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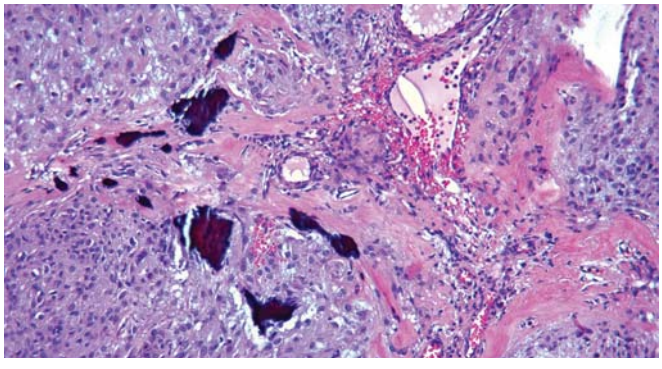
Case of the Month

A 70-year-old woman underwent hysterectomy and salpingo-oophorectomy for endometrial adenocarcinoma. The left ovary was enlarged and showed the following macroscopic and microscopic appearance.

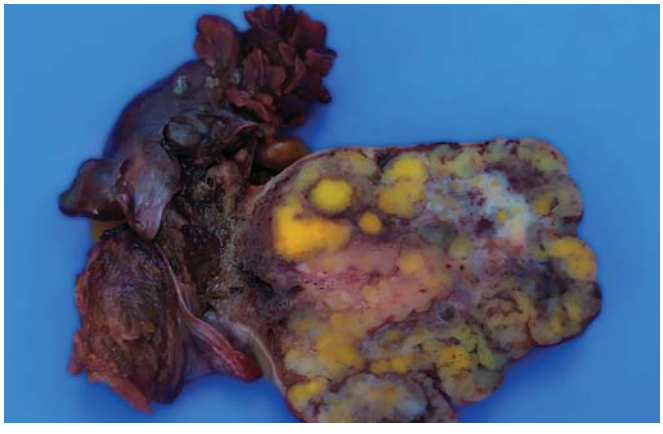
Which of the following immunostains would be most helpful to confirm the diagnosis?

a. *Calretinin*
b. *p53*
c. *CK AE1/AE3*
d. *SMA*



What are these tumors frequently associated with?

a. *Paraneoplastic syndromes*
b. *Estrogenic changes*
c. *Meigs syndrome*
d. *Lynch syndrome*



Answer to last issue's Case of the Month…

B. More likely to obtain deep molecular response with imatinib therapy

Adult patients with CML are more likely to achieve remission with imatinib tyrosine kinase inhibitor (TKI) therapy. Whether children may respond better to second generation TKIs is under investigation. Pediatric patients presenting with CML tend to have a higher white blood cell count and are more likely to present in accelerated or blast phase than their adult counterparts. Both populations often present with splenomegaly, but it may be more noticeable in children.

Courtesy of PathologyOutlines.com. Case by K.V. Vinu Balraam and S. Venkatesan, Armed Forces Medical College, Pune, Maharashtra, India; discussion by Genevieve M. Crane, Weill Cornell Medicine, New York, USA.

To register your guess, please go to http://tp.txp.to/0919/case-of-the-month
We will reveal the answer in next month's issue!

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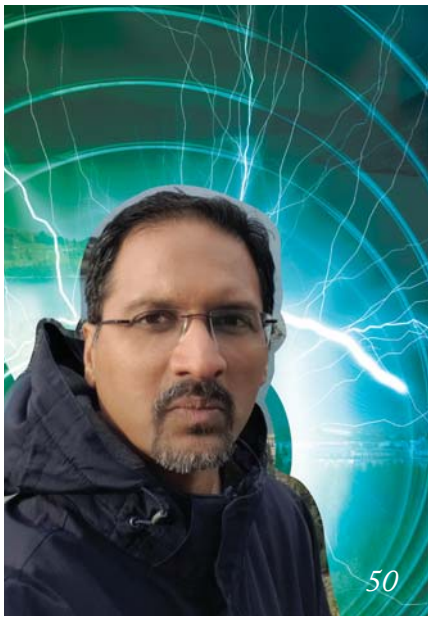

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Editor - Michael Schubert
michael.schubert@texerepublishing.com

Assistant Editor - Luke Turner
luke.turner@texerepublishing.com

Content Director - Rich Whitworth
rich.whitworth@texerepublishing.com

Publisher - Lee Noyes
lee.noyes@texerepublishing.com

Business Development Manager - Sally Loftus
sally.loftus@texerepublishing.com

Business Development Executive, America - Danny Crowe
danny.crowe@texerepublishing.com

Head of Design - Marc Bird
marc.bird@texerepublishing.com

Designer - Hannah Ennis
hannah.ennis@texerepublishing.com

Designer - Charlotte Brittain
charlotte.brittain@texerepublishing.com

Digital Team Lead - David Roberts
david.roberts@texerepublishing.com

Digital Producer Web/Email - Peter Bartley
peter.bartley@texerepublishing.com

Digital Producer Web/App - Abygail Bradley
abygail.bradley@texerepublishing.com

Audience Insight Manager & Data Protection Officer - Tracey Nicholls
tracey.nicholls@texerepublishing.com

Traffic & Audience Database Coordinator - Hayley Atiz
hayley.atiz@texerepublishing.com

Project Manager – Webinars - Lindsey Vickers
lindsey.vickers@texerepublishing.com

Traffic Manager - Jody Fryett
jody.fryett@texerepublishing.com

Traffic Assistant - Dan Marr
dan.marr@texerepublishing.com

Events Manager - Alice Daniels-Wright
alice.danielswright@texerepublishing.com

Event Coordinator - Jessica Lines
jess.lines@texerepublishing.com

Marketing Manager - Katy Pearson
katy.pearson@texerepublishing.com

Social Media Manager - Joey Relton
joey.relton@texerepublishing.com

Commercial Director - Richard Hodson
richard.hodson@texerepublishing.com

Finance Director - Phil Dale
phil.dale@texerepublishing.com

Accounts Assistant - Kerri Benson
kerri.benson@texerepublishing.com

Chief Executive Officer - Andy Davies
andy.davies@texerepublishing.com

Chief Operating Officer - Tracey Peers
tracey.peers@texerepublishing.com

Senior Vice President (North America) - Fedra Pavlou
fedra.pavlou@texerepublishing.com

Change of address:
info@texerepublishing.com
The Pathologist, Texere Publishing,
175 Varick St, New York, NY 10014.

General inquiries:
www.texerepublishing.com
info@texerepublishing.com
+1 (646) 876-0852
sales@texerepublishing.com

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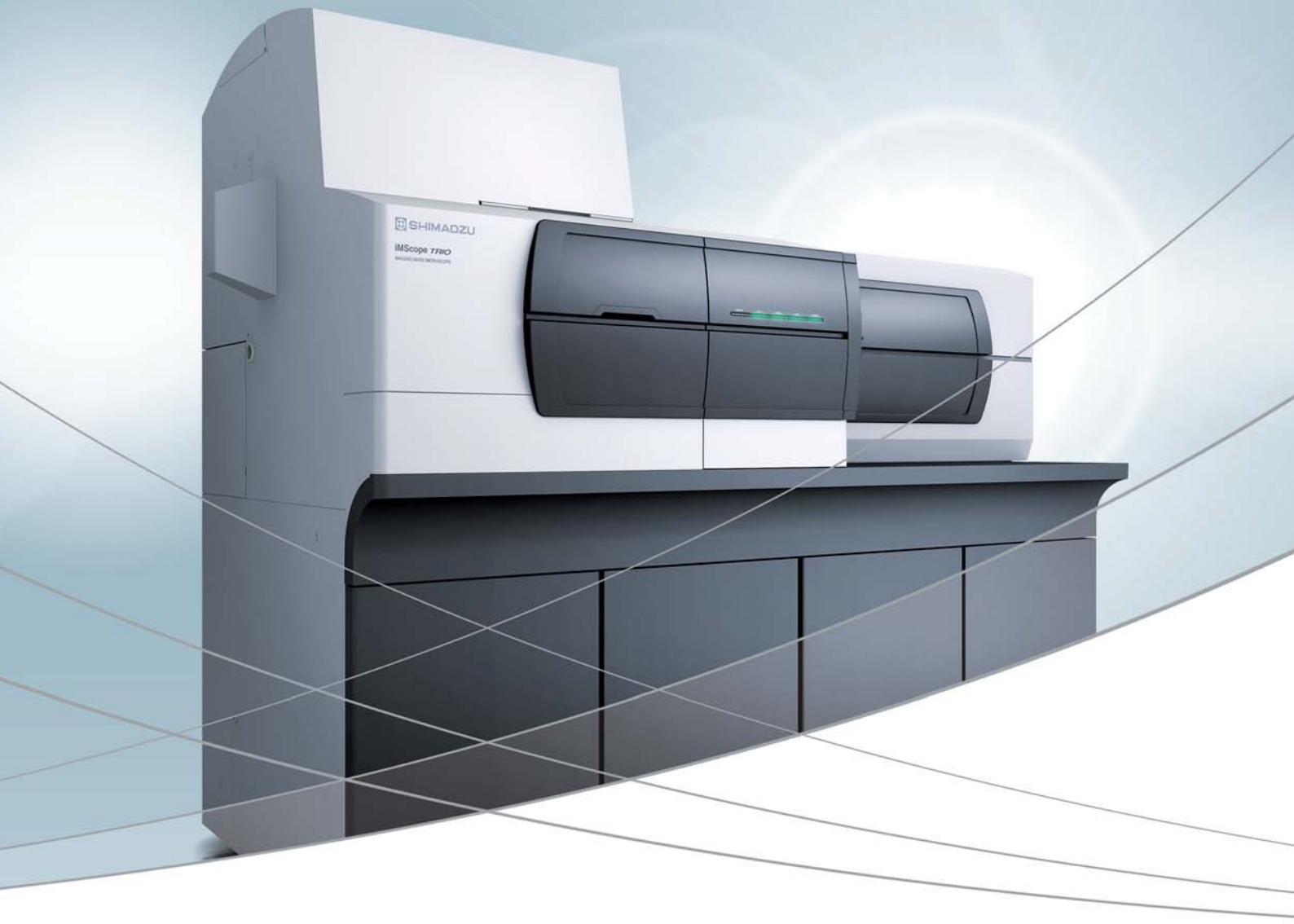

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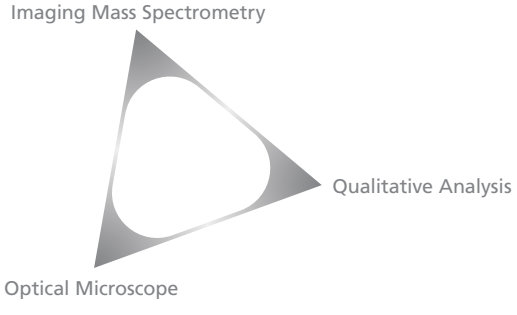

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You Have the Power

How does the Power List come to pass each year – and how can you shape its future?

Welcome to our 2019 Power List – an endeavor I'm sure you've heard a lot about over the past few months. It's one of my favorite issues each year because I learn so much about the movers and shakers in the field – more so than ever this year with our "trailblazing" theme. Rather than the equivalent of a "lifetime achievement" award, this year's list highlights the people who are bringing pathology and laboratory medicine into the future.

But, as pleased as I am to bring you this year's results, I know that the Power List may seem like a black box to many of you. Nominations go in and the list comes out – but what happens in between? Some of you believe the list operates like a nomination aggregator or a popularity contest, wherein the more nominations a person receives, the more likely they are to make the final cut. But that is not accurate – in fact, each nominee is added to the selection process, whether they are nominated once or a hundred times. What happens next? The full list of nominations (including name, institution, and a brief biography that incorporates nominators' comments) are submitted to a panel of expert judges, all of whom work in the field of pathology and laboratory medicine. We keep the jury as diverse as possible – in terms of career stage, location, field of expertise, and more – so that we can trust that every candidate has a fair chance of selection.

Once the judges return their results to us, they are combined into a single ranking that reveals the year's 100 winners. For us here at the headquarters of The Pathologist, this is the most exciting part – our own private preview of the year's superstars. It's a feeling we hope we're able to replicate as we finally share The Power List with you. Best of all, it's exciting to see how diverse the list is each year, and how creative the nominees are with their efforts to further pathology, laboratory medicine, and patient care.

The Power List is a celebration – our thanks to you for your devotion to your field. And, because it's your list, we'd like to ask: is there anything you'd like to see in future iterations? Is there a theme you'd like us to focus on, or a particular group of people you'd like to see recognized? Let us know (edit@thepathologist.com) and you may see your suggestions – and your nominees – on a future Power List!

Michael Schubert
Editor

Upfront

Reporting on research, innovations, policies and personalities that are shaping pathology today.

Do you want to share some interesting research or an issue that will impact pathology?

Email: edit@thepathologist.com

Forging a New Path

Points of interest from the 2019 annual meeting of the Association of Pathology Chairs

Early Education

How can we help undergraduate medical students achieve their potential – in pathology and beyond? Alan Rampy presents an integrated curriculum, tested at his institution, that includes case-based learning, student feedback, and PILLARS: professionalism, inquiry, learning, and leadership through active research and synthesis. Robin LeGallo further explores how to assist a struggling student by identifying the problem and developing a plan that includes deliberate practice, feedback, and self-assessment. How can educators promote success? By giving students permission to change, presenting reasonable challenges, setting an expectation of growth, providing connections to faculty and peers, and offering them choice.

Social Media Strengths

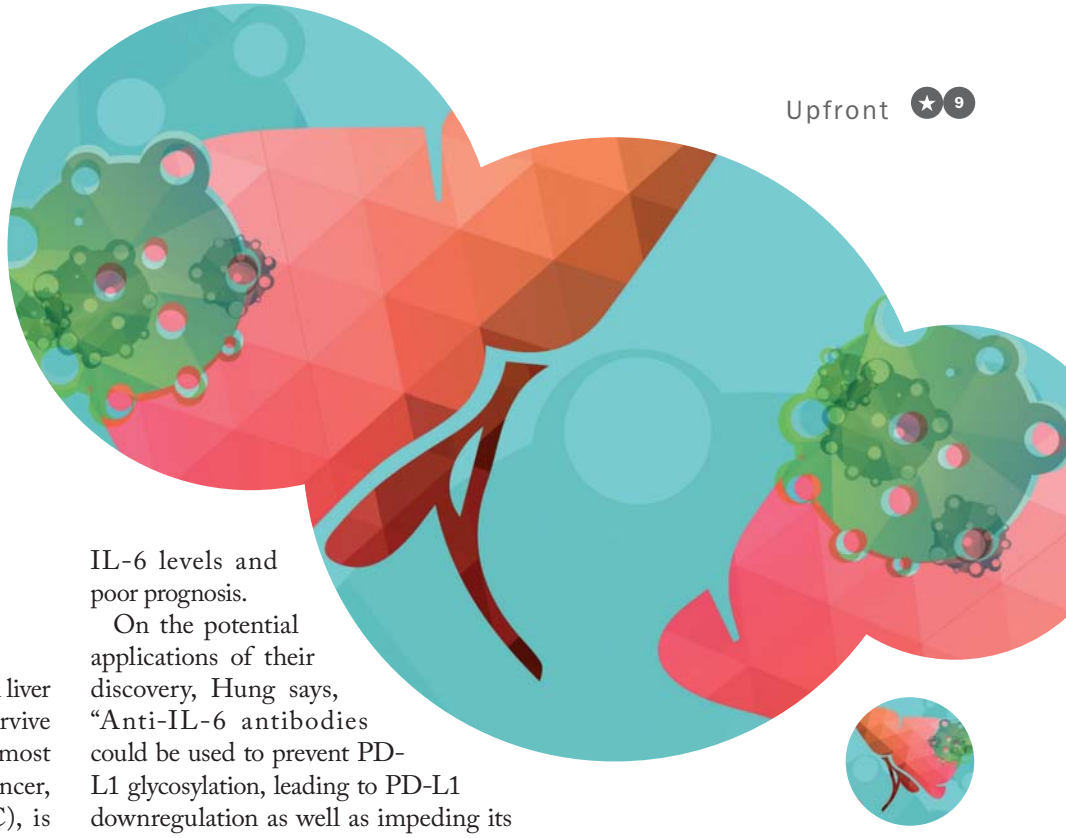
Valerie Fitzhugh recommends using social media platforms for education and interaction – but she warns: follow your institution's social media policy, don't use your academic account for private content, remember that everything you post on the Internet is public (even on a private account), and take great care over HIPAA. Don't post anything that could identify your patient – and don't post anything you might regret later! With those cautions in mind, pathologists and laboratory medicine professionals can benefit greatly from social media.

The Future of Pathology

Is informatics the future of our discipline? Karen Kaul thinks so – and notes that the conversation is increasingly shifting from "traditional" digital pathology to artificial intelligence (AI). The goal? To make systems foolproof for primary care providers and to encourage them to use laboratory data. Alexis Carter adds that interoperability is the key to widespread adoption, particularly with the rise of AI. Currently, we lack good standards for AI in medicine, but with greater adoption comes greater experience – and pathologists are vital to its continued improvement.

Leading the Way

Pathologists and laboratory medicine professionals interested in leadership roles often find themselves unsure of how to proceed. Pathology's wide-ranging influence on other medical disciplines makes us ideally positioned for educational leadership – but those opportunities must be made available to those who desire them. Paul Hemmer introduces Schein's classification of occupational subcultures and suggests that current leaders often adopt the "executive" style, whereas policy-based leadership requires a move toward the "engineer" style and evidence-based leadership mandates the "operator" style.



A Longer Life With Liver Cancer

Could anti-IL-6 antibodies that downregulate PD-L1 expression prolong immunotherapy?

Statistics for patients diagnosed with liver cancer are bleak – only 18.4 percent survive past five years in the US (1). The most common form of primary liver cancer, hepatocellular carcinoma (HCC), is notoriously difficult to treat, with multikinase inhibitors, such as sorafenib and regorafenib, only extending overall survival by less than three months. But the future looks brighter; new research from a team led by Mien-Chie Hung at the University of Texas MD Anderson Cancer Center shows that a cellular pathway closely linked to cancer may prolong immunotherapy and reduce its side effects.

The pathway in question forms when the interleukin-6 (IL-6) protein activates the Janus kinase 1 (JAK1) enzyme. This process often occurs in tumors and has been linked to the regulation of programmed death ligand 1 (PD-L1), a protein known to suppress the immune system. "We discovered that the IL-6/JAK1 pathway enhances PD-L1 expression in HCC cells, making it a promising target for the development of treatments," Hung explains.

To combat the action of the IL-6/JAK1 pathway, the team found that combining anti-IL-6 antibodies and anti-T-cell immunoglobin mucin-3 (anti-Tim-3) boosted T cell-killing effects in mouse models (2). They also showed that, across 183 HCC patients, those with high IL-6 expression had elevated PD-L1 expression – confirming the link between high IL-6 levels and poor prognosis.

On the potential applications of their discovery, Hung says, "Anti-IL-6 antibodies could be used to prevent PD-L1 glycosylation, leading to PD-L1 downregulation as well as impeding its localization on the cell surface." Given that immune checkpoint inhibitors have been shown to stimulate IL-6 production, blocking the IL-6 pathway could also lessen the side effects of immunotherapy and extend its duration for HCC patients.

After showing synergistic efficacy in animal models, a combined therapy of anti-IL-6 and anti-Tim-3 certainly appears promising. "We are looking forward to collaborating with the scientific and medical community to initiate clinical trials to treat HCC patients, who currently lack access to effective treatment," says Hung.

References

1. *National Cancer Institute, "Cancer stat facts: liver and intrahepatic bile duct cancer" 2016. Available at: https://bit.ly/2j97Dnm. Accessed August 13, 2019.*
2. *LC Chan et al., "IL-6/JAK1 pathway drives PD-L1 Y112 phosphorylation to promote cancer immune evasion", J Clin Invest, 129, 3324–3338 (2019). PMID: 31305264.*

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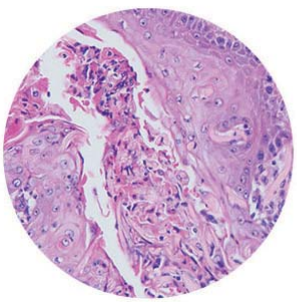

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A Day at the (sncRNA) Zoo

What the genetic signatures of animals can tell us about miRNA biomarkers in humans

Small noncoding RNAs (sncRNAs), such as microRNAs (miRNAs), are ubiquitous and play an important role in the control of cellular processes, making them suitable targets for the investigation of human disease. But before we can fully understand their function, we must distinguish between valid miRNAs and false positives – a task with which machine learning methods often struggle. In an attempt to elucidate the most resilient miRNA biomarkers, a team from Saarland University took an unusual approach by sequencing the blood of different animals (1). We spoke to lead researcher Andreas Keller to find out more.

Why analyze the blood of animals?

When we collect sncRNA data from humans, there can be up to 20 million data points per patient, which leaves us with numerous miRNA features. But because patient cohorts are typically small, machine learning methods have difficulty recognizing true biomarker signatures without overtraining the models. Confounding patient factors, such as age, gender, and ethnicity, add to the diversity of miRNA profiles and increase this complexity. Our aim is to exclude miRNA signatures that are likely artifacts.

Evolutionarily conserved biomarkers that occur in different species in similar form and function are much more likely to be resilient. And that's where the animals come in. We took 21 blood samples from 19 different species – including a coati and a Humboldt penguin – and performed next-generation sequencing of the miRNAs expressed in their blood cells.

How does the conservation of miRNA expression between different species help with human disease biomarkers?

Studies on sncRNAs often rely on genomic sequence similarity rather than expression data. We realized that, for many conserved animal miRNAs, there was no actual expression data available. When we evaluated and compared the data across species, we found that miRNA sequences and expression were even more conserved than previously thought. Now, we can incorporate our findings into computer models to improve our ability to find reliable biomarkers in the future.

How many animals do you aim to analyze?

The more animals we sequence, the better! There are currently 40 different animals in the database and we continue to make discoveries with each new species. But we don't just want more species; it will also be beneficial to sequence a number of different animals of the same species to build on the data. Finally, we want to apply a variety of technologies alongside bulk sequencing, such as single-cell RNA sequencing of animal blood cells.

Reference

1. *T Fehlmann et al., "The sncRNA Zoo: a repository for circulating small noncoding RNAs in animals", Nucleic Acids Res, 47, 4431–4441 (2019). PMID: 30937442.*

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In My View

In this opinion section, experts from across the world share a single strongly held view or key idea.

Submissions are welcome. Articles should be short, focused, personal and passionate, and may deal with any aspect of laboratory medicine. They can be up to 600 words in length and written in the first person.

Contact the editor at edit@thepathologist.com

Mistakes Happen

Alleviating the emotional impact of medical errors on healthcare staff

By Bamidele Farinre, Senior Executive Officer (HCS), Clinical Services Unit, National Infection Service, Public Health England, London, UK

"Oh, no! What have I done? Now they won't get this patient's result in time for treatment because of my mistake. How could I do this? What's wrong with me today? I performed the wrong test on that precious sample – and now I don't have enough for the right test. I can't bring myself to call the ward and tell them – I'll have to speak with my manager..."

After work, this laboratory staff member is still thinking about what happened. She can't seem to get the mistake out of her head. The emotional turmoil is unending!

We have all been there before; we've all had that hollow pit-of-the-stomach feeling after an avoidable error. Making a mistake at work can leave anyone lacking confidence and unsure how to proceed – and the feeling only intensifies for medical staff, who are responsible for the health and wellbeing of others. The emotional and psychological effects of a mistake can be deep and long-lasting. We healthcare professionals have been encouraged, as part of our professional obligation, to be open and transparent when things go wrong, so that errors can be constructively analyzed and dealt with – and so that lessons can be learned to prevent another occurrence.

But that brings about the question: what constitutes a mistake or error? I would succinctly define it as "a deviation from accuracy or correctness." In our professional duties, we all strive for excellence and perfection – which means that openly accepting mistakes can be difficult. Despite the recent push by the UK's National Health Service to encourage "no blame" cultures – a patient safety initiative involving the introduction of Freedom to Speak Up champions in hospitals nationwide – mistakes are still viewed as shameful, embarrassing, and demoralizing events.

When an error occurs, our principal concern as healthcare professionals is for the welfare of the patient. Unfortunately, this often means that we ourselves are left behind to contemplate the consequences and deal with not only the professional and personal implications, but also the emotional distress. Healthcare professionals have varied emotional responses to mistakes – most commonly guilt, anxiety, anger, shame, and embarrassment. Because laboratory medicine professionals believe that we should not make mistakes, these emotions can have permanent or long-lasting consequences including loss of self-confidence, sleeplessness, self-blame, reduced job satisfaction, anxiety about a harmed reputation, and fear of disciplinary action.

Elbert Hubbard said, "The greatest mistake you can make in life is to continually fear you will make one." I can remember my first mistake during my period of training as a biomedical scientist. I was very upset with myself. That feeling, and the thought – "How

could I have done something like that?" – stayed with me for the rest of the week. It significantly affected my confidence because I know that any error has the potential to negatively affect patient management. But efforts to avoid mistakes can sometimes backfire; I often find that I am most prone to making mistakes when I am trying my hardest to avoid them!

It's not possible to eliminate errors completely, so handling them in the right way when they occur is of paramount importance. So what resources are available to us as healthcare professionals in the aftermath of an error?

To learn from an error, you must first understand how it happened. Enter root cause analysis, a retrospective technique used to identify the contributory factors involved in the error by providing a structure for reviewing patient safety incidents. When we gain insight into the causes of errors, we are empowered to implement corrective changes to prevent them or to reduce the deleterious impact of future occurrences. Denis Waitley once said, "Mistakes are painful when they happen but, years later, a collection of mistakes is what is called experience."

Understanding why mistakes happen is key to decreasing their impact – but not just on the patient. It can also help laboratory medicine professionals identify procedural problems, resolve guilt, and put into place action plans that can alleviate the emotional impact of the error. With our goals aimed squarely at improving patients' outcomes, it's important not to overlook the other people in care – ourselves and our colleagues.

Not Just Small Adults

The ongoing evolution of pediatric laboratory medicine

By Charles van Heyningen, Clinical Biochemistry Representative on the Specialty Advisory Committee for Prenatal, Perinatal, and Pediatric Pathology at the Royal College of Pathologists, UK

For most of the 20th century, laboratory investigations for children were usually undertaken as part of a service for patients of all ages. There was limited appreciation of the differences between results for adults and those for children. What might be a concerningly high serum alkaline phosphatase activity for an adult, for instance, would have been a normal result for a growing child – but, without including age-related reference ranges, the report may not have conveyed this information. Some of the earliest books to describe pediatric reference intervals were published in the 1980s by Blackwell Scientific Publications and by the American Association for Clinical Chemistry – and, from then on, we have become increasingly aware of the many differences between younger and older populations. In fact, an experienced pathologist suggests that the greatest advances in pediatric biochemistry over the last 40 years have been in newborn screening and more accurate pediatric reference intervals (1).

The authors of a 2002 review concluded that the practice of pediatric laboratory medicine (PLM) involves unique challenges related to development, nutrition, growth, and diseases during different periods of infancy, childhood, and adolescence (2). They proposed that subspecialty pediatric laboratory testing offers many opportunities for improved pediatric patient care, research, and education – and that it is best practiced with close collaboration between pathologists and clinicians. They described the many challenges involved, including the need to deal with small sample volumes and the need for reference center provision of esoteric tests.

An editorial in 2009 described a worldwide PLM network (3). The opinion was expressed that children cannot just be regarded as small adults – a fundamental approach that holds for diagnostic services for the management of sick children.

In 2017, leading international specialists in the field reflected on reasons for developing a PLM subspecialty distinct from adult pathology and laboratory medicine (4). In many countries, young patients are treated in children's hospitals. The blood volumes available for testing are lower than those for adults, and urine collection can be problematic – issues that make microanalysis especially useful. The test menu is different for children, too, particularly with regard to the diagnosis of inborn errors of metabolism and follow-up of newborn screening. A good network of reference laboratories is needed to evaluate rare diseases presenting in childhood. All of these considerations favor the provision of specialist pediatric clinical laboratory support for the management of childhood disease.

The International Federation of Clinical Chemistry (IFCC) Task Force on Pediatric Laboratory Medicine was established in 2006 as the successor to the International

"Many experienced scientists work in pediatric biochemistry laboratories – but it is difficult to recruit new staff with suitable specialty experience."

Association of Pediatric Laboratory Medicine. The task force has several aims: to coordinate the establishment of worldwide reference ranges for laboratory test results in pediatric patients of all age groups; to form a sound support basis for the continuation of the successful International Congresses of Pediatric Laboratory Medicine; and to create a worldwide network of scientists working in laboratories that specialize in pediatric medicine. In keeping with this mission, the triennial congresses focus on scientific and technological achievements in all areas of pediatric clinical and diagnostic laboratory medicine. The most recent one, in South Africa, was the most successful yet (5), and next year's meeting in South Korea, will tackle emerging technologies.

To address the challenges and issues specific to PLM, specialists in the United Kingdom formed a new national collaborative network in 2014: the Pediatric Laboratory Medicine Network (PaLMnet). The network aims to provide expertise and advice on the best laboratory techniques for use in both pediatric specialist and non-specialist clinical laboratories alike. And it is already making a difference; a recent audit of sweat testing in the UK was carried out and, from the evidence obtained, recommendations on sample collection were made. Further differences have been recognized between pediatric and adult laboratory medicine, such as different typical presentations, test repertoires and priorities, and the higher proportion of abnormal results in children. Testing may require greater urgency and different critical action limits.

In the UK, many experienced scientists work in pediatric biochemistry laboratories – but it is difficult to recruit new staff with suitable specialty experience. Discussions have started on establishing pediatric metabolic training with a curriculum and funding. But these advances are not exclusive to the UK; we now have good evidence that several of the initiatives to establish this specialty elsewhere have been successful. The first edition of a textbook entitled "Pediatric Laboratory Medicine" was published in 2017 (6) and is intended as a resource for basic PLM training. It discusses the unique characteristics of pediatric practice and covers a range of biochemical aspects, as well as molecular diagnostics, microbiology, and hematology for children.

The UK metabolic biochemistry network, MetBioNet, is a good example of what we can achieve through collaboration and networking. Its participants have developed a range of useful resources, delivered analytical quality improvements, and are addressing training and educational needs. By engaging with other strategic groups, such as the national newborn screening and inherited metabolic disease groups, MetBioNet has helped to influence the provision of children's laboratory services in the UK.

Current pediatric pathology training in the UK focuses on histopathology. I believe that it would be of value to have full specialty recognition by one or more professional regulators and a curriculum, courses, and a recognized qualification to cover laboratory blood sciences for children – especially clinical biochemistry, hematology, and immunology. Qualified specialists might run clinics for inborn errors of metabolism or lipid disorders for both children and young adults so as to provide continuity of care.

Because of the many important differences between children and adults, PLM is rapidly becoming a pathology specialty in its own right. The scope of knowledge typically covers the pediatric aspects of various non-histopathology disciplines, mainly clinical biochemistry, metabolic medicine, toxicology, hematology, blood transfusion, immunology, genetics, microbiology, and virology. This evolving focus is likely to result in better medical care for the children of the future.

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Leadership in a Changing Environment

We must not only recognize, but build upon, our profession's achievements

By E. Blair Holladay, CEO of the American Society for Clinical Pathology, Chicago, USA

Once a year, ASCP recognizes the top 40 Under Forty pathologists, laboratory professionals, and residents across the world. It's a chance to acknowledge and celebrate those who are making a difference, changing the way we practice, and helping us to achieve better patient care.

This is our sixth year of recognizing ASCP's 40 Under Forty, including our Top Five honorees, who are selected by committee and through member voting.

"When we expand and encourage the diversity of thought and leadership that exist within our profession, we strengthen our position as leaders in healthcare."

This year's group joins the program's 200 alumni, adding to the constellation of rising stars within pathology and laboratory medicine. These men and women rigorously and relentlessly pursue advancement and accomplishments, inspire others, lead by example, and effect change locally and globally. It is remarkable what they have achieved, and acknowledging their work is critical to the success of our science now and in the future.

But the ASCP 40 Under Forty program is about more than just recognition. It's also a glimpse of how these leaders of tomorrow will shape our science and move it forward. It's an opportunity to see where pathology and laboratory science is headed in an ever-changing environment, based on what these stellar scientists are bringing to the table and how they are positioning not only themselves, but pathology and laboratory medicine, for growth. Each generation shapes the trajectory of our science based on myriad factors, from technology to political climate to advances in science or educational initiatives. It's exciting to see just how profoundly things can change – or stay the same – over time. It is hopeful and inspiring to see those who follow build on what the previous generation began.

Moving science forward is no small effort. Harnessing the power of our research findings, or developing new testing methods and putting them into practice, takes time and support. Recognizing and building upon others' achievements is exactly what gives our profession momentum and solidifies our position as the linchpin of healthcare. Today's leaders in pathology and laboratory medicine embody the belief that there is strength in collaborative efforts – that we are #StrongerTogether.

When we expand and encourage the diversity of thought and leadership that exist within our profession, we strengthen our position as leaders in healthcare. When we hold others up and appreciate what they've done for the profession, we can more accurately and completely guide the direction of the evolving healthcare landscape. We laboratory scientists are at our most powerful and our most effective when we share our knowledge and accomplishments – and recognize both as essential to better healthcare.

Welcome to

THE POWER LIST 2019
the Pathologist

Breakthroughs at the bench, in the clinic, and in every facet of the laboratory have helped diagnostic medicine grow from strength to strength. But whom do we have to thank for those breakthroughs? After months of collating reader nominations and judging by an expert panel, we proudly present The Pathologist's 2019 Power List, featuring 100 of the industry's top trailblazers.

1 // Jerad Gardner

Few people fit the description of trailblazing pathologist better than Jerad. As Associate Professor of Pathology and Dermatology at the University of Arkansas for Medical Sciences, Jerad is one of the leading adopters of social media in pathology, commanding an online influence of almost 20,000 Twitter followers. He uses this platform to discuss cases, disseminate valuable information from live events, and engage with an ever-growing online community.

Talking about the most unexpected moment of his career, he says, "There was a point last year when I realized that my YouTube pathology videos were being viewed every single hour of every single day, meaning that I am teaching even while I am sleeping! As an educator, that is powerful and meaningful." Jerad speaks regularly at national and international meetings on bone and soft tissue tumors, skin disease, and the professional use of social media platforms. An active volunteer in numerous sarcoma and rare disease patient groups on Facebook, he uses the opportunity to conduct formal medical research and to advocate for patients.

"Over the next few years, molecular pathology will answer many questions, but also create many new ones. Although artificial intelligence will begin to help pathologists, it will not replace us. Also, the use of social media will become an essential skill – not just a fun hobby – for pathologists who want to get fellowships, leadership positions, or jobs," says Jerad. His best advice? "Join Twitter now! Aside from working with the amazing mentors who made me the pathologist I am today, social media has definitely been the most powerful and effective tool in my career. It has taken me further than any paper I've ever published – it's the best way to get rapidly plugged in to the global community of pathologists and, from there, the sky is the limit."

2 // Christina Arnold

Christina is Chief of GI Pathology, Associate Director of the GI pathology fellowship, and pathology faculty lead for the clinical gastroenterology fellows at The Ohio State University. She was nominated for the Power List thanks to her passion for creating the next generation of leaders in pathology through both faculty development and her work with medical students. She created the #PSIG and #FASTPath hashtags on social media to assemble exciting, interactive teaching sessions and share mentorship, support, and tips for students. Christina is particularly interested in novel GI injury patterns, including inflammatory bowel disease and mimics, infectious agents, and emerging drug injuries. "I would never have guessed that my phone would play such a dominant role in my career," she says. "Social media provides instant connectivity with the world and helps me feel supported, engaged, and surrounded by all the good that is in pathology. It has also bestowed profound opportunities that I would not have had access to without developing a presence on social media, such as invited lectures, leadership roles, research collaborations, and more."

3 // Melissa P. Upton

"My greatest influences were my parents, who instilled in me my conviction that access to education is the most powerful tool for good," says Melissa, Professor Emeritus and Associate Director of the Pathology Residency Program at the University of Washington. Currently President of the American Society for Clinical Pathology (ASCP), she has been responsible for launching crucial conversations and initiatives in the ASCP to enhance diversity, create inclusive workplaces, and empower the leadership potential of pathologists and laboratory professionals around the world. Why does she love pathology? "As an academic pathologist, not only do I enjoy helping patients to get the correct diagnosis, allowing them to get appropriate care, but I also love working with medical students, residents, and fellows in pathology. There is nothing more satisfying than helping them to gain insight into themselves to maximize their potential."

4 // Eva Wojcik

Eva is Chair of the Department of Pathology and Helen M. and Raymond M. Galvin Professor of Pathology at Loyola University Stritch School of Medicine in Maywood, Illinois. After completing her medical training at the Academy of Medicine in Gdansk, Poland, she moved to the US to begin her illustrious career in cytopathology. One of Eva's major contributions is her support for the "See, Test & Treat" program at Loyola, which provides free cancer screening and health education to local patients. As a founding member of the Paris System Working Group, she also led a team of world leaders in cytopathology and urology to conceive a standardized platform for the cytologic interpretation of urine samples when diagnosing bladder cancer. Nominators commend her career as "a testament service to others" and describe her as a "champion for the underserved." Her best advice? "Coincidence can lead you to a very fulfilling and satisfactory career; just don't be afraid to say yes. If I can do it, so can you!"

5 // Kamran Mirza

"My favorite part of pathology is the ability to give a definitive diagnosis and start a patient on a journey to recovery. I enjoy nothing more than being part of the team that helps patients feel better," says Kamran, Assistant Professor of Pathology and Laboratory Medicine and Medical Education at Loyola University Stritch School of Medicine in Maywood. With an active and influential presence on social media, Kamran was nominated for his tireless contributions to pathology and laboratory medicine education and his work to improve communication between pathology and other medical fields. His passion for teaching has been recognized through various honors, such as the 2019 Teaching Excellence Award from The Ohio State University Pathology Student Interest Group. He was also voted one of the top five honorees in ASCP's 40 Under Forty in 2017. On the future of the field, Kamran says, "I see the role of the pathologist becoming more widely understood and valued. Add to this the routine inclusion of molecular pathology as part of oncology testing and the explosion of algorithm-assisted and AI-involving diagnostics, and I think the accuracy with which we can render a diagnosis is set to improve further still. It's an exciting time!"

6 // Fergall Magee

Fergall is Provincial Department Head of Pathology and Laboratory Medicine at the University of Saskatchewan. He specializes in pediatric pathology and his biggest interests include pediatric autopsy and prenatal and newborn screening. Nominators praise his strong leadership within the Royal College of Physicians and Surgeons of Canada, his contact with patients and families, and his work with medical students and residents. Notably, he was recognized for his efforts in hosting an outreach program for high school students to help expose them to laboratory careers from an early age. He is also a founding organizer and presenter for the Choosing Wisely Saskatchewan conference, which encourages appropriate test utilization and management by providing education to all healthcare professionals. Away from the laboratory, Fergall enjoys art galleries, cross-country skiing, and kayaking.

7 // Michael Arnold

"As technical barriers, costs, and regulatory hurdles continue to drop over the next five years, I envision that digital interactions among pathologists will include educational and clinical activities that incorporate whole slide images," says Michael, Director of Surgical Pathology at Nationwide Children's Hospital in Columbus, USA. A practitioner whose specialties include gastrointestinal and sarcoma pathology, Michael co-founded an online pathology journal club set up to discuss and scrutinize new research in live sessions on Twitter. Nominators describe him as a trailblazer in pediatric pathology and social media, and Michael's recent videos on grossing and other aspects of the medical laboratory have made him a viral sensation on Twitter and beyond. He can be found via the #PediPath hashtag, which he uses to contribute to education on pathology and oncology in young patients. "The best pieces of advice I got in training were to not be afraid to try something outside your comfort zone and to always look for new ways to do something. Social media was definitely outside my comfort zone when I started, but it has been worthwhile to meet so many wonderful people and learn so much!"

8 // Richard Scolyer

Richard is a pathologist, medical researcher, and the current Co-Medical Director at Melanoma Institute Australia. He is also the president of the Australasian Division of the International Academy of Pathology and clinical professor at the University of Sydney. "My biggest influence has been the Melanoma Institute Australia Research Database that was set up by the late Gerry Milton 60 years ago," he says. "This is now the largest melanoma patient database in the world, with over 50,000 patients, and is a major international resource that has provided me with many opportunities to perform important research that correlates pathological and clinical features with patient outcome data in large cohorts." Richard's research discoveries have changed clinical and pathology practice worldwide; he is a leader in determining mechanisms of enhanced response versus resistance to drugs in development, such as immunotherapies – data that underpins the design of current clinical trials. His biggest wish? "That people of all ages, but especially young people, were more vigilant in protecting themselves from the sun. UV exposure leading to sunburn is the single biggest risk factor for developing skin cancer, which claims one Australian life every five hours."

9 // Eduardo Alcaraz Mateos

With a particular interest in cytology and dermatopathology, Eduardo currently works as a pathologist and cytopathologist at the Hospital General Universitario Morales Meseguer in Murcia, Spain. One of his most innovative achievements to date was the invention of FioNA, a simulator that helps students practice fine needle aspiration. Eduardo is also an active social media educator, using his influential online presence to discuss cases and give advice. Nominators describe him as a pioneer who makes pathology more visible for medical students, something he makes a conscious effort to achieve. "Pathology's visibility is something that I try to change on a daily basis, not only at the hospital, but also through social media," Eduardo says. "My favorite part of the job is providing solutions to patients one biopsy at a time, and I also enjoy the collaboration with radiologists and gastroenterologists when completing rapid on-site patient evaluation."

10 // Rachel Jug

Rachel is a resident and future cytopathology fellow at Duke Health in Durham, North Carolina. She was nominated for her passion and dedication to innovations in education and patient care, which nominators say are at the level of a pathologist with many more years in practice. Rachel is driven by her ambition to improve the practice of medicine, from the way that feedback is given and received, to making ultrasound phantoms for ultrasound-guided fine needle aspiration training, to bringing pathologists to the forefront of communication and patient care. When asked what she would change about the field if she could, Rachel says, "I would give pathologists a stronger voice to advocate for their patients. Pathologists are remarkable educators with a unique breadth and depth of knowledge; they are best suited to help patients, their clinical colleagues, hospital administrators, and health policy makers understand disease processes and drive evidence-based, cost-effective care."

Adam L. Booth

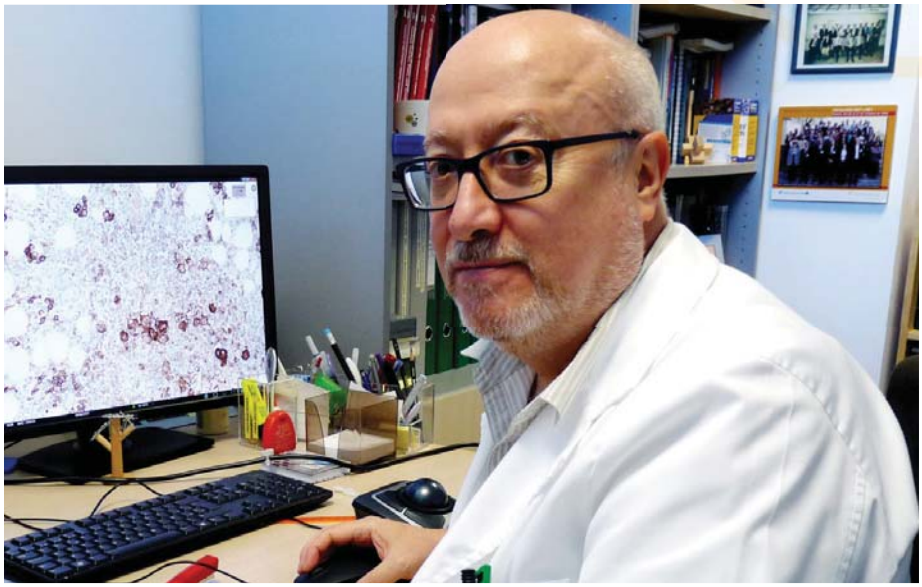
"I never anticipated that I would be so involved with social media when I started out in pathology, but it has opened doors to research, collaboration, and leadership opportunities that have made me a stronger trainee," says Adam, a resident in Anatomic and Clinical Pathology at the University of Texas Medical Branch. He was nominated thanks to his unrelenting desire to improve connections between pathologists, foster collaboration and education, and develop pathology's image. To achieve this, Adam uses social media to increase patient interaction and to inspire the next generation of pathologists through advocacy.

Abdulkarim Hasan Kohail

Abdulkarim can be found at Al-Azhar Faculty of Medicine in Cairo, where he is a histopathologist and pathology lecturer. Formerly an observer at University Hospital of Wales, he was nominated for his trailblazing approach to education, engaging teaching style, and innovative learning materials that help students and trainees better understand the practical aspects of pathology. Talking about the future of medical education, Abdulkarim says, "Integrated medical education will become the norm worldwide. Pathology as a basic science subject will take its place in most modules in more interesting and informative ways, linking basic general pathology with practical anatomical pathology."

Adrian Newland

Adrian, a consultant hematologist for 30 years, has been a Professor of Hematology at Barts and The London NHS Trust since 1995. He is a past President of the Royal College of Pathologists and has chaired the London Cancer New Drugs Group. Currently, as Specialist Clinical Advisor and Chair of the UK's National Pathology Implementation and Optimisation Delivery Group, Adrian works to achieve the kind of change in pathology that will ensure long-term sustainability. "I have always been driven to provide a quality service with old and new diagnostics made universally available, both internationally and in the UK," says Adrian.



Agustín Acevedo

Agustín is Head of the Pathological Anatomy Service at Hospital Universitario Quiron Pozuelo in Spain. Having worked in the field for more than 25 years, Agustín has extensive scientific and clinical experience, with a special interest in the diagnosis of neoplastic processes – especially lymphomas and other hematological processes. He was nominated for both his trailblazing work in bone marrow pathology and his successful integration of clinical, pathologic, and molecular issues to achieve a diagnosis.

Ahmed Kalebi

As Founding Partner, CEO, and Chief Consultant Pathologist at Lancet Group Laboratories, East Africa, Ahmed has successfully brought affordable, quality, and accessible pathology services across the region. He was nominated for the positive impact he has had on medical practice, pathology resident education, and research in Africa. "I had my epiphany moment when I was told to look at a Merkel cell tumor. I literally saw the proverbial light down the microscope and realized that pathology provides the diagnosis and enables appropriate patient management. I immediately decided that I wanted to become a pathologist rather than a surgeon," Ahmed says.

Alison McEvoy

Alison is Hematology Laboratory Operational Manager at Milton Keynes University Hospital NHS Foundation Trust in the UK. She is a brilliant leader who always has the needs of her team in mind and involves them in decision-making, something that is reflected in the laboratory's continually improved outcomes. "Alison achieves all this with a gentle touch, a smile, and hard work," according to her nominators – attributes that have earned her a place on the Power List.

Amy H. Deeken

"Pathology is one of the most exciting and dynamic fields in medicine. With the onset of social media and digital pathology, the distance between continents and barriers to collaboration are quickly disappearing," says Amy, Assistant Professor of Pathology and Director of Hospital Autopsy at Summa Health. She is an art enthusiast and regularly uses photography to create captivating images from the tissue she examines as a pathologist. "It's so exciting to be part of this generation of physician visionaries who have followed the natural path to explore what pathology looks like in this uncharted digital space."

Anant Madabhushi

As the Director of the Center for Computational Imaging and Personalized Diagnostics at Case Western Reserve University in Cleveland, Anant works on numerous multidisciplinary projects focused on computer-aided diagnostics, pattern recognition, and image analysis tools. His pioneering work on the spatial architecture of immune cells has allowed us to use machine learning methods to better predict which lung cancer patients will benefit from chemotherapy. "The collaborative teams that I have been part of and the ability to provide that multi-disciplinary education and training to my students ranks as the most exciting and inspiring aspect of my career thus far," says Anant.

Angela Douglas

Angela is a Consultant Clinical Scientist who has worked in the National Health Service (NHS) in genetics for over 38 years. In her role as Deputy Chief Scientific Officer for NHS England, she is partly responsible for the 50,000 healthcare scientists working in the NHS. In 2016, Angela was commended in the Queen's 90th birthday honors list as a Member of the Order of the British Empire for her contribution to research and mentoring students. "If I could change one thing, I would ensure that all healthcare science professionals had genomics and genetics included in their training," says Angela.

Anil Parwani

Anil is Professor of Pathology and Vice Chair and Director of Anatomic Pathology at The Ohio State University, and Director of Pathology Informatics and of the Digital Pathology Shared Resource at The James Cancer Hospital. Anil's research focuses on diagnostic and prognostic markers in bladder and prostate cancer and molecular classification of renal cell carcinoma. He says, "My favorite part of the job is the ability to stay at the cutting edge of new technologies […] I love using these tools to train the next generation of pathologists, who can become as excited and passionate about pathology as I am!"

Bennet Omalu

Bennet is the President and Medical Director of Bennet Omalu Pathology. He was the first to identify and describe chronic traumatic encephalopathy (CTE) in athletes in 2002, providing the first evidence that American football can cause permanent brain damage. He has since campaigned to raise awareness of CTE, leading the National Football League to make rule changes to protect players. "If I could make one change, I would include business communication and management in the training of pathology residents. I believe it would make us more effective, more innovative, and more significant in the business of health and patient care."

Bamidele Farinre

Bamidele is Senior Executive Officer (HCS) of the Clinical Services Unit, National Infection Service, for Public Health England in the UK. Nominated for her dedication to encouraging women and minorities into STEM subjects, she works with numerous organizations, including the British Science Association, to achieve this goal. On the future of her field, Bamidele says, "Virology will continue to develop and expand due to driving forces such as an increased viral disease burden, changing patient demographics, and further technology improvements."

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Bobbi Pritt

Bobbi is Director of the Clinical Parasitology Laboratory in Mayo Clinic's Department of Laboratory Medicine and Pathology. She is widely renowned as a trailblazer thanks to her tireless work in parasitology education, including "Parasite Wonders" – Bobbi's website and blog, which showcases the creepy, yet fascinating, world of parasites. The funniest moment of her career? "I was once able to diagnose a large foreign body in a man's bladder as a fishing lure – but only because of its similarity to fishing lures I had sent to my lab as mock specimens on April Fool's Day three years before!"

Caddie Laberiano Fernández

Caddie is a researcher at MD Anderson Cancer Center in Houston, a post she took up after several years as a cytopathologist at the Arias Stella Institute of Pathology and Molecular Biology in Peru. She was nominated for her trailblazing series of YouTube videos, in which she aims to educate other medical specialties about basic procedures in pathology to foster effective communication and collaboration with clinical colleagues. "The most unexpected moment of my career came when I was asking a particular speaker questions at a conference," says Caddie. "It ultimately led me to start a rotation in the US!"

Catarina Shaletich

Catarina is an anatomic pathologist at the Dr. Prates Laboratory of Surgical Pathology in Brazil. An experienced and well-respected figure, Catarina has published papers on numerous topics, including malignant chondroid syringoma. She was praised by her nominators to the Power List for her "never-ending knowledge of dermatopathology and other fields, which makes her one-of-a-kind."

Cécile Badoual

Cécile is an anatomic cytopathologist at the Georges Pompidou Hospital and a teacher at the Paris Descartes Faculty of Medicine in France. Spearheading the fight against human papillomavirus (HPV), Cécile was instrumental in establishing France's first multidisciplinary medical consultation for patients affected by HPV-related cancer. She was nominated for the Power List due to the worldwide impact of her research on the immune microenvironment of head and neck cancers associated with HPV. "As pathologists, we must never forget our essential role in patient management," says Cécile. "We are part of a care team and must be innovative with multidisciplinary approaches."

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César Augusto Alvarenga

César was nominated to the Power List in recognition of his dedication to patients – a theme that arises frequently when his name is mentioned and that has placed him on two prior Power Lists. Having previously held observerships in thyroid pathology at IPATIMUP and in soft tissue pathology at Brigham and Women's Hospital, César currently works at the Instituto de Patologia de Campinas in São Paulo, Brazil, where he specializes in surgical pathology and immunohistochemistry.

Dana Razzano

"Pathology is no longer a field typified by doctors hiding behind microscopes; pathologists truly are at the forefront of patient care now more than ever," says Dana, Chief Resident of Anatomic and Clinical Pathology at New York Medical College, Westchester. Dana appeared in the ASCP 40 Under Forty in 2018 and has worked alongside CAP and ASCP to promote involvement in global health. "I believe that we will see a mindset change in the next five years whereby pathology will no longer be considered the neglected cornerstone of global health, instead serving as the unshakeable foundation."

Christina Zioga

Christina is a Consultant Cytopathologist at George Papanicolaou General Hospital in Thessaloniki. She was nominated for her passionate approach to cytopathology education – something that transcends geographical boundaries. Christina invented an algorithm called Diagnostic Medicine ABCDE, which is now an important guideline for medical image interpretation not only in pathology, but also in radiology and nuclear medicine. She was the winner of a 2018 Digital Pathology Association award for her work on informatics. Her favorite part of the job? "I am intrigued and fascinated by the emerging role of cytopathology in the world of minimally invasive medicine."

Christopher D.M. Fletcher

Christopher is Director of Surgical Pathology at Brigham and Women's Hospital in Boston and Professor of Pathology at Harvard Medical School. As Chairman of the World Health Organization Working Group for the Classification of Tumors of Soft Tissue and Bone, Christopher has challenged the more traditional aspects of tumor classification and endeavored to extend our knowledge of soft tissue neoplasia at the genetic level. Looking to the future, Christopher says, "We need to reverse the trend of diminishing pathology content in medical school curricula, which is gradually becoming a worldwide problem, to ensure the future supply of high-quality trainees."

Daniel Holmes

"My career has put me in a position to help patients at their greatest time of need and vulnerability. Although I don't often meet them, patients are always in my line of sight and this helps me to keep perspective on what's important when deliberating on administrative matters," says Daniel Holmes, Clinical Professor of Pathology and Laboratory Medicine and Division Head of Clinical Chemistry at the University of British Columbia. Daniel is renowned as a leader in clinical lipidology, endocrinology, and mass spectrometry.

Darren Treanor

According to his nominators, Darren – who is Consultant Pathologist and Honorary Clinical Associate Professor at the University of Leeds – has "fostered trust and confidence" for all stakeholders within the pathology department at St. James's University Hospital in the UK. Driving full adoption of digital pathology for diagnosis, he is lauded for having set standards for its safe use – in addition to accurate and effective validation – laying a solid foundation for his colleagues to build on in the future.

David Wells

As Head of Pathology Services Consolidation at NHS England and NHS Improvement, David continues to drive the type of unprecedented change in UK pathology that has attracted global attention, especially due to his excellent work with networking and consolidation. He strives to embed pathology into the heart of healthcare by supporting the adoption of digital systems, while also influencing key national health policies and government-funded initiatives. His trailblazing approach to the modernization of the field is ensuring the sustainability of pathology expertise for the future – but he still manages to find time to inspire future laboratory medicine professionals.

Elaine Jaffe

Elaine is Head of the Hematopathology Section at the US National Institute of Health's National Cancer Institute. She has led pioneering studies in relation to the classification of malignant lymphomas and sits at the forefront of an international effort for consensus among clinicians and pathologists. Nominators are effusive in their praise for her trailblazing work, which has been instrumental in the establishment of a new paradigm for lymphoid neoplasm classification. "Hematopathology has always been an ideal subspecialty for me because of the integration of pathology with clinical information, and the incorporation of modern molecular techniques," says Elaine.

Emilio Madrigal

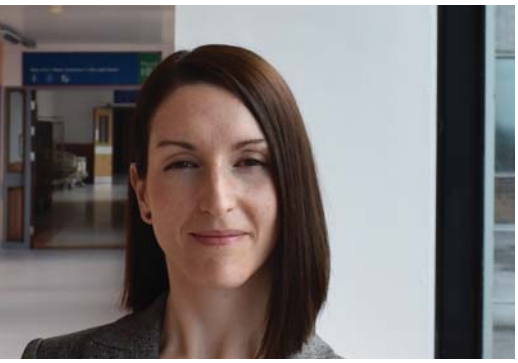
Emilio is an Assistant in Pathology and a Fellow in Clinical Informatics at Massachusetts General Hospital. "I'm passionate about building innovative, data-driven platforms to facilitate diagnostic decisions and improve educational delivery. Working alongside a gifted computational pathology team allows us to quickly advance from concept to completion and bring tangible solutions to our department," says Emilio. He is an active member of several national and international committees and is co-founder of pathCast (pathologycast.com), which broadcasts free pathology lectures across the world.

Elizabeth Montgomery

Specializing in gastrointestinal (GI) and soft tissue pathology, Elizabeth is a Professor of Pathology, Oncology, and Orthopedic Surgery at Johns Hopkins School of Medicine. She is described by nominators as "a world expert who has shaped the careers of many pathology residents and fellows." A successful teacher and mentor, Elizabeth is also an innovator – she founded Innovative Pathology Press, a producer of surgical pathology books. Her biggest influences? "Sharon Weiss, Jeanne Meis, and the late Franz Enzinger all enabled me to spring off into GI pathology."

Emily Volk

Emily is currently the Senior Vice President of Clinical Services at University Health System in San Antonio and Assistant Professor of Pathology at the University of Texas. Over the past two decades, she has endeavored to ensure that patient safety is a top priority throughout healthcare; more recently, she has worked with state and federal governments to achieve this. On her favorite part of the job, Emily says, "It's a privilege to touch so many patients' lives each day. Almost every patient in the hospital is impacted by the policies we set and the oversight we provide in the laboratory."



Gemma Clark

Gemma can be found at Nottingham University Hospitals NHS Trust, where she works as a clinical scientist. A leader in innovation, she has introduced new technologies and delivered quality laboratory service in her institution. Her specialty lies in molecular diagnostics for infectious diseases and molecular microbial typing methods. Her favorite part of the job? "The fast-paced and continually evolving nature of clinical virology. We are constantly learning new things about viruses and this creates a real challenge for the field of diagnostic virology, in which we are tasked with detecting and monitoring viruses that have significant impacts on human health."

Esther Youd

A histopathologist based in South Wales, Esther also has a national position as Chair of the Academy Medical Royal Colleges Wales and is an Assistant Registrar with the Royal College of Pathologists and one of the first doctors in the UK to qualify as a Medical Examiner. Speaking about how to grasp new opportunities, Esther says, "Always put yourself forward for leadership roles… You don't have to be the foremost expert in your area; your experience and knowledge will contribute to the existing wealth of views and you will play a part in promoting high standards and improving patient care."

Felipe S. Templo, Jr.

Few have been as active as Felipe in harnessing social media's power for pathology education. He is an anatomic and clinical pathologist, program director of the Pathology Residency Training Program at the Philippine Heart Center, and Assistant Professor at the University of the City of Manila College of Medicine. His trailblazing work promoting pathology via social platforms is particularly innovative in the context of developing countries such as the Philippines, which have limited resources for medical education. Looking to the future, Felipe says, "Through social media, the presence of pathologists will increasingly be felt by patients and the general public."

Genevieve Marie Crane

"Pathology provides a truly unique opportunity to build a niche based on your passion and skillsets, directly impacting the field and potentially the lives of others," says Eve, Assistant Professor of Pathology at Weill Cornell Medicine in New York City. Alongside her research interest in investigating the influence of host and environmental factors on lymphoma development, she is also passionate about education and outreach, especially through social media. With over 5,000 followers on Twitter, she frequently uses her powerful online presence to prompt and engage in discussions surrounding her specialty – diagnostic hematopathology.

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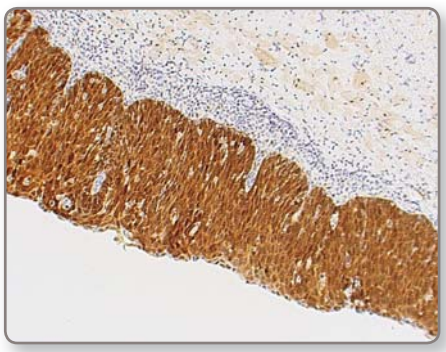

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Han van Krieken

As a Professor of Pathology at Radboud University Medical Center, Han specializes in blood and digestive tract diseases, especially lymph node cancer. He played a key role in the discovery of mantle cell lymphoma as an entity, founded the Journal of Hematopathology, and has received numerous awards – including an honorary fellowship of the Royal College of Pathologists and a knighthood by the King of the Netherlands. Han says, "Early and complete diagnosis is becoming increasingly crucial for patients, which requires that histopathologists collect and integrate information from many sources, including genetics, radiology, and other forms of clinical pathology."

Iffat Jamal

Iffat is an Assistant Professor in the Department of Hematology at the Indira Gandhi Institute of Medical Science in Patna. She was nominated for the Power List thanks to her hard work and dedication to the field. Why did she choose pathology? "It is the science of all sciences because all medical fields are related to it. What we see behind the microscope paves the way for clinicians in terms of the appropriate management of patients. Pathology is fascinating and breathtaking; I am proud to be a pathologist!"

Jaime Arturo Mejia

Jaime has been a practicing pathologist for over 20 years. He combines academic and community practice effortlessly and has served as Professor at both the Universidad del Valle and Universidad Santiago de Cali. He is currently CEO and founder of the Instituto de Patología Mejia Jimenez in Colombia. Nominators praise his kind, unassuming, and considerate nature, saying he has a terrific sense of humor in addition to being a brilliant pathologist. His quest for knowledge is relentless and he regularly brings his unique viewpoints to conferences and meetings.

Jason Hornick

Jason is Director of Surgical Pathology and Director of the Immunohistochemistry Laboratory at Brigham and Women's Hospital, as well as a Professor of Pathology at Harvard Medical School. Jason's main research interest lies in soft tissue sarcomas, including evaluating histologic and immunohistochemical parameters that predict clinical outcome and identifying diagnostic and predictive biomarkers. He serves on 12 editorial boards and was nominated for his prolific research on soft tissue pathology, having published around 400 original papers, review articles, and book chapters.

Jason Wasserman

Jason is a head and neck pathologist at The Ottawa Hospital and an Assistant Professor at the University of Ottawa. Although he has only been in practice for one year, he was nominated for the website he created to explain pathology reports to patients (mypathologyreport.ca). It now includes articles from pathologists across Canada and is recommended for patients in several cancer centers. "As experts, we have a responsibility to empower patients by helping them find answers," Jason says. "Pathologists are going to need to learn how to communicate increasingly complex results not only to other doctors, but also to patients."

Jo Martin

"I love my job! I learn all the time, work with great colleagues and students, discover through research, and I especially value the privilege of highlighting the contribution pathologists make to care – both human and veterinary," says Jo Martin, President of the Royal College of Pathologists. Jo leads the UK pathology community in matters of quality, training, exams, and recruitment. Under her leadership, this year – for the first time in years – all the histopathology junior doctor training posts were filled. "The biggest influence on my career has been my colleagues and students – I am always supported and encouraged by them."

Joanne Horne

Recently crowned Biomedical Scientist of the Year for 2019, Joanne continues to trailblaze in GI histopathology, changing the face of modern medicine reporting and ensuring that low consultant numbers don't increase cancer waiting times to diagnosis. Joanne is proactive in raising the profile of biomedical science using her strong social media presence and curated the highly popular NHS Twitter account in January 2018. "My advice would be to work hard, not take rejection and failure personally, and try to see the viewpoint of others," says Joanne. "It's important to be bold and brave to challenge traditional hierarchies and barriers!"

Jorge Reis-Filho

The author of over 470 papers on rare cancer types, Jorge is currently the youngest-ever Fellow of the Royal College of Pathologists based on published work. He leads the way in integrating histopathology with innovative genetics to discover new classes and characteristics of cancer genes. On his biggest influences, Jorge says, "Both my mentors and collaborators have taught me that, in this day and age, no professional is able to comprehend the intricate complexities of every step in the journey from making a new scientific discovery to translating it into patient benefit. Working together in a collaborative manner is absolutely essential."

Jon Morrow

Jon is Raymond Yesner Professor of Pathology, Chair of the Department of Pathology, and Chief of Pathology at Yale New Haven Hospital. His innovative research has focused on the structure, function, and genetics of complex cell membrane scaffolds. These studies were among the first to reveal the molecular basis of several hereditary blood cell disorders most commonly afflicting young children, as well as that of movement disorders such as hereditary ataxia. His hopes for the future? "Pathologists should embrace emerging technologies and lead their adoption in the diagnostic process; those who can integrate multiple analytical tools will be invaluable."

Jonathan Epstein

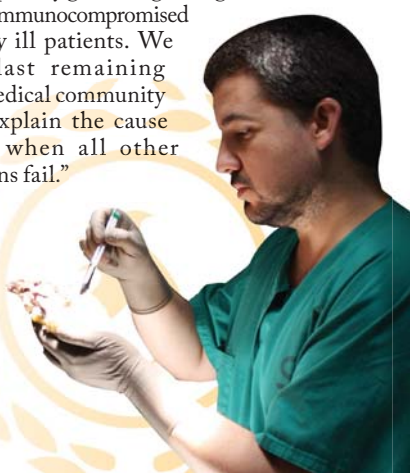
Jonathan is Professor of Pathology, Oncology, and Urology and Director of Surgical Pathology at the Johns Hopkins School of Medicine. A world expert in uropathology, Jonathan runs the world's largest genitourinary pathology fellowship, training four fellows each year, and previously won the Koss Medal for Advancement of Urological Pathology. His advice? "Find a niche where you can contribute based on access to unique patient groups or novel techniques, such that you can add to the literature in a meaningful way. Carve out a couple of hours each day for things you want to do in your area of expertise!"

Kalyani Bambal

Kalyani is a surgical pathologist and molecular oncologist who trained at Tata Memorial Hospital in India and the University of Illinois in Chicago. Having posted over 96,000 tweets, she is a prolific user of social media and regularly engages with her global following by sharing informative content. Nominators describe her as "an unselfish, hardworking pathologist who provides the online community with invaluable educational material." Kalyani is actively involved with teaching residents and junior pathologists by moderating a number of online study groups, which she describes as "a mission very close to my heart because I hold the firm belief that knowledge should be free and open-access."

Juan Daniel Prieto Cuadra

Daniel can be found at Virgen de la Victoria Hospital, where he specializes in hematopathology and autopsy. He dedicates a lot of time to helping students understand biopsies under the microscope and uses his considerable Twitter following to disseminate cases and prompt discussion. "If I could make one alteration to my field, it would be to change the perception surrounding clinical autopsies. Hospital mortality is a serious care quality problem, especially given the growing number of immunocompromised chronically ill patients. We are the last remaining hospital medical community there to explain the cause of death when all other explanations fail."



Katrina Collins

"As a resident, I decided early on in my training that I would never say no to an opportunity," says Katrina, who is currently completing a surgical pathology fellowship at the University of Texas MD Anderson Cancer Center. A former hematopathology fellow at Hartford Hospital in Connecticut, she was nominated thanks to the beautiful hematopathology cases that she posts on her Twitter profile alongside detailed reviews of markers and flow histograms. "I am continuously amazed at the enormous impact of social media – it has allowed me to educate and learn from my peers while also bringing pathology closer to patients!"

Liron Pantanowitz

Liron is Professor of Pathology and Biomedical Informatics and Vice Chairman for Pathology Informatics at the University of Pittsburgh Medical Center. He is also the Director of Cytopathology and of the Pathology Informatics Fellowship Program. A founder of the Journal of Pathology Informatics, he also published the subject's first textbook. His most unexpected moment? "When I found out I was a natural on stage! At the American Society of Cytopathology's annual meeting in 2017, I hosted a cytology 'shark tank' event and I had a blast – the event was highly successful and I was invited back for the following year!"

Kyle Bradley

Kyle is an Associate Professor of Hematopathology at Emory University Hospital, Atlanta. He was nominated for his contribution to online education and his ability to create diagnostic algorithms. His favorite part of the job? "The daily opportunity to learn about anatomy, biology, physiology, and various diseases, all with my own eyes! Every day is filled with scientific inquiry and the chance to significantly impact patient care, all while sharing my love for the field by teaching medical students, residents, and fellows."

Lara Pijuan

Lara is a Consultant in Pulmonary Pathology and Cytopathology and Coordinator of the Digital Pathology Project at Hospital del Mar in Barcelona. Her positivity and willingness to help others make her a true power pathologist, according to her colleagues. Lara was instrumental in the introduction of digital techniques in pulmonary pathology and regularly offers to help laboratories around Spain implement digital pathology into routine practice. Her advice to others? "Always do things that you enjoy and that make you happy."

Lorand Kis

Lorand is a pathologist at the Karolinska University Hospital in Sweden. Specializing in immunohistochemistry, he appears on the Power List thanks to his "clever and passionate approach to education," a trait nominators praise. Lorand is active on social media and can be found on Twitter most days, sharing photos of interesting cases, discussing immunohistochemistry and molecular pathology, and inspiring the next generation of pathologists in the process. "The people who had the biggest influence on my career were my PhD supervisors, Eva and George Klein," says Lorand.

Luis Humberto Cruz Contreras

Luis is a Pediatric Pathologist at Hospital Materno-Infantil in Irapuato, Mexico. He is active on social media and enjoys sharing posts with his wide following for education and advocacy. "I have two big influences on my career," says Luis. "The level of commitment I saw from Lourdes Cabrera Muñoz while I was training in pediatric pathology was contagious, and she taught me that there is always room for improvement. In addition, I learn so much from my #PathTwitterFamily – the time, dedication, and passion they put into everything they share is incredible."

Malak Abedalthagafi

As a strong advocate for women in science, technology, engineering, and medicine in Saudi Arabia and the Middle East, Malak was nominated for her "passionate leadership and great teaching" in clinical pathology, anatomical pathology, neuropathology, and molecular genetics. Malak worked in a number of universities – such as Georgetown, Stanford, and Harvard – before becoming Founding Chair of the genomics research department and Primary Investigator of the Saudi Human Genome Lab at King Fahad Medical City Research Center in Riyadh. Her ultimate goal is to improve the application of personalized medicine and targeted therapy in the clinical management of patients.

Malcolm Robinson

"My favorite part of the job is showing young patients the science behind their healthcare and that there is someone working hard in the laboratory to help them get better," says Malcolm, a biomedical scientist from Western Sussex NHS Hospitals Foundation Trust. He founded a charity called Harvey's Gang, which gives children across the UK laboratory tours to show them the journey their blood samples take. His work with Harvey's Gang crowned him Biomedical Scientist of the Year in 2018. "We aim to reduce fear, enlighten, educate, and empower these youngsters, who might just become the next generation of scientists!"

Mariam Molani

An Anatomic and Clinical Pathology resident at the University of Nebraska Medical Center, Mariam is trailblazing with her use of technology and social media. She commands a large following across various social media platforms, which she uses to increase engagement with students, patients, and the wider public. On her biggest influence, Mariam says, "My father is a community pathologist and my mother practices family medicine. After school during my childhood, my mother would talk about different disease processes and how she treated them, and my father would break down the pathophysiology. These experiences helped shape my drive to pursue pathology."

Marilyn Bui

Marilyn is an Anatomic and Clinical Pathologist and Scientific Director of the Analytic Microscopy Core at Moffitt Cancer Center. She is also Director of the Cytopathology Fellowship at the University of South Florida Health Morsani College of Medicine. She promotes the image of pathologists in her many speaking engagements – nominators call her humble, generous, and supportive. "The most unexpected moment of my career was during my PhD study at the University of Florida," says Marilyn. "I received the President's Outstanding Achievement and Contribution Award, for which I am grateful to my graduate program director and the leadership of my mentor."

Mario Plebani

Mario is Professor of Clinical Biochemistry and Clinical Molecular Biology at the University of Padova and the Chief of the Department of Laboratory Medicine at the University Hospital in Padova. Recognized as a pioneer and trailblazer in patient safety, he is committed to reducing and preventing laboratory errors through creating a system of quality indicators in the lab. Mario is a strong leader and has mentored a number of students throughout his career. His most unexpected moment? "Becoming a member of the Accademia Galileiana, a very prestigious recognition of my scientific work."

Mario Prieto

Mario is an anatomical pathologist at San Chinarro Hospital in Spain; his research interests lie in hematopathology, breast pathology, and lymphoma. With an active presence on social media, he was nominated for his contribution to online education through the #CaseOfTheDay hashtag, which he uses to prompt discussions into interesting and unusual cases. "My one piece of advice would be to follow your own path; it can be tempting to emulate the steps of your idols, but you should embrace the activities that increase your self-confidence and happiness," Mario says.

Marta Cohen

Marta is Head of the Department of Histopathology and Clinical Director of Pharmacy, Pathology, and Genetics at Sheffield Children's Hospital. An Honorary Professor of the University of Sheffield since 2018, she was the first woman in the UK to be appointed a Professor in Pediatric Pathology – and the Royal College of Pathologists recently designated her Academic Lead for Pediatric and Perinatal Pathology. "I am forever grateful to my friend and mentor Roc Kaschula, who had an enormous influence on my career by inviting me to apply for a training position at Red Cross Children's Hospital in Cape Town," says Marta.

Martina Bosic

Martina is Assistant Professor at the Institute of Pathology at the University of Belgrade in Serbia. Specializing in chronic inflammatory skin disease, she was the first person to implement molecular pathology methods in her country. Her active work to bring molecular pathology into everyday practice and into residency programs wins her a place on this year's Power List. On her hopes for the future, Martina says, "We need to be prepared to use genomics, proteomics, and other new methods in everyday practice to provide the best possible patient care."

Mary Landau

Mary is a practicing pathologist from Arizona who founded MPathy Art, a website dedicated to showcasing beautiful and intriguing artwork from the lab. She has always envisioned science as an art form and believes that scientists and artists are united by the fact that they're dreamers. "I still feel as though pathology is the best kept secret in medicine," says Mary. "MPathy Art allows me to share the exquisite patterns of human pathology while teaching the general public a little about the role of pathologists."

Massimiliano Marco Corsi-Romanelli

Massimiliano is a Professor in the Department of Biomedical Sciences for Health at the University of Milan and Laboratory Head of the Diagnostic Department at IRCCS Policlinico San Donato in Milan. A dedicated educator and prolific publisher, he was nominated for his trailblazing work with the study of epicardial adipose tissue. "My favorite part of the job is teaching clinical pathology and studying cellular and molecular pathology," Massimiliano says.

Marta Garrido Pontnou

Marta is an anatomical pathologist at Vall d'Hebron University Hospital in Barcelona, Spain, where she is dedicated to pediatric and developmental pathology and electron microscopy. She was nominated for her invaluable contributions to fetal and placental pathology. Talking about her favorite part of her field, Marta says, "Understanding a complex malformation can be a great challenge – I liken it to finding an exit door in a Minotaur's labyrinth, but fetal autopsy is a thorough and highly rewarding job."

Matthew Cecchini

After completing residency in anatomical pathology at Western University in Canada, Matthew is now a pulmonary pathology fellow at the Mayo Clinic. On the future direction of the field, Matthew says, "I believe the advancing fields of genomics, digital pathology, and artificial intelligence will fundamentally change the way we practice. These advances will allow us to better classify disease, share challenging cases, and increase our accuracy and efficiency. By embracing these emerging technologies, pathologists will increasingly be able to stand up from behind the microscope to collaborate with our clinical colleagues and ensure the best care for our patients."

Michael Laposata

Michael is Professor and Chair of the Department of Pathology at the University of Texas Medical Branch at Galveston. He was instrumental in creating a diagnostic management team within his institution, a patient-centric process whereby pathologists are consulted to ensure the correct diagnostic tests are ordered. A leader in patient safety, he is eternally committed to the identification and prevention of diagnostic errors. His biggest inspiration? "Lockard Conley embraced me and became my career advocate when I was doing research in a hematology lab the summer before medical school; he built the foundation for my career!"

Michael Misialek

Michael is Associate Chair of Pathology and Medical Director of the Vernon Cancer Center at Newton-Wellesley Hospital, Massachusetts. He is active on social media and regularly shines a light on his profession via Twitter. His latest venture involves a collaboration with a founding member of the popular band The Doors, in which he strives to raise awareness of the great work of pathologists. On the future of the field, Michael says, "AI will work its way into widespread practice, immunotherapy will be further refined, and patient consults will be more common. I believe the future is bright for pathologists."

Michal Michal

Michal is a Professor of Urologic Pathology at Charles University in Prague, Czech Republic, and at the Department of Pathology in Pilsen. He is a true trailblazer in his field and has described several new entities in urologic pathology, including mixed epithelial and stromal tumor, renal cell carcinoma with (angio)leiomyomatous stroma, and signet ring stromal tumor of the testis. Nominators also commend his ongoing commitment to educating the pathologists of the future.

Nicole Riddle

Currently working at Tampa General Hospital as a pathologist, nominators praise Nicole's active and continued involvement in pathology advocacy. In her role as a member of the Young Physician Section Governing Council for the American Medical Association, she has given pathology a strong voice to ensure that the profession has a seat at the top table of medicine. Given the chance, the one thing that Nicole would change about her field is inter-specialty communication. "The lack of basic understanding of what we do in pathology often causes frustrations on both sides and, unfortunately, sometimes leads to patient care issues."

Oana C. Rosca

"Every day of a pathologist's career is unexpected; we touch patients' lives in so many ways," says Oana, a molecular pathologist and cytopathologist at Northwell Health Systems – Staten Island University Hospital in New York. As an Associate Residency Program Director and Assistant Professor at Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, she enjoys teaching residents and medical students and is involved in translational research with a focus on molecular assays using limited material. "I believe in communication as one of the greatest tools to educate and initiate change, allowing pathologists to play a significant role in the clinical team."

Patrick C. Mathias

"What I enjoy most is the ability to apply my skills to help change the system and improve care for patients from behind the scenes," says Patrick, Associate Medical Director of Laboratory Medicine Informatics and Assistant Professor in the Department of Laboratory Medicine at the University of Washington School of Medicine. "By shaping our information systems and workflows, I am able to help my colleagues, from the front-line staff to the laboratory professionals, across our whole organization." Patrick's ambition is threefold – to reduce the per capita cost of health care, increase the health of populations, and improve the patient experience.

Paul van Diest

Paul is Head of the Department of Pathology at the University Medical Center Utrecht. A world-renowned breast pathologist, Paul has rearranged the infrastructure within his department to put digital pathology at the center of the diagnostic flow. This led to the creation of the world's first academic routine digital diagnostic pathology department. His advice to those who wish to follow in his footsteps? "Think outside the box and believe in your own solutions."

Pembe Oltulu

Pembe is Associate Professor of Pathology at Necmettin Erbakan University, Meram Faculty of Medicine, in Turkey. With a focus on dermatopathology and hematopathology, she devotes a lot of time to education and training through social media. She was nominated for her active use of Twitter at major global meetings to disseminate knowledge and for helping to create a dynamic and engaged pathology community on social media in Turkey. Her best advice? "Join the amazing #PathTwitterFamily to discover how advanced technology, social media platforms, and the Internet can all be used as useful tools for collaboration and communication."

Peter M. Sadow

"I love being part of each patient's life – even though most don't know it – and I enjoy helping them to find answers about their health," says Peter, Director of Head and Neck Pathology at Massachusetts General Hospital. He oversees the clinical service, quality initiatives, and head and neck fellowship training within the Anatomic Pathology Division. He is also Associate Professor of Pathology at Harvard Medical School and plays a prominent teaching role within the hospital and on medical education courses.

Pranav Patwardhan

Pranav works in the Department of Pathology at Seth G.S. Medical College in Mumbai. With his educational Facebook page, "Understanding Pathology," he provides a platform for over 5,000 pathology trainees around the world to share practical tips. Pranav was nominated as a trailblazer for his algorithmic approach to organ systems, which highlight relevant diagnostic features that help with histopathology specimen evaluation. "If I could make one change, I would create a single platform for pathology education worldwide," says Pranav. "That would enable all trainees to begin on an equal footing, even those in institutions that lack the latest technological advances."

Ramineni Ashok Kumar

Ramineni can be found at MNR Medical College and Hospital in Hyderabad, India, where he works as a Professor and Medical Superintendent of a thriving pathology department. His nominators praised his "insightful and immense knowledge of the subject," his discipline, and his dedication to the field. He has published on a variety of subjects ranging from unusual skin disorders to rare congenital abnormalities.

Raul S. Gonzalez

Raul is a pathologist at Beth Israel Deaconess Medical Center and Assistant Professor of Pathology at Harvard Medical School. "The most unexpected moment of my career was the response to my 2018 'tweetorial' on neuroendocrine neoplasms of the GI tract," says Raul. "Although I delivered it with pathologists in mind, I received several messages from patients living with neuroendocrine tumors. They shared stories with me and expressed their appreciation for how my posts helped them to understand their disease. I now keep a larger audience in mind whenever I post on social media."

Richard Levenson

"There seems to be a crisis of confidence in pathology. Fewer and fewer medical students are choosing it for their residency training, and medical school curricula have relegated pathology to a sort of adjunctive contributor to the education process," says Richard Levenson, Professor and Vice Chair for Strategic Technologies in the Department of Pathology and Laboratory Medicine at UC Davis Health. "We need to change pathology's role in both education and the entire clinical domain to resurrect it." Richard has been instrumental in the development of Microscopic Ultraviolet Sectioning Excitation (MUSE), which eliminates the need for conventional tissue processing.

Rifat Mannan

Nominated for his excellent teaching and inspiring mentoring of residents, Rifat is Assistant Professor of Clinical Pathology and Laboratory Medicine at the University of Pennsylvania's Perelman School of Medicine. Although still relatively early in his career, Rifat has already assisted many residents, fellows, and budding pathologists with their research. He was a cofounder of PathCast, an open-access academic platform that aims to bridge knowledge gaps in pathology by live-streaming lecture series for a global audience. "I am passionate about globalizing medical education and helping to improve patient care in the remotest corners of the world," says Rifat.

Rola Ali

Rola currently works as an Associate Professor in Kuwait University's Department of Pathology. Nominators commend her educational tweets and passionate approach to teaching, which has inspired many to pursue pathology. On the future of the field, Rola says, "In this part of the world, the demands on pathologists are ever-increasing, with a shortage of pathologists and a growing number of increasingly complex cases. Fortunately, digital pathology and social media platforms have melted away geographic barriers, connecting pathologists from all over the world, and I think they will continue to play an important role in enhancing collaboration and knowledge exchange."

Samson W. Fine

Samson is a genitourinary pathologist at Memorial Sloan Kettering Cancer Center in New York. He was nominated for being one of the early in situ pathologists who engaged with audiences on social media at USCAP. On his hopes for the future, Samson says, "As a pathologist involved in researching urologic cancers, I hope that we can increasingly embrace robust statistics. Instead of simply reporting more and different features of tumors, careful multivariable analyses will enable nuanced incorporation of histologic and molecular features to produce the most clinically relevant and actionable pathology reports."

Sanjay Mukhopadhyay

Sanjay is Director of Pulmonary Pathology at Cleveland Clinic. He recently first-authored a landmark publication, which is the largest in the US to date to compare whole-slide imaging with conventional microscopy. A prolific user of social media for pathology education and advocacy, Sanjay established the #PathTweetAward that is now a popular educational tool on social media. On the future of the field, Sanjay says, "I see increasing acceptance of whole slide imaging for primary diagnosis, widespread recognition of social media platforms as vehicles for free global education and networking, and even more widespread use of immunotherapy across different tumor types."

Santiago Prieto

Santiago is President of the Spanish Association of Medical Biopathology – Laboratory Medicine and Head of the Clinical Laboratory at the Hospital of Fuenlabrada in Spain. Throughout his career, Santiago has placed considerable emphasis on delivering a patient-centered strategy. He is a firm believer that everything a pathologist does should serve the patient and improve their health, an approach that has become much more prevalent in recent years. His biggest influences? "My father, Michael Laposata, and listening to patients' expectations."

Silvana Di Palma

Silvana is a Consultant, Lead Researcher, and Lead Educational Supervisor at the Royal Surrey County Hospital. She has long had an interest in cutting-edge research and innovation, but she also inspires her co-workers and instills passion into the next generation of doctors. Because she believes that molecular biology is the future of pathology, Silvana instigated a collaboration between two labs in her institution, which resulted in the first robust HER2 in situ hybridization test for breast cancer patients in the UK. She says, "Confidence in myself, a supportive friend, and inspirational academics were integral to my successful professional career."

Sarah Coupland

"I love Pathology for its contrasts and challenges – some cases are very simple, others extremely complex and demanding, like a hard-to-crack puzzle," says Sarah, George Holt Chair in Pathology and Consultant Histopathologist at the University of Liverpool's Institute of Translational Medicine. As Lead of the Liverpool Ocular Oncology Research Group, Sarah is trailblazing in ophthalmic pathology, oncology, and hematopathology. She recently contributed to the fourth volume of the World Health Organization Tumors of the Eye classification, published in 2018, and has won several awards, including the International Council of Ophthalmology's Eye Pathology Award in 2018.

Severino Rey

Severino is Head of the Anatomical Pathology Service at Hospital Universitario de Torrevieja, Spain. He has delivered lectures at over 80 national and international conferences and, in the last year, he has taught endocrine and mediastinal pathology courses internationally. Severino says, "There are some countries, such as in Latin America and Africa, where laboratory medicine is not well positioned – pathologists don't get the recognition they deserve and young people don't want to enter the field. I would love to work on international projects where universities, laboratories, and professionals from these countries are actively supported with training and resource exchange."

Stephen Master

Based within the Division of Laboratory Medicine at the Children's Hospital of Philadelphia, Stephen has served as Director of Central Laboratory Services in addition to his role as a faculty member in the Division of Pathology Informatics. His work focuses on machine learning for cancer diagnosis, an emerging and highly promising field that will become invaluable in the years to come. He's also a leader in service, active within the American Association for Clinical Chemistry and on the scientific committee for the Mass Spectrometry: Applications to the Clinical Lab conference.

Suzy Lishman

Suzy is a consultant cellular pathologist at Peterborough City Hospital, as well as the Head of Department and lead for gastrointestinal pathology. She is also one of only two women to serve as President of the Royal College of Pathologists in the UK. Suzy is a true social media ambassador for pathology and appears on this year's Power List thanks to her tireless advocacy work on television and radio. Her best advice? "Get to know your colleagues! Social events, sponsored sporting activities, and charity cake sales all help to bring people together, flatten hierarchies, and improve working relationships and morale."

Syed T. Hoda

Syed is Director of Bone and Soft Tissue Pathology at New York University (NYU) and Director of Surgical Pathology at the NYU Langone Orthopedic Hospital. His trailblazing approach to new technologies, such as the use of educational apps and the development of remote frozen section systems, sees him appear on this year's Power List. "I would like my pathologist colleagues to be bold, thoughtful, and creative in helping patients and physicians deal with human disease – and these are the same qualities we should use in teaching the next generation of doctors to inspire them for the future," says Syed.

Wendy L. Frankel

Wendy is Kurtz Chair and Distinguished Professor of Pathology and Chair of the Department of Pathology at The Ohio State University Wexner Medical Center. Wendy currently serves as the President of USCAP and is a leader in gastrointestinal pathology. She played a key role in the Columbus-area HNPCC study to determine the prevalence of Lynch syndrome among all newly diagnosed colorectal and endometrial cancer patients. The results of this study have changed the standard of care for colorectal cancer patients around the world. Her best advice? "Follow your interests, but have the flexibility to take opportunities and modify your plans."

Timothy Craig Allen

Timothy is Professor and Chair of the University of Mississippi Medical Center. His work and advocacy for bringing pathology out of the shadows and for building patient-pathologist communication pathways is extremely encouraging for all in the profession. "If I could change one thing about the field, it would be our attitude," Timothy says. "We must become more proactive and assertive as physicians, involving ourselves in our hospitals, our communities, and our patients' lives." Timothy's dedication to promoting pathologists as critical patient advocates in all aspects of healthcare makes him a true leader and role model for others.

Valerie Fitzhugh

Valerie is Associate Professor of Pathology and Laboratory Medicine at Rutgers New Jersey Medical School. A strong advocate for women in medicine, Valerie is trailblazing with her passionate quest to achieve equality in the lab, which she promotes in the classroom and on social media. Nominators praise her active role in sharing her own experiences to inspire the next generation of pathologists and applaud her generous encouragement and support of others. Her favorite part of the job? "They might not know I exist, but to know that I am truly helping patients get the right treatment gives me incredible joy."

Yael Heher

Yael is Assistant Professor of Pathology at Harvard Medical School and Director of Quality and Patient Safety in the Department of Pathology at Beth Israel Deaconess Medical Center. Pathologists play a critical role in patient safety – and the importance of Yael's trailblazing work in developing that role cannot be understated. "I love that successful pathology quality and safety initiatives empower frontline lab employees while helping senior staff understand and improve the lab's performance," Yael says. Thanks to her dedication, the role of the pathologist in patient safety, error communication, and patient disclosure is more defined than ever.

Yuchun Ding

A trained computer scientist from Newcastle University, Ding works alongside pathologists to develop practical solutions in digital pathology. He is the creator of X-WOW!, which he set up to improve access to microscopy equipment for pathologists who work in remote areas. On his ambitions, Yuchun says, "One day I suddenly realized a cruel fact – my efforts are useless to those who can't afford the equipment to produce whole-slide images for analysis. That's why I created X-WOW! in my own time; I want to focus on making digital pathology easier to access for those who have been forgotten."

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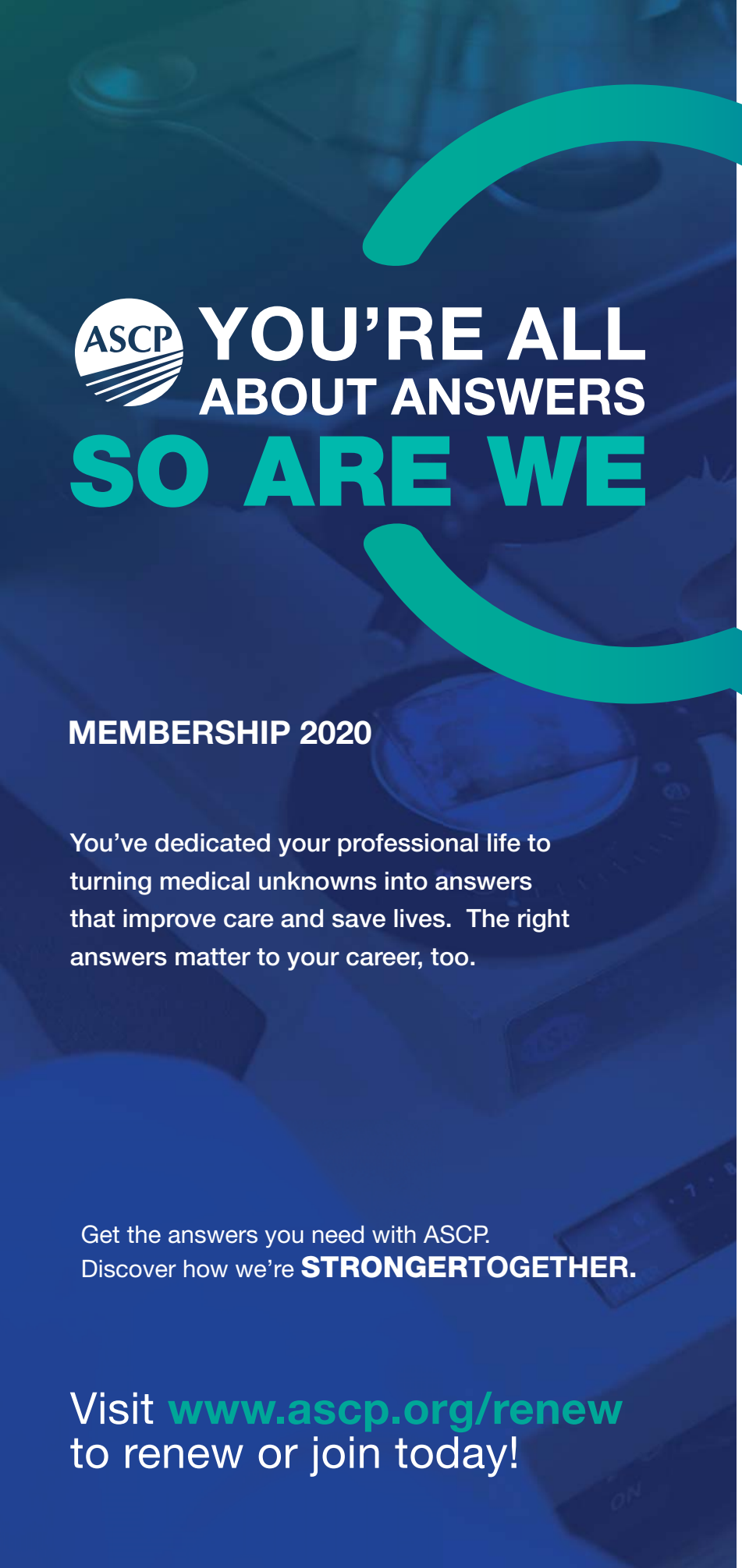

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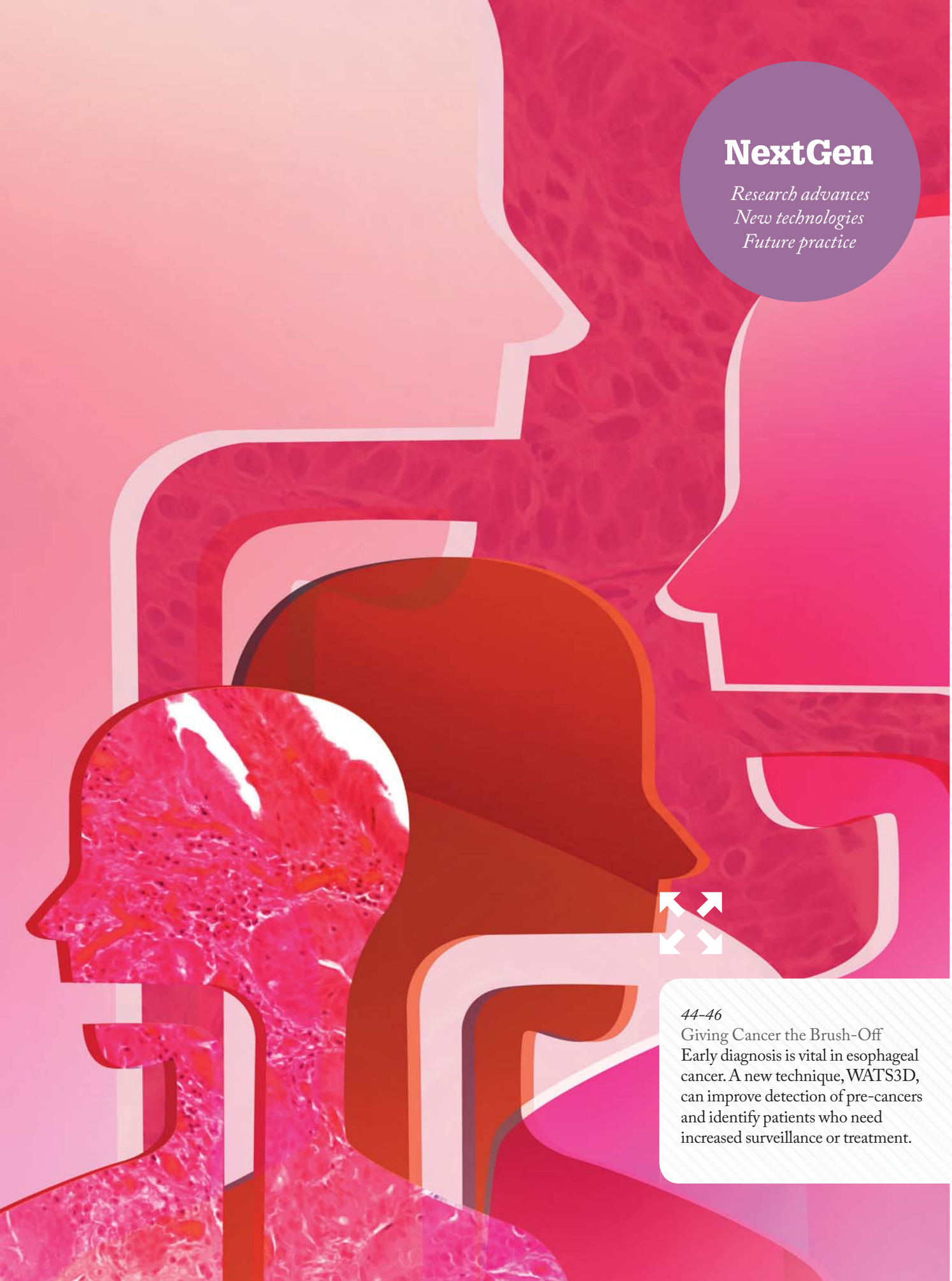

44–46
Giving Cancer the Brush-Off
Early diagnosis is vital in esophageal cancer. A new technique, WATS3D, can improve detection of pre-cancers and identify patients who need increased surveillance or treatment.

Giving Cancer the Brush-Off

WATS3D – a new brush-based biopsy technique, combined with computer-assisted analysis – can improve detection rates for pre-cancerous conditions in patients with Barett's esophagus

By Robert Odze

Esophageal cancer may not be among the most common forms of cancer, but it's certainly one of the most fatal. Only about one in five people diagnosed with esophageal cancer will survive five years (1), and over two-thirds are diagnosed with late-stage disease (2). The key precursor to esophageal cancer is Barrett's esophagus (BE), a metaplastic change that is often followed by transition to dysplasia. Patients who exhibit signs of BE or esophageal dysplasia (ED) must undergo increased surveillance or ablation so that cancer can be preempted. However, current screening and surveillance technologies are flawed – a dangerous situation for patients at risk for esophageal cancer.

At a Glance

- *Forceps biopsy screening for esophageal pre-cancers has a high degree of sampling error*
- *Inter-observer variability further limits the protocol's ability to detect significant disease*
- *A new technique, WATS3D, combines wide-area trans-epithelial sampling with 3D computer-assisted analysis*
- *WATS3D reduces sampling error, improves detection of goblet cells and dysplasia with assistance from computer-generated images, and highlights the most atypical areas of tissue*

What's the current gold standard for identifying BE and ED?

The current gold standard for screening and surveillance of BE and associated neoplastic lesions is forceps biopsy of patients with known or suspected BE. The Seattle protocol requires biopsies from all four quadrants of Barrett's mucosa – every centimeter for patients who have dysplasia; every two centimeters for those who don't – as well as any visible lesions. The diagnosis is based on histologic evaluation of mucosal biopsies.

However, this method is fraught with problems. Foremost of these is that it results in a high degree of sampling error because the biopsies cover only a small fraction of the Barrett's mucosa (in some cases, less than 5 percent). Several studies have shown that up to one-third of BE patients present with high-grade lesions and even cancer within one year of endoscopic screening or surveillance (3). This indicates that sampling error resulting in false negatives is a huge problem with the Seattle protocol.

The second problem is inter-observer variability regarding establishing a diagnosis of dysplasia in forceps biopsies. Although pathologists have been assessing biopsies for several decades now, we haven't seen any significant gain in inter-observer agreement, whether general or expert, over that period of time. Pathologists still differ quite strongly in interpretation of dysplastic lesions, particularly when it concerns distinguishing regenerating epithelium from low-grade dysplasia – a common problem – and secondarily differentiating low-grade from high-grade dysplasia. These are critical decisions because non-dysplastic, low-grade dysplastic, and high-grade dysplastic BE may be treated differently, so an accurate diagnosis is important for patient care.

Tell us about the wide sampling approach…

It's called wide-area transepithelial sampling with 3D computer-assisted analysis (WATS3D). From the name, you can probably determine that the test consists of two major components aimed at decreasing the common problems associated with the Seattle biopsy protocol.

WATS3D uses a proprietary brush composed of longer and harder needles than conventional soft-brush cytology brushes. Soft brushes typically acquire superficial exfoliated cells from the top portion of the mucosa, but dysplasia and early cancer often reside in the deep mucosal crypts. If one doesn't want to miss those areas, one needs to acquire tissue from deeper in the mucosa. The WATS3D brush is useful because it acquires full-thickness mucosal fragments – that is, tissue all the way down to the muscularis mucosa. And because it's a brush that sweeps across the mucosal surface and acquires a lot of tissue, it greatly decreases sampling error. We've seen significant increases in detection rates for both goblet cells (required for fulfillment of the BE criteria) and dysplasia using the WATS3D diagnostic platform.

The second aspect of WATS3D is computer-assisted analysis. The computer system scans all of the tissue acquired by the brush, then uses a neural network and artificial intelligence (AI) to analyze it. This analysis includes a battery of morphologic assessments on the nuclear characteristics of the tissue; it also ranks tissue fragments according to degree of atypicality; and it performs a unique extended depth-of-field (EDF) imaging analysis on the cell aggregates. Ultimately, it synthesizes images of the most atypical tissue fragments and presents them to the pathologist on a computer screen to be used when the pathologist signs out the specimen at the microscope.

In EDF imaging, tissue fragments – typically between 150 and 200 microns thick on a WATS3D smear – are scanned

at 5 µm intervals all the way through the tissue, similar to a CT scan of the human body. The system then uses neural network programming to synthesize all of those 3D cuts into one crisp, clear, artifact-free 3D image. That way, the pathologist has a unique view of the tissue fragments, including whole crypts and their features, which leads to improvement in diagnosis. In one recent study, the degree of inter-observer agreement was much higher for WATS3D specimens (all kappa values >0.7) than for forceps biopsies alone (4).

Tell us about your own experience with WATS3D…

WATS3D specimens come in two forms. The first is a formalin-fixed, paraffin-embedded, H&E-stained slide similar to a normal mucosal biopsy. However, the fragments of tissue are very small – I would consider them "micro"-biopsies. The other specimen is the tissue smear I've described above. I refer to these two approaches as "histocytology," because we can see clear histologic features of dysplasia in what amounts to cytology brush specimens. The addition of the computer analysis is unique – and it's fascinating, because you get to see crypts almost in their natural form.

Overall, the learning curve for WATS3D is very short. I have a lot of experience diagnosing BE via traditional means – and, after I went through a teaching process of about 20 cases, I felt very capable of diagnosing the vast majority of WATS3D cases. By the time I hit 30 cases, I felt extremely comfortable. Despite the novel technique, one evaluates all the same features in WATS3D specimens that one sees in traditional forceps biopsies, so it's really nothing new from the histologic point of view. I view it as a crisper, more visually accurate and specific method of evaluating tissue.

The recommendation right now is to use WATS3D with any patient who is endoscopically identified as having salmon-colored mucosa in the esophagus and therefore suspected or previously known to have BE. Why? Because WATS3D is proven to be more efficacious for both identifying goblet cells (that can help confirm the diagnosis of BE) and for identifying neoplastic precursor lesions. In my opinion, the technique should be used not only for surveillance, but also during each patient's initial index endoscopy (screening), because most dysplasia and early cancer that we see in BE is detected at that point in time (prevalent dysplasia). That's when the chances of finding dysplasia are greatest, so that's when we should be using our most powerful detection tool.

Why is it so important to detect these conditions early?

At the moment, 95 percent of esophageal cancers are diagnosed outside the setting of surveillance (5). Even among patients in a surveillance program, at least one-third develop cancer within a year of an endoscopic surveillance (3). It's clear that endoscopic surveillance in its current form is not efficient. We recognize from our experience with cancers in other parts of the body, such as in the cervix and the colon, that early (often endoscopic) detection of neoplastic precursor lesions can drastically reduce the incidence of invasive cancer worldwide. The same is true for esophageal cancer, which is particularly deadly. To make headway in helping patients with this condition, we must work to detect its precursors and prevent its development, because once a patient has esophageal cancer, the fatality rate is high.

We know that cancer develops through a metaplasia–dysplasia–cancer pathway. We know that when a patient transitions from metaplasia to dysplasia, regardless of how small or isolated the lesions, they have already acquired the necessary mutations to be considered at high risk for progression to cancer. There's no reason we wouldn't want to eliminate it at that stage, so it makes biological and ethical sense to try to find and eliminate pre-cancer before it develops into invasive cancer.

What are the next steps for WATS3D?

WATS3D is ready for routine clinical use. There have been five prospective trials (some randomized) and an inter-observer study that have all shown a greatly increased detection rate of BE and ED by WATS3D when used as an adjunct to mucosal biopsies. Those studies have been performed in both high-risk academic centers and low-risk general community populations with uniformly positive results. As a result, I believe that if you or I had BE, we would be better off having forceps biopsies plus WATS3D, rather than forceps biopsies alone, because the data unequivocally show that this combination approach has a greater chance of detecting pre-cancer, which is the goal of surveillance. Now that we have a safe and effective ablation treatment for pre-cancer (which was formerly treated by esophagectomy), WATS3D is ready for prime time.

Of course, our knowledge will continue to grow. There are studies currently underway to evaluate WATS3D in various patient groups, such as post-ablation, short-segment BE, low- and high-risk European and North American patients – so we'll have even more information in a few years' time than we do now. The field of BE is also moving toward biomarker-based evaluation of patients with non-dysplastic BE to determine which patients are at risk for progression and which aren't, so that we can modify our existing surveillance programs accordingly. So far, randomized, long-term outcome studies in patients without dysplasia haven't revealed any efficacious non-histological biomarkers, so that's where I think we're headed next. We need the ability to predict which patients without neoplastic precursor lesions are at risk of developing them. Luckily, because WATS3D tissue fragments are virtually all epithelial (with very little lamina propria and soft tissue), they are primed for molecular biomarker studies. I think, in the future, we'll see WATS3D brush specimens used not only for morphological evaluation, but also in concert with biomarker panels.

Regardless of where the next few years take us, I think the data are already so compelling that WATS3D should already be considered standard of care – and I hope the rest of the world soon agrees.

Robert Odze is Professor of Pathology at Harvard Medical School and Chief of Gastrointestinal Pathology at Brigham and Women's Hospital, Boston, USA.

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Goblet Cells

An ongoing controversy in the definition of Barrett's esophagus

In the US, the major governing bodies in gastroenterology all require two criteria to establish the diagnosis of BE. One is endoscopic recognition of salmon-colored mucosa in the esophagus, for the most part greater than 1 cm in length; the second is confirmation of the presence of goblet cells in biopsies from those areas of salmon-colored mucosa. In many other parts of the world, BE can be diagnosed by endoscopic evidence of salmon-colored mucosa alone (in other words, those governing bodies do not require pathologic identification of goblet cells to establish a diagnosis).

So why were goblet cells incorporated into the diagnostic criteria in the US? It's partly based on the belief that only patients who have goblet cells in esophageal mucosa are at risk of neoplastic progression. However, we now have plenty of data to suggest otherwise. Many patients can develop dysplasia and cancer in esophageal columnar mucosa without goblet cells – something that has been proven in scientific cloning and lineage experiments (1).

It's true, though, that most patients who do develop dysplasia and cancer do have goblet cells – even though they aren't strictly required. And most gastroenterologists who see endoscopic evidence of salmon-colored mucosa in the esophagus, even if the biopsies fail to reveal goblet cells, still put those patients into a surveillance program, because there's always a risk that the lack of goblet cell identification was due to sampling error. The sensitivity and specificity of biopsies to detect goblet cells, particularly in patients with shorter segments of BE, is very low.

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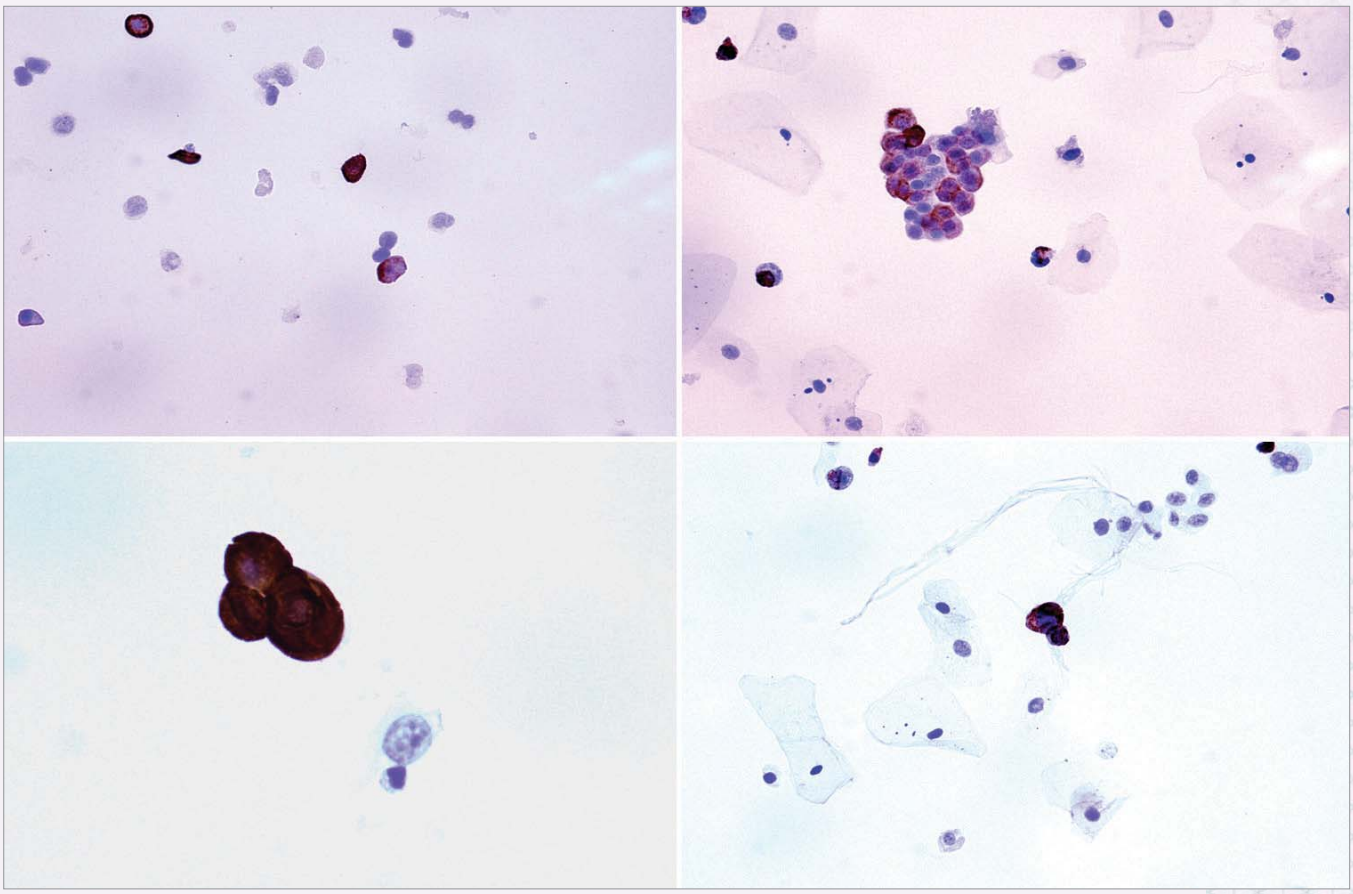

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When the Current Serves

Sitting Down With… Anant Madabhushi, F. Alex Nason Professor II of Biomedical Engineering and Director of the Center for Computational Imaging and Personalized Diagnostics at Case Western Reserve University, Cleveland, USA

Why did you pursue digital and computational pathology?

My initial plan was to study medicine, but my application was unsuccessful. Biomedical science seemed like the next best thing and it was a subject I could get excited about, so I began my degree in biomedical engineering in Bombay, India. During my studies, I was exposed to medical imaging and realized that the integration of computer science and imaging was a sweet spot for me. I began to develop pattern recognition algorithms, not to find cancer, but to find people in videos and to recognize certain movements.

During my PhD, I really started to zero in on the computational analysis of medical images, starting with radiography. I was fortunate enough to meet two pathologists: Mike Feldman and John Tomaszewski. One day, Mike said to me, "Imagine if you could digitize this little slide and start to interrogate it computationally; think about the opportunities." I picked it up and replied, "This little thing? That should be trivial!" I didn't realize that one small slide would produce gigabytes of data! That was just the beginning – shortly thereafter, we published the first paper on digital pathology.

How close are we to using algorithms in routine clinical practice?

In the US, my sense is that many artificial intelligence (AI) and machine learning algorithms will now receive 510(k) designation from the FDA, rather than the traditional premarket approval. And that's a big deal; we'll see many more submissions and much faster turnaround times, leading to new algorithms' being approved within two to three months. However, despite getting approval from the FDA, we must achieve certain inflection points to see wide-scale deployment.

Fundamentally, it's about monetization. If hospitals and medical institutions buy and deploy this kind of technology, they need to know where the return on their investment will come from. For that to happen, AI technology needs its own Current Procedural Terminology (CPT) codes for billing. Once the technology justifies its own CPT codes, I believe we'll see a significant inflection point.

What are you most excited about when it comes to computational pathology?

The proteomics, genomics, metabolomics, and transcriptomics of a tumor are fundamentally reflected in traditional H&E slides. I am extremely excited by this because it's the lowest common denominator; you can take breast cancer tissue from patients in Liberia, Birmingham, Sydney, and Cleveland, and they will all produce the same slide stained with the same two things – hematoxylin and eosin. We can now digitize those slides, upload the images to the cloud, and analyze them from anywhere in the world. That global impact will be a great leveler for low- and middle-income countries that can't afford expensive molecular diagnostic tests.

How do you balance your leadership positions, research areas, and personal interests?

"There is a tide in the affairs of men. Which taken at the flood, leads on to fortune; omitted, all the voyage of their life is bound in shallows and in miseries. On such a full sea are we now afloat, and we must take the current when it serves, or lose our ventures." This quote from Shakespeare's play Julius Caesar reflects my career journey so far. I didn't deliberately seek out all of the fields I currently work in, but when opportunities presented themselves, I started moving into different disease areas and "took the current when it served."

It also demonstrates my love for theater and literature; I even have a Diploma in Speech and Drama from Trinity College London. I indulge my interest in literature through my eight-year-old son, who can quote the entire opening monologue from Henry V! Although there's no magic recipe to maintaining a healthy work-life balance – and, sometimes, something has to give – I exercise every week to ensure I don't go insane!

I pursue so many different avenues to continue to build visibility and excitement in this space. Back in 2007, when a few of us started the first digital pathology meeting, we held it in a classroom because only 14 people attended. It's fantastic that, in just 12 years, we've gone from a very small niche to having several large annual meetings. But we haven't forgotten the pain that came with early failures. It has made us resilient; I think we recognize that we must continue to champion the idea to sustain and grow interest.

What are the proudest moments of your career so far?

I am most proud of things that relate to the visibility of the field as a whole, rather than to personal recognition. For example, in 2017, I was honored with the Institute of Electrical and Electronics Engineers (IEEE) Engineering in Medicine and Biology Society (EMBS) Technical Achievement Award. This was the first time it was awarded for contributions to digital pathology, so I felt as though I was carrying the flag for the whole community.

For me, the real accomplishment will be when these technologies are actually used to modulate treatments for patients – that's the ultimate goal. My present focus is on increasing the visibility of digital and computational pathology, laying the platform to transition these technologies to the clinic on a large scale.

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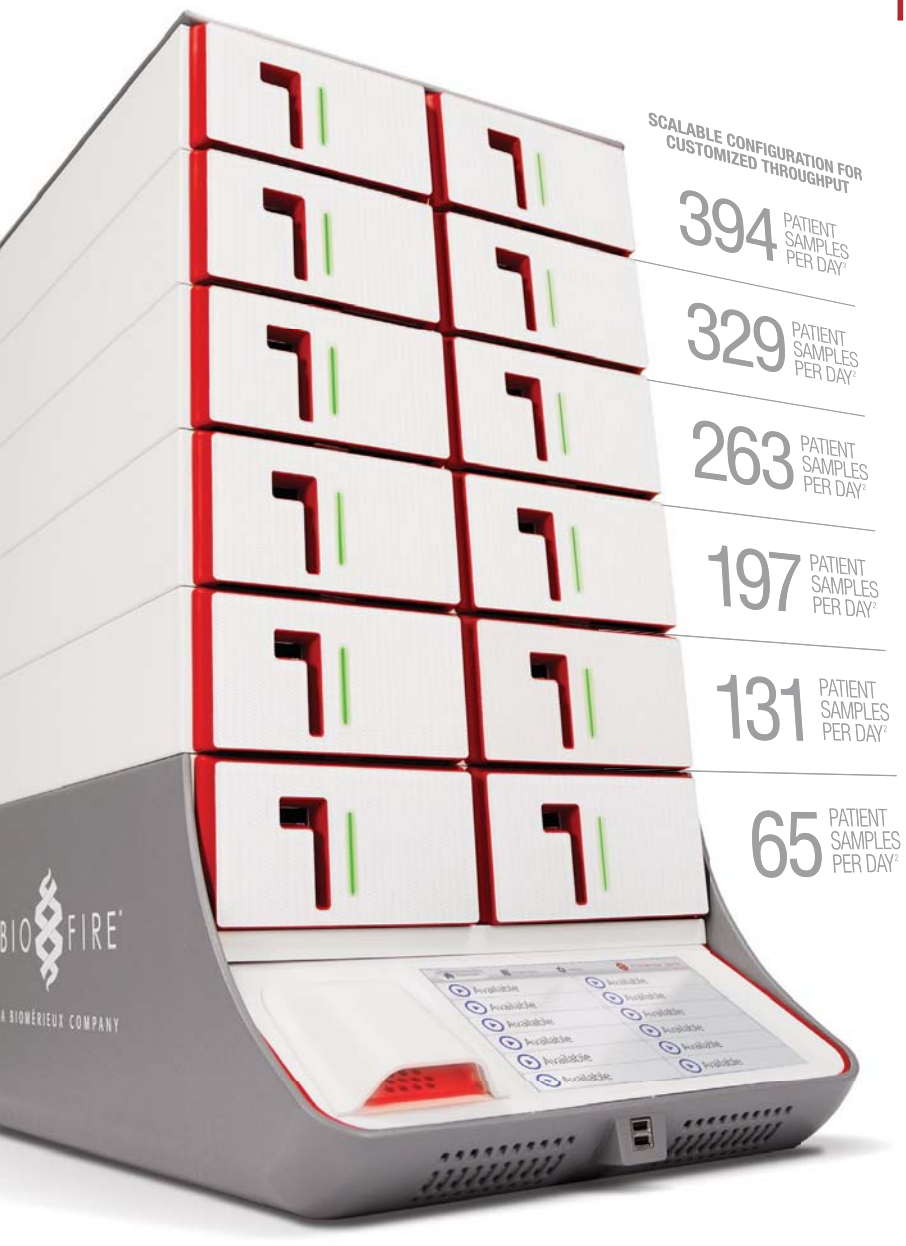

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