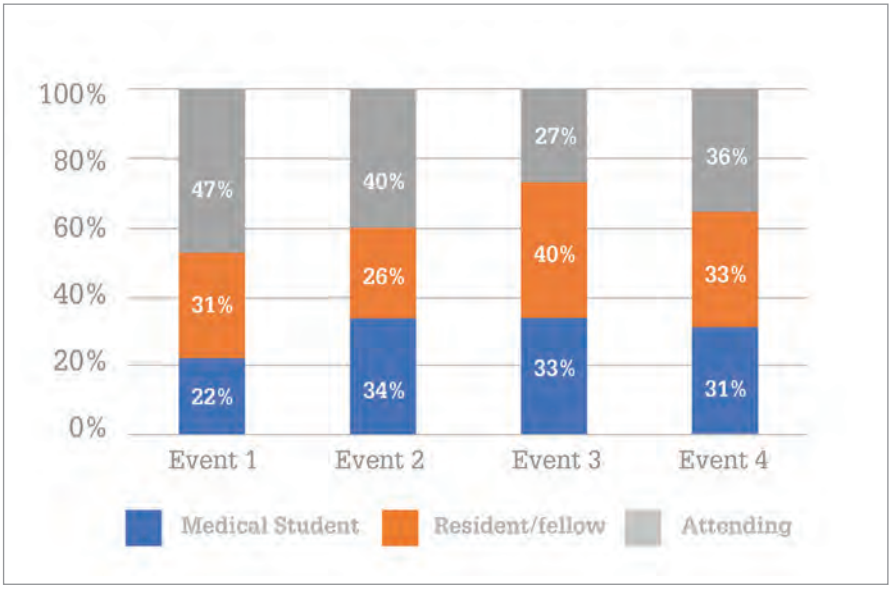

Figure 2. #Path2Path event attendance by career stage.

Although a career in pathology and laboratory medicine has never been the most popular choice for medical students, recent years have demonstrated an alarming downward trend (1). There are many possible reasons medical students avoid pathology. Negative stereotypes about the field may potentiate the problem (2). Lack of exposure to the real-life practice of the specialty during medical school (because a pathology clerkship is not required) doesn't help. Concerns about the job market have also been reported as a potential deterrent (3). Although some students are highly informed about pathology and actively choose the field, effective recruitment strategies will give those who are uncertain about their choice of specialty adequate opportunities to explore pathology. Improving the visibility of pathology and lowering the barriers to learning more about it may also increase the number of applicants from underrepresented groups. And even students who don't ultimately choose pathology will become doctors with a better understanding of our field.

In 2018, a team of pathologists, fellows, and residents ("Team Pathology") formed to create #Path2Path, a social media initiative to counter negative messages about careers in pathology. The team hosts a series of "Twitter chat" events to expose medical students to the online pathology community and career possibilities in the field. The inspiration came from a similar outreach effort by the virtual radiology community – a Twitter chat event called "#6StepstoRad" aimed at recruiting medical students to radiology (4).

Team Pathology's goals were to reach out to the medical student community on Twitter and help inform anyone that might be considering pathology as a career. We wanted to foster a positive, supportive medical culture – and, at the same time, dispel negative stereotypes and misconceptions about our field.

Figure 3. #Path2Path social media impressions by event.

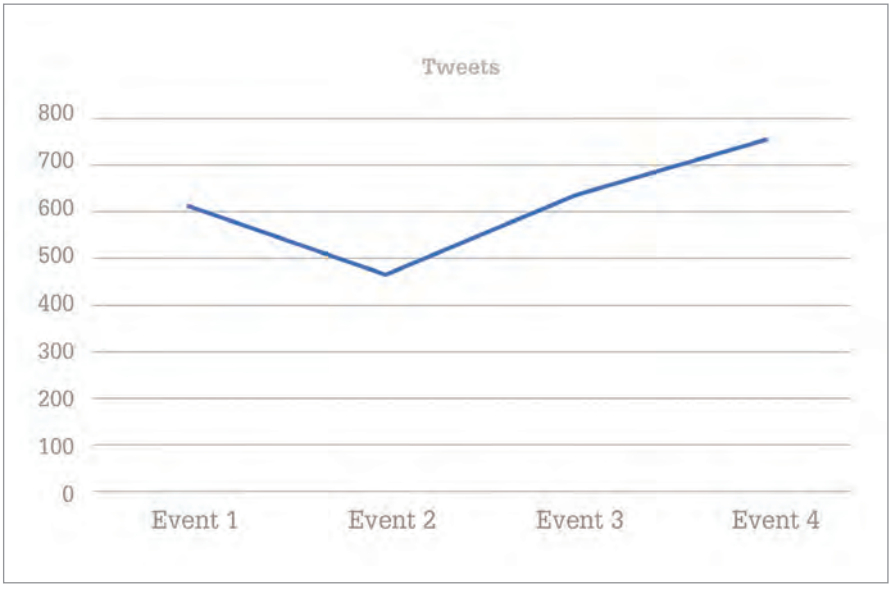

Figure 4. #Path2Path tweets by event.

"We wanted to foster a positive, supportive medical culture – and, at the same time, dispel negative stereotypes and misconceptions about our field."

How did we do it?

#Path2Path is a series of Twitter chats hosted by the pathology community to reach the virtual medical student community. A Twitter chat is designed as i) a real-time conversation through incorporation of the hashtag #Path2Path and ii) a repository of information accessible by searching for the #Path2Path hashtag.

Between 2018 and 2020, four events were held. The chats were advertised on Twitter, on the Path2Path website *(path2path.net)*, and in various pathology student interest groups throughout the USA. The first two were pathology-focused residency and career question-and-answer chats; the third focused on preparing for the pathology match and interview process; and the fourth focused on the pathology match and choosing the best program. All four events were organized and hosted by the #Path2Path group, who also prepared questions to stimulate and guide conversation. However, spontaneous questions were also welcomed, and all questions were answered in a real-time public forum to be accessed on the #Path2Path Twitter thread.

Many residents, fellows, and attendings participated in the events – and now, the #Path2Path hashtag is so popular that individuals and pathology organizations use it to communicate other pro-pathology content.

Did it work?

Reaching out to medical students on Twitter was a fun and productive experience for everyone involved. Many medical students from around the world joined the events, and tweets tagged #Path2Path generated impressions in the millions. Medical students

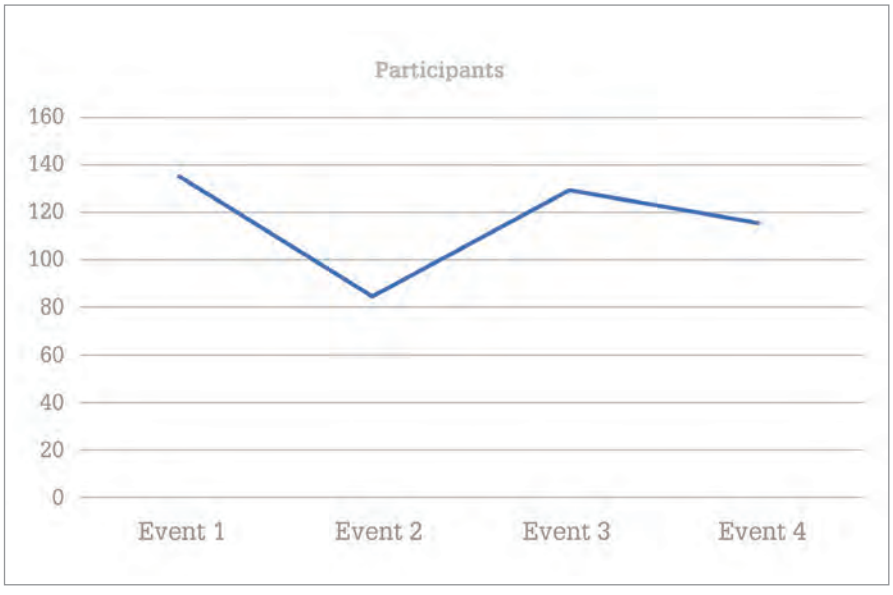

Figure 5. #Path2Path participants by event.

and pathology match applicants interacted directly with pathologists, fellows, and residents, often asking specific questions unique to their application process.

An informal survey querying the helpfulness of events received mostly positive responses (see Figure 1) – and, anecdotally, many members of the pathology community who joined in to reach out to the medical students reported that it was a positive, enjoyable community-building experience.

Due to the public nature of social media, #Path2Path Twitter events could purpose our mission on a number of levels in synchronous motion. First, medical students who may not have the opportunity to visit a pathology

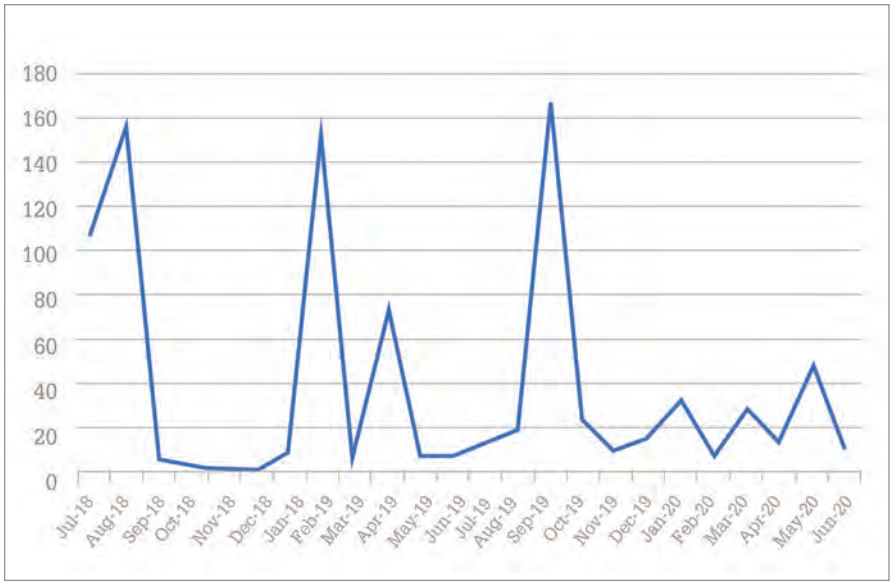

Figure 6. #Path2Path website views over time.

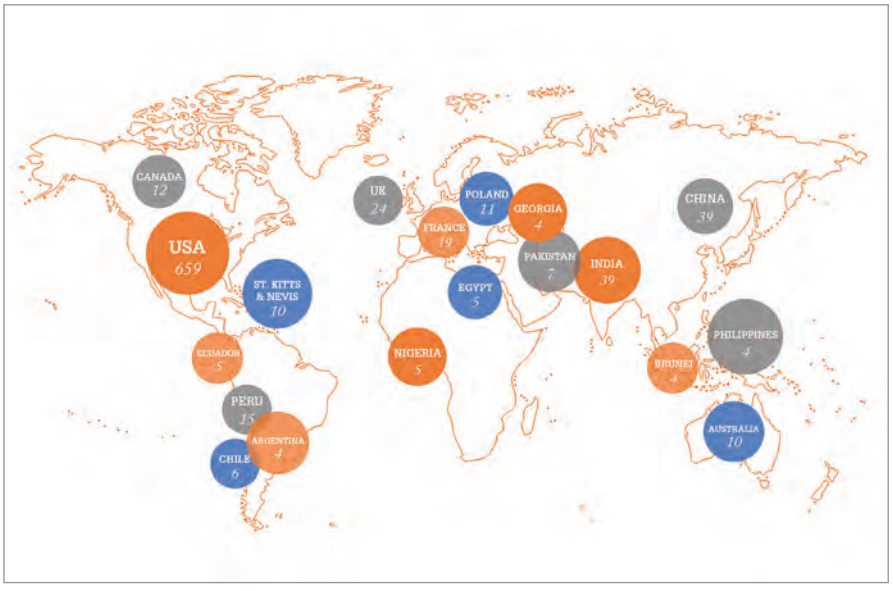

Figure 7. #Path2Path website views by location.

department had a window into the collegial working dynamics and warm interactions between colleagues, peers and participants. Furthermore, these students have direct access to experts and trainees, alike, breaking down any archaic professional hierarchies, while generating an inclusive and accessible atmosphere, both within the virtual space and bricks and mortar space.

Team Pathology's efforts are focused on supporting medical students in exploring and possibly choosing a career in pathology and laboratory medicine. Through our #Path2Path events (see Figures 2–7), we fostered curiosity, freely educated students about our field, demonstrated our warm and collegial community spirit, and joined others who are already advocating for this cause.

"Through our #Path2Path events, we fostered curiosity, freely educated students about our field, demonstrated our warm and collegial community spirit, and joined others who are already advocating for this cause."

Now what?

We need to work harder at recruiting students into pathology – a need that has prompted outreach efforts from major pathology organizations. The College of American Pathologists launched a resource-rich webpage aimed at medical students considering pathology (5). The American Society for Clinical Pathology created an Ambassador Program to encourage contact between medical students and the laboratory medicine community (6). And the Association of Pathology Chairs developed a Pipeline Development

Council to focus on increasing the number of students entering the field.

Individual pathologists are also working hard on recruitment. Elizabeth Morency has debunked the myths that surround our discipline (7). Kamran Mirza works with medical students to advocate for a universal pathology clerkship to help broaden medical education and bring more talent to the field (8). In response to the COVID-19-related restrictions disrupting pathology electives, Mirza and Cullen Lilley created a virtual pathology elective rotation for students to access online. Others, like Rick Mitchell, have written to advocate for the field of pathology, encouraging medical educators to provide more exposure (9).

Through these combined efforts, we hope to see more trainees pursue pathology – not just because of the pressing need for more pathologists, but we also want to provide every opportunity for students to be exposed to pathology and learn about the potential of pursuing our amazing field.

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Diagnosing Cancer With Confidence

How bringing AI into the laboratory workflow can benefit both pathologist and patient

An interview with Filippo Fraggetta

What does digital pathology mean to you?

Even though the term "digital pathology" has been gaining momentum over the years, digital pathology is just pathology. It is how we implement it into our own laboratories that matters. Back in 2015 we made the shift to a digital workflow and incorporated artificial intelligence (AI) into our toolbox to help manage our increasing workload.

How did you approach this?

With an array of innovative AI tools, it can be difficult to know where to begin. A good first step is to understand how a given tool can help improve an existing diagnostic process. We approached ContextVision about its AI tool for prostate core needle biopsies and we quickly understood how INIFY Prostate Screening could fit into our digital workflow – and we also saw the improvements it could bring.

We were also impressed with a simple, but important choice INIFY presents: you can ask to be pointed in the right direction before manually making a diagnosis – or you can choose to approach the diagnosis yourself before checking the tool's suggestion. For those who take pride in the confidence of their assessments, rest assured this is not a forced diagnosis; rather, you have the freedom to simply consider the suggestion alongside your own opinion and expertise. Quality patient care is at the heart of our work and that freedom of choice has proven valuable in our laboratory. For example, consider a case that was going to be signed off as negative for cancer until an AI tool caught suspicious areas the human eye had missed… In fact, the pixel accuracy outline of suspicious cancer areas is a unique feature of INIFY – and provides an extra boost of confidence in making a diagnosis.

What are the cornerstones of using AI tools in pathology decisions?

It is an "all or nothing" approach. To reap the full benefits of an AI tool within your workflow, LIS integration is key. A standalone tool forces you to step outside your workflow to receive results, interrupting the efficiency of the process. We worked closely with ContextVision and our LIS vendor, TESI, to integrate INIFY into our LIS. We also realized that the quality of support from the providers is just as important as the product itself. Just as patients want to feel listened to by their doctors, pathologists want to feel listened to and have impact on the people who supply their tools! Today, the LIS automatically recognizes the prostate biopsy samples we scan and sends INIFY a link to the digitized whole slide images – and then we receive an answer that highlights and quantifies any suspicious areas. When time is working against the patient on the other side of the sample, the importance of efficiency throughout the process cannot be underestimated.

What do you think the future holds for pathology?

In the past, if you wanted a second opinion from a colleague, you had to walk down the hall and show them the slide. With a digital workflow, the process is streamlined within the hospital – and it doesn't stop there. Pathologists have long faced the isolation of working in a laboratory. A digitized future offers us the ability to work remotely without feeling alone – knowing there is a pathologist in another hospital, perhaps in another country, who is working with you on your case. A collaborative approach that joins up pathologists across the world and accesses the power of AI is the future of pathology. And, for some of us, the future has already arrived.

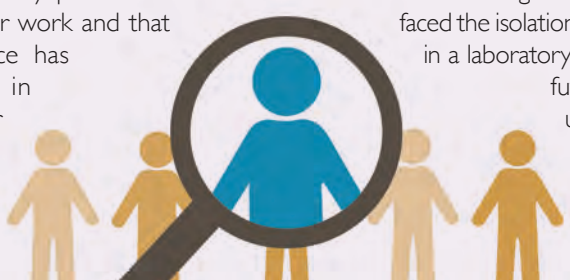
A shortage of pathologists does not have to equal a shortage of resources. It's time for pathology departments to embrace the digital future with workflows that support the pathologist every step of the way. To pathologists who are still skeptical about implementing digital pathology, I usually say: try out a digital workflow and see for yourself the benefits it can bring to your laboratory. In my experience, once a pathologist gets a taste of AI and a digital workflow, they never look back. That's the beauty of digital and of tools like INIFY – they will make you question how you were ever efficient with a manual workflow.

What benefits do you see from this change?

Justifying the cost of a digital transition can be a barrier to change in some hospitals – but the true return on investment is measured in the benefits it brings to patients. My view: if we can improve the quality and speed of diagnosis, we should do so – no matter the cost. But let's not forget that putting patient needs first also confers a financial benefit; early, accurate diagnosis and treatment is much more cost-effective than treating an advanced stage of disease.

AI tools like INIFY are here to shape digital pathology, helping us tackle the key issues we face as a profession, while still placing us – and our patients – at the heart of the solution.

Filippo Fraggetta is the Director of Pathological Anatomy at Azienda Ospedaliera per l'Emergenza Cannizzaro, Catania, Italy.



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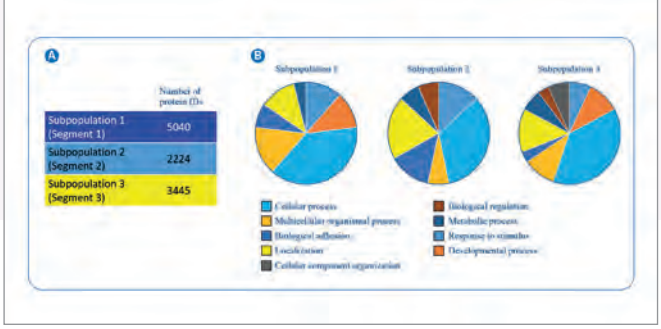

Figure 1. Proteomics of tumor subpopulations and biological process characterization. Proteins from microdissected tissue (approx 160 ng) were extracted, digested with trypsin, and peptide extracts were run on the timsTOF fleX using PASEF. Number of protein IDs per tumor subpopulation segment A and biological process characterization per segment as revealed by PANTHER B.

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Learn more about new SpatialOMx workflow and its powerful approach in identifying distinct proteomic profiles for different tumor subpopulations in breast cancer: https://www.bruker.com/products/mass-spectrometry-and-separations/lc-ms/o-tof/timstof-flex.html

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The shift to digital pathology will require pathology departments to create flexible and stable ergonomic workspaces that accommodate both a digital pathology viewer and a microscope. As other digital clinical departments have discovered, a well-designed workspace also facilitates collaboration and teaching and maximizes the use of space.
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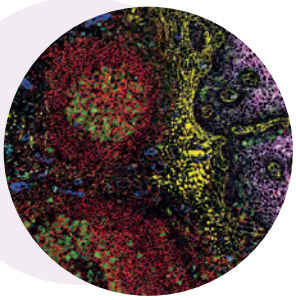

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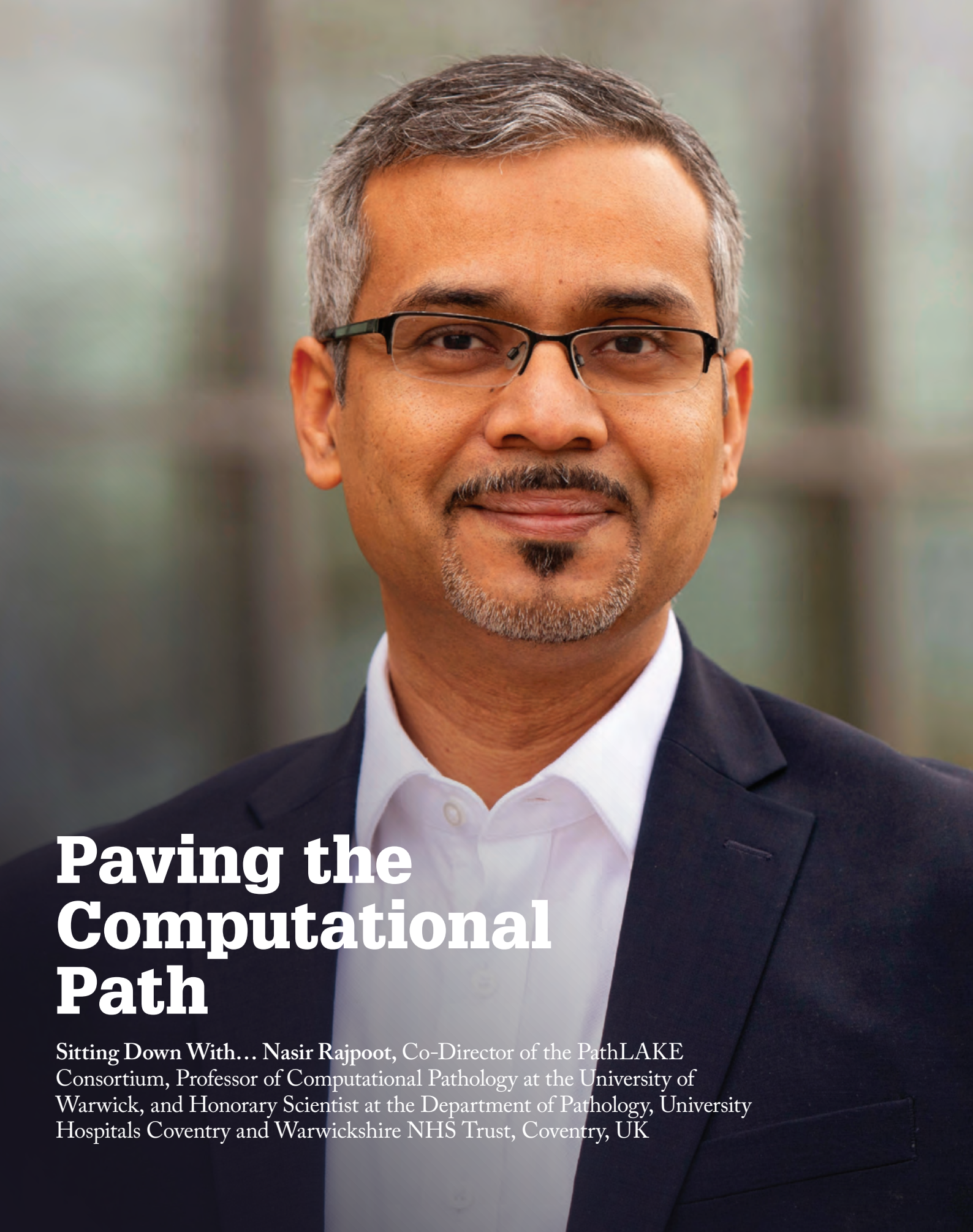

Paving the Computational Path

Sitting Down With… Nasir Rajpoot, Co-Director of the PathLAKE Consortium, Professor of Computational Pathology at the University of Warwick, and Honorary Scientist at the Department of Pathology, University Hospitals Coventry and Warwickshire NHS Trust, Coventry, UK

How did you get into digital pathology?

I was visiting a collaborator in the Yale University applied mathematics department in 2002 when he shared some multi-spectral images of colon histology sections for me to look at; It was fascinating to see nuclear and subcellular level details in those images. I did some initial image analysis on them using texture and morphological descriptors and found it amazing that one could differentiate between normal and cancerous features based on digital descriptors. I have been glued to pathology images since. After my return from the US, I initiated collaborations with other colleagues in the UK and Germany to work on pathology images myself before digital scanners were available – and before it became known as "digital and computational pathology."

In 2008, we organized a computational histopathology workshop at the International Symposium for Biomedical Imaging; to the best of my knowledge, it was the first international meeting on computational pathology. A unique opportunity then came along in December 2010; a US slide scanning manufacturer looking for a demonstrator site and center of excellence in the UK chose Coventry and Warwickshire Hospital, at least partly due to our existing humble track record in digital pathology. That led to what still remains the world's largest validation study on digital pathology for primary diagnosis, published in Histopathology 2016. The Coventry pathology lab became the first UK hospital pathology laboratory to do live reporting on digital slides and I was fortunate enough to be involved in that stellar effort, led by Ian Cree, from day one. That was a real turning point for us because it generated tons of imaging data being digitized on a daily basis. Today, most of the histopathology reporting in the lab is done digitally.

Over the last few years, we have focused on gaining insights from the billions of raw pixels in each of the digitized tissue images for large cohorts of cancer subtypes to discover new markers for predicting survival, clinical outcome, and response to therapy. And we are now developing machine learning algorithms that can reveal histological signatures that may not be recognizable by the naked eye, with a view to guiding diagnosis and treatment.

What is PathLAKE – and what do you hope to achieve?

PathLAKE is a national center of excellence for artificial intelligence (AI) in pathology that will house a large-scale data lake – a centralized and accessible repository of clinical pathology imaging data for AI researchers. It involves sourcing high quality annotations from pathologists, which will be made available with the pathology images together with linked clinical metadata. Such resources will be unquestionably key for training high-quality AI algorithms for further downstream analysis. A unique aspect of PathLAKE is that it not only allows you to access data for research and AI innovation purposes, it features an in-lake central analytics engine to allow you to conduct experiments within the data lake; for example, if you don't have sufficient computational resources or storage.

How will accessible data affect the adoption of digital and computational pathology?

I think making large data repositories available to researchers and industrial players will be critical in further driving AI innovation. It will help accelerate the development of algorithms that will solve some of our most fundamental problems and optimize their solutions. It will also help us to make new discoveries – allowing us to stratify patients into previously unknown subgroups.

Right now, it's a little early to see the direct impact of computational pathology on patient healthcare, as I don't believe many algorithms have been adopted in clinical practice. But it is coming. Several hospitals in the UK are now in the process of being digitized. The recent £13 million awarded to PathLAKE Plus will further digitize several more hospitals in the UK and road-test some of the AI solutions in a clinical setting.

What does the future hold for computational pathology?

I believe the key game-changer will be data repositories that simplify the development of algorithms for machine learning researchers. You won't need to put together your own datasets, which requires a huge effort in itself, before you can develop cutting-edge algorithms that can push the state of the art and make translational impact. That's the philosophy we are following with PathLAKE. There's so much that can be achieved when you make data and computing resources available to smart, young people who are quickly bringing themselves up to speed with the latest deep-learning technologies.

What advice would you give to trainees who have an interest in computational pathology?

Try to be brave through the initial daunting experience and don't hesitate to jump into what may seem like an unknown territory. It's only by crossing the boundaries of disciplines that you are going to make a true difference and impact. Some of the best ideas come from people working in other domains that bring new perspectives into the field. These people are future leaders – not the ones who are comfortably sitting in their own space and sticking to what they are happy with, but those who are willing to step outside of their comfort zones.

And a take-home message for pathologists?

Change is coming your way, but it's change for the better. Embrace it and be adaptable rather than resisting it, because digital and computational pathology is the future. We are all going to have to live with that or else risk becoming dinosaurs.

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