JUNE 2019 # 55

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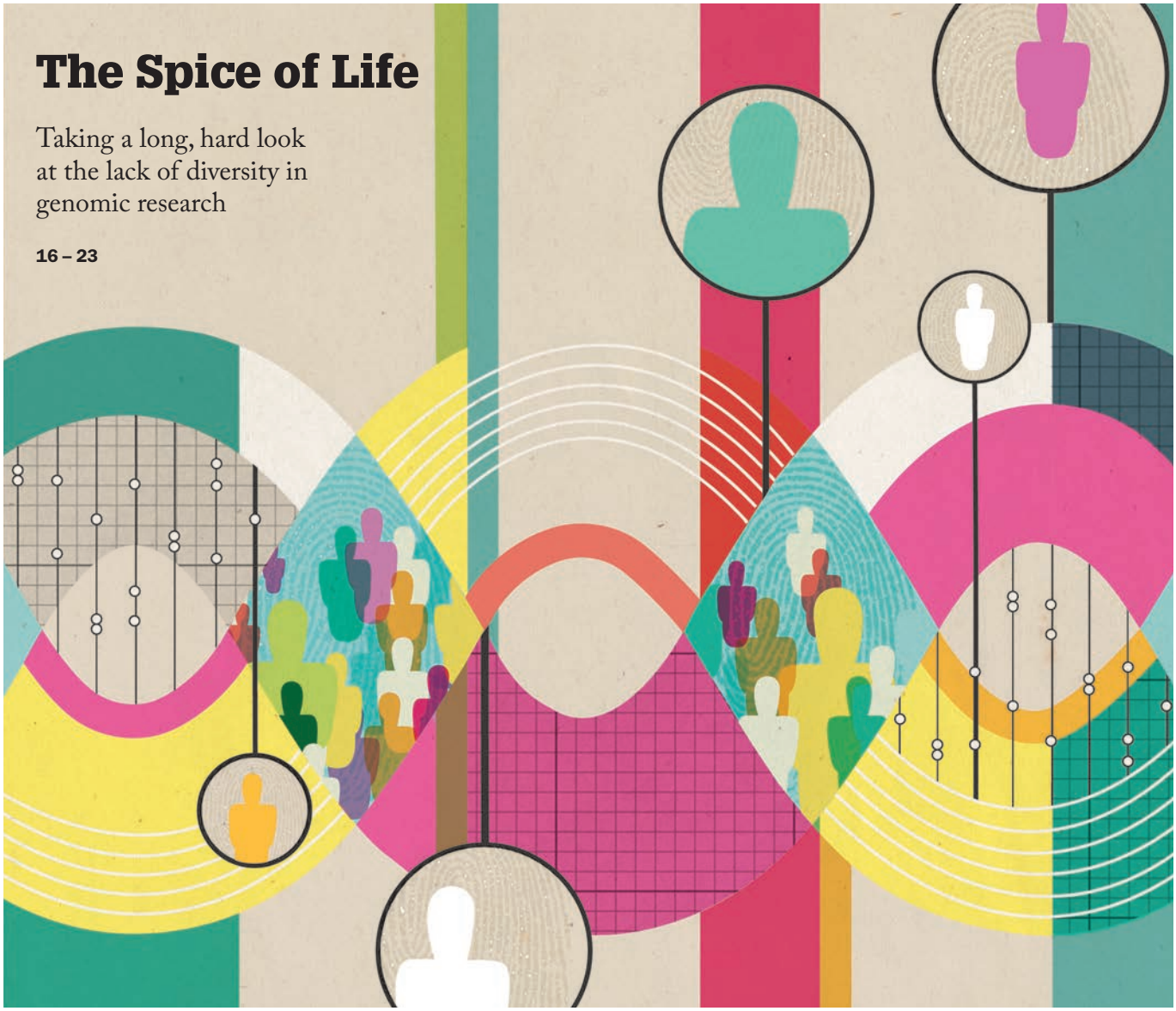
The Spice of Life

Taking a long, hard look at the lack of diversity in genomic research



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Case of the Month

A 53-year-old man presented with scrotal pain and a 1.5 cm testicular mass. Special stain for mucicarmine was negative. Immunohistochemistry was negative for pancytokeratin, CK7, CK20, CDX2, inhibin, OCT-3/4, and chromogranin.

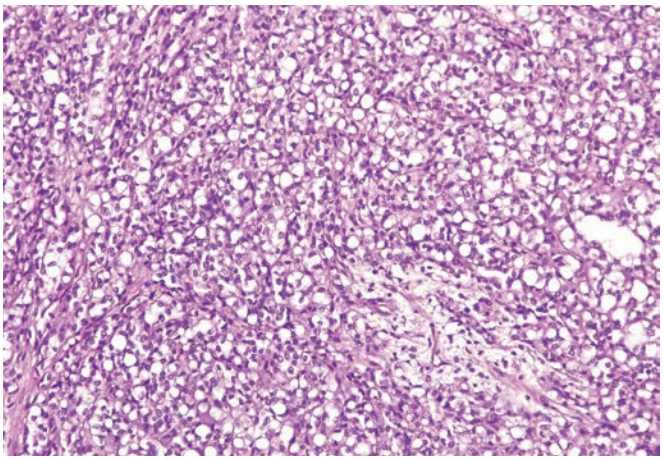
What is the most likely diagnosis?

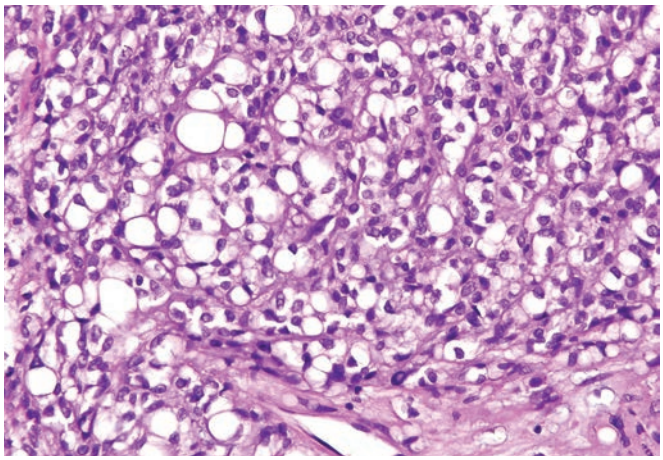
A. Leydig cell tumor

B. Sertoli cell tumor

C. Metastatic signet ring carcinoma from the colon

D. Primary signet ring stromal tumor of the testis





Answer to last issue's Case of the Month…

C. Mucoepidermoid carcinoma

This is a Warthin-like variant of mucoepidermoid carcinoma. At low power, the cystic nature of the process and the prominent lymphoid stroma are similar to Warthin's tumor, but the classic bilayered oncocytic epithelium of that lesion is absent. There is no sebaceous type epithelium present, and the irregular, haphazard nature of the cystic spaces is somewhat unusual for sebaceous adenoma or lymphoepithelial cyst. In difficult cases, diagnosticians can pursue testing for the *MAML2* translocation, which is present in mucoepidermoid carcinoma and absent in the other entities.

Submitted by Frank Ingram and Patrick Ware, Presbyterian Pathology Group, North Carolina, USA.

To register your guess for this month's case, please go to http://tp.txp.to/0619/case-of-the-month
We will reveal the answer in next month's issue!

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Upfront

On The Cover

A design to reflect the diversity we should ideally see in our genomic research populations.

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In Practice

NextGen

Profession

Sitting Down With

the Pathologist

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Preaching Beyond the Choir

You want to interact with patients – but how do you let them know you exist?

After nearly five years on The Pathologist, I feel like I've become well acquainted with many of you. We interact on Twitter. We get to know one another through articles. And, of course, we meet up in person at conferences throughout the year – to take selfies; to start hashtags; to have conversations. Nothing makes me happier than to spot a name or a face I recognize in the bustle of an exhibition hall or in the rush from one session to the next.

I consider myself privileged to be able to interact like this with so many pathologists and laboratory medicine professionals. But I also know that, as soon as I get home, things won't be quite the same. The next time I have a blood test or a biopsy of my own, I won't know the person who analyzes or interprets it. It will be whisked away into the laboratory "black box" to return as an anonymous result typed on a sheet of plain paper. I wouldn't even know whom to ask if I wanted to know more about the testing – and I'm not sure my doctor would either.

That's not the future I want for this very special profession. To my friends who are neither scientists nor doctors, I often find myself explaining, "You know. The people who read your blood tests and diagnose diseases and decide which treatments will work best for which people…" It's hard to summarize all facets of laboratory medicine in a single sentence! When my doctor asks me what I do for a living, but then responds with a hesitant, "Oh… okay…" after I tell them that I write about pathology – that's slightly more worrying.

Other medical professionals, of course, should know who their laboratory colleagues are – and many feel that patients should have the same education and access. But are we missing a vital first step? A patient won't ask about pathology – let alone reach out to the lab – if they don't know it exists in the first place. So how can that barrier be breached? Some suggest social media. Others place leaflets in public areas of hospitals. Still others have recommended explanatory sections on pathology reports or in patient access portals. What methods do you use – and have any been particularly successful? Tell us about it at edit@thepathologist.com; we'd love to help spread the word!

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

Delivering Better Care

A blood test for pre-eclampsia can speed up diagnosis and treatment, reducing adverse events for both mother and child

Pre-eclampsia – a term no couple anticipating a child wants to hear. A hypertensive disorder of pregnancy, the condition can lead to impaired maternal organ function, seizures, and even death if left untreated. And it's not a rare occurrence. Approximately one in every 10 women shows evidence of hypertension in pregnancy, and 3 percent of singleton pregnancies will be affected by preeclampsia. The risk increases for certain groups of women, including those with multiple pregnancies and those with coexisting medical conditions such as chronic hypertension and chronic kidney disease.

At the moment, pre-eclampsia is diagnosed by looking for evidence of hypertension along with one or more of:

- proteinuria (assessed with a protein:creatinine ratio or a 24-hour urine collection)
- evidence of maternal organ dysfunction (maternal symptoms,raised creatinine, elevated transaminases, thrombocytopenia, disseminated intravascular coagulation, or hemolysis)
- evidence of fetal growth restriction

"All of the methods we use to diagnose pre-eclampsia are nonspecific," explains Kate Duhig. "Most are associated with maternal end-stage organ damage as a result of the disease." Duhig is first author of a study that seeks to improve pre-eclampsia diagnosis (1). She and her colleagues found that measuring the concentration of placental growth factor (PlGF) in blood allowed them to diagnose the condition up to two days earlier than conventional methods.

Do those two days really make a difference? "Preterm disease can deteriorate very rapidly with serious consequences for both mother and baby," says Duhig. "The ability to reach a diagnosis two days earlier can help determine the appropriate place and frequency of management – for example, whether a woman needs admission or transfer to a hospital with appropriate neonatal care facilities. It can also be important for guiding steroid administration for fetal lung maturity and timing of delivery of the baby (the only cure for the disease)." Duhig's study showed that by monitoring PlGF, a pathophysiologically relevant biomarker, women experienced fewer serious adverse events. Low PlGF (<100 pg/mL) has a high diagnostic accuracy for pre-eclampsia requiring delivery within 14 days, ensuring that women who need rapid treatment can be identified and assisted. Furthermore, researchers were able to reassure women who did not need investigation and intensive follow-up, minimizing unnecessary health resource use.

Reference

1. *KE Duhig et al., "Placental growth factor testing to assess women with suspected pre-eclampsia: a multicentre, pragmatic, stepped-wedge cluster-randomised controlled trial", Lancet, 393, 1807 (2019). PMID: 30948284.*

The Right Dose for the Right Person

CYPC29 genotyping guidelines can help labs ensure that patients receive the correct dose of commonly prescribed drugs

Warfarin – the most widely used anticoagulant in the world, it's a well-known drug even amongst non-experts. Phenytoin, an anticonvulsant, is also among the most commonly prescribed drugs in its class. But despite their ubiquity, it can be difficult to establish the minimal effective dose for a patient. This is especially true in situations where their genotypes might be affecting metabolism of the drug – for instance, in patients who exhibit mutations in genes coding for the cytochrome P450 enzyme CYP2C9. For this reason, the Association for Molecular Pathology (AMP) Pharmacogenetics Working Group has developed a series of guidelines to help standardize clinical testing for these genes. The AMP-led working group included organizational representation from both the College of American Pathologists and the Clinical Pharmacogenetics Implementation Consortium (CPIC). To learn more, we spoke to Victoria M. Pratt, Associate Professor and Director of Pharmacogenetics and Molecular Genetics Laboratories at the Indiana University School of Medicine, AMP President, and PGx Working Group Chair.

What is the value of CYP2C9 genotyping?

The AMP PGx Working Group started with CYP2C19 and CYP2C9 genotyping panels due to the widespread adoption of these tests and our desire to help physicians, pharmacists, researchers, and other stakeholders better understand what these panels include and what the test results mean. The cytochrome P450 2C9 is one of the most abundant and important drug-metabolizing enzymes. It is involved in the phase I metabolism of many commonly prescribed medications, including the anticoagulant warfarin and the anticonvulsant phenytoin. The new CYP2C9 report focuses on testing that can be applied to all CYP2C9-related medications.

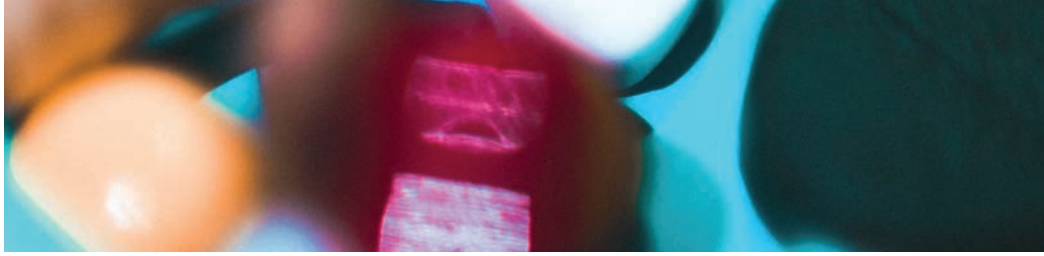
When is CYP2C9 genotyping most useful?

Because CYP2C9 testing is closely associated with the metabolism of warfarin and phenytoin, genotyping tests could be used to elucidate why a particular person reacts a certain way to medication. The CYP2C9 enzyme metabolizes the more potent S-warfarin enantiomer, and the CYP2C9 *2, *3, *5, *6, *8, and *11 alleles are associated with reduced S-warfarin clearance. Data consistently demonstrate reduced warfarin dose requirements in individuals who carry these variant alleles.

Patients with a reduced- or no-function CYP2C9 allele are more likely to have impaired phenytoin metabolism and require lower doses of the drug to prevent neurologic toxicity. CPIC guidelines recommend consideration of lower phenytoin doses in patients who carry such alleles.

What are the key points of the new guidelines?

This new report offers a two-tier categorization of CYP2C9 alleles as an aid for designing CYP2C9 genotyping assays. Our goal is to promote standardization of pharmacogenomic gene/allele testing across clinical laboratories. Using criteria such as allele frequencies in different populations and ethnicities, the availability of reference materials, and other technical considerations, we recommended a Tier 1



list of a minimum set of alleles and their defining variants that should be included in all clinical CYP2C9 pharmacogenomic tests. We also defined a Tier 2 list of optional CYP2C9 alleles that do not currently meet one or more of the criteria for inclusion in Tier 1. These recommendations are not to be interpreted as restrictive, but to provide a reference guide.

What should diagnostic professionals know about CYP2C9 genotyping?

We considered a number of important factors, including the functional impact of the variants, allele frequencies in different populations and ethnicities, the availability of reference materials, as well as other technical considerations for pharmacogenomic testing. We highly recommend that clinical laboratory professionals include our Tier 1 set of alleles, which

- have been well-characterized and shown to significantly affect the function of the protein and/or gene leading to an alteration in a drug response phenotype,
- have an appreciable minor allele frequency in a population/ethnicity group, and
- have publicly available reference materials.

These recommendations should help to standardize testing and genotyping concordance between laboratories.

Pharmacogenetics is a rapidly changing field, and we intend to update these recommendation documents as new data and reference materials become available. AMP members are among the early adopters of molecular diagnostic testing in clinical settings, and we are committed to continuously improving professional practice and patient care. We recognize that there are additional alleles not listed in the guidelines – there are more than 60 CYP2C9 alleles currently listed in the PharmVar database – and we expect to add some of them to our Tier 1 or Tier 2 lists in the future as new data concerning functional impact, frequency, and reference materials becomes available.

We are also aware that our recommendations to include the alleles more prevalent among African and African American populations may be difficult to implement with currently available genotyping platforms. We concluded that failure to include these alleles could lead to inaccurate CYP2C9 phenotype prediction among individuals with known or unknown African ancestry and could potentially contribute to existing health care disparities in these populations.

A SMArter Way to Diagnose Diabetes

Could a polymer that "biopsies" living cells lead to improved diabetes diagnosis and monitoring?

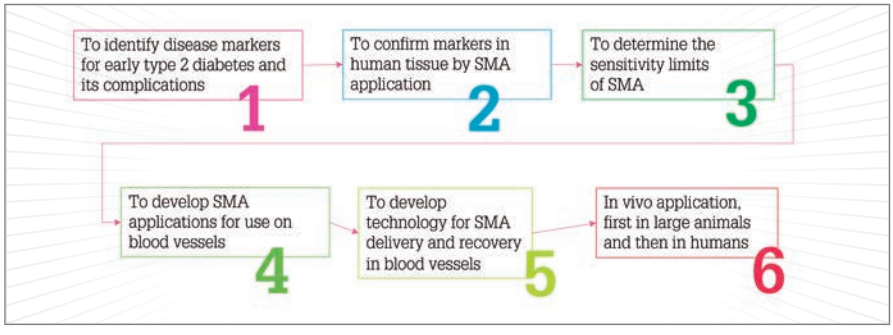


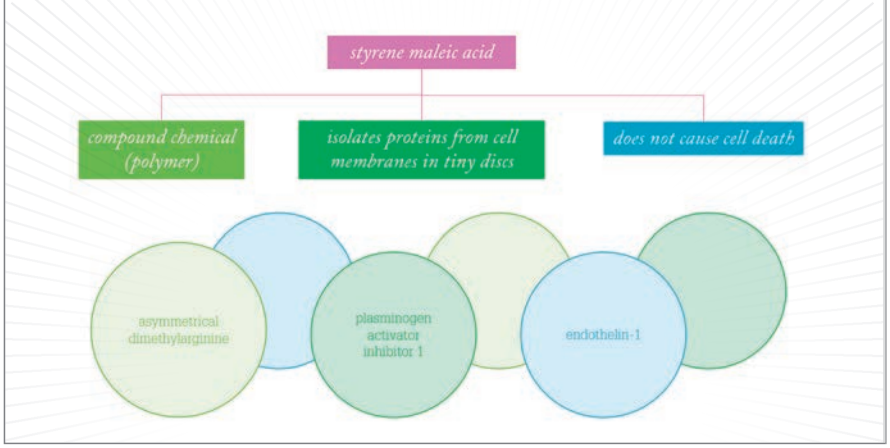
Figure 1. The research team's six goals for SMA.

Diabetes – a disease so common that almost everyone knows someone who has it, but so comprehensive that few members of the public are fully aware of the risks it can pose to patients. For example, the disease can cause severe damage to blood vessels throughout the body, and that damage begins early on. The silver lining? A method of detecting that blood vessel damage could also offer a route to earlier diagnosis and treatment of diabetes (1).

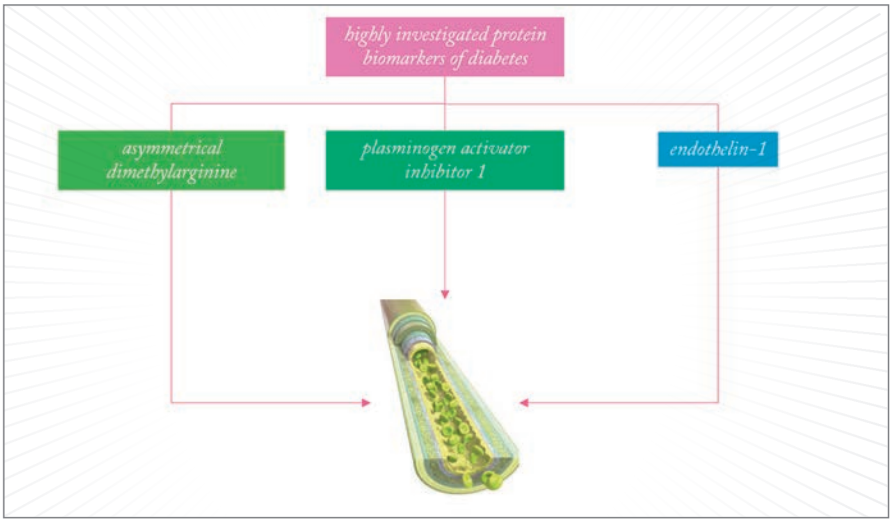
"We wanted to exploit our recent discovery that a novel chemical tool, the polymer styrene maleic acid (SMA), can 'biopsy' human cells, extracting proteins without causing cell death," explains Andrew Smith, a researcher from the School of Biomedical Sciences at the University of Leeds. "This project will build on our previous findings with SMA by using it as a tool to investigate diabetic vascular disease development and identify markers linked to specific aspects of this disease."

SMA isolates proteins from cell membranes in tiny, disc-like nanoparticles due to its structure, which cuts through the membrane to release the disc and maintain its stability. "We found that we were able to identify proteins from membranes and elsewhere in the cells in our collected material," says Smith.

The research group now plans to exploit their finding that SMA can nondestructively sample proteins from cells and intact tissues. With that in mind, they have a series of six goals (see Figure 1).



But what about once the proteins that could signal disease progression are identified? "Detecting a biomarker of change in cells due to the pre-diabetes state will give solid evidence of the need for intervention," explains Smith. "Early diagnosis of type 2 diabetes is linked to significant risk reduction, with scope for further reduction if treatments can be directed by evidence obtained from the site of disease damage." To that end, the researchers will not only identify biomarkers of disease development in patients with established diabetes, but also search for markers of higher risk of disease complications.



Reference

1. *University of Leeds, "University of Leeds researchers awarded Heart Research UK grant to spot diabetes early" (2019). Available at: https://bit.ly/2HN5fPr. Accessed May 23, 2019.*

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 editors at edit@thepathologist.com

Long Live the (Digital) Revolution!

Pathology strides forward: the era of digitization and artificial intelligence

By Dariusz Borys, Professor of Pathology and Orthopedic Surgery, Chief of Orthopedic and Pediatric Pathology, and Director of the Digital Pathology Lab, Loyola University Chicago, Maywood, USA

Pathology has witnessed many changes over the last few decades– it seems like we're applying new technologies and developing new molecular studies every day. Digital pathology is just one such example: a dynamic, image-based technique that enables the acquisition, management, and interpretation of diagnostic information obtained from a digitized glass slide. Healthcare applications for digital pathology are incredibly wide-ranging: primary and intraoperative diagnosis, diagnostic consultation, medical student and resident training, manual and semi-quantitative review of immunohistochemistry (IHC), clinical research, diagnostic decision support, peer review, tumor boards, and more.

In the last 10 years, digital pathology has rapidly expanded as an essential tool to support medical education, tissue-based research, drug development, and the practice of clinical pathology. Recently, the field has begun integrating artificial intelligence (AI) and machine learning software as tools for efficiency and accuracy within pathology. Applying AI and machine/deep learning to high-resolution digital tissue images should ultimately allow pathologists to automate the analysis of routine clinical slides. And the pathologist may use software to create algorithms to spot cancerous areas – or even identify individual cancer cells – within such a digitized tissue sample. How? Such software uses annotated areas to memorize and create criteria that can help pathologists narrow down morphologic diagnosis and interpretation. In fact, we already use similar software algorithms to evaluate percentage expression of IHC staining – a function that has proven especially useful for evaluating ER, PR, and Ki67 in breast pathology services. Software like this helps to standardize data and improve patient care.

In my view, the integration of AI and machine learning software into the daily clinical workflow of pathologists will cut down work time, reduce misdiagnoses, and create more comfortable work environments. At the same time, I anticipate that it will make pathology departments more efficient and cost-effective. In our digital pathology laboratory, we use our system to cover intraoperative frozen section evaluation, liver and kidney transplants, tumor boards, and clinical education for two hospitals. Our data on the application of digital pathology to evaluating frozen sections has garnered great interest at national and international meetings and, in the near future, we plan to expand our laboratory so that we can digitize all slides for daily base morphologic interpretation.

In short, I believe that new technology is set to help pathologists get out of the basement and take up the challenge of our increasingly important role in personalized health care.

Serving China's Breast Cancer Community

With diagnoses on the rise in China, decentralized genomic tests give physicians and patients access to more tailored breast cancer treatment

By Franklin Libenson, Senior Vice President of Strategic Marketing and Market Development at Agendia, Inc., Irvine, USA

Breast cancer is a significant health burden in China, affecting roughly 300,000 women each year (1). As the country's population grows, this number will continue to rise, fueled in part by advancements in screening technologies that help diagnose breast cancer earlier. As such, the markets for diagnostic testing and newly developed treatments are rapidly growing to meet this new demand.

Genomic testing will play an important role in China, helping to guide treatment decisions by providing unique insights into the biology of a patient's cancer and more clarity on its risk of recurrence. Traditionally, physicians have based treatment decisions on the clinical pathological factors of a tumor – so patients with clinically high-risk cancers, including large tumor size, high grade, or lymph node positivity, usually receive chemotherapy. However, recent research from the landmark MINDACT trial (2) has shown that almost half of these clinically high-risk women actually have a low genomic risk of their cancer's returning and can safely forgo chemotherapy.

In the US and Europe, multiple genomic tests that predict breast cancer recurrence risk are already on the market. However, servicing the Chinese market remains challenging because of laws that prevent the export of biological samples outside of China.

One answer to this roadblock is to transition from traditional centralized testing to a decentralized system. This way, physicians in China can send patient samples to local hospitals and laboratories to be processed and analyzed using genomic assays or kits that can be run on their own equipment. The country's first decentralized breast cancer genomic testing platform has recently been launched, so early-stage breast cancer patients will now have access to clinically validated, prospectively proven tests for both molecular subtyping and risk of recurrence, allowing them both tailored treatment and peace of mind. The model may be applicable in other countries with similar restrictions around exporting human tissue, as well as those countries that lack government reimbursement for testing done outside the country. Although the reasons behind the need for decentralized testing are fundamentally different, it's clear that several markets would benefit from a localized processing solution.

At the moment, the availability of genomic testing in China is limited. With the increase in breast cancer screening, though, more women are being diagnosed earlier. Many of these women will have early-stage cancer and won't require aggressive treatment but, without access to genomic testing, physicians and care teams are basing treatment decisions on clinical factors alone – and potentially administering chemotherapy to patients who might not need it. Ultimately, access to decentralized genomic tests in China will provide patients and their physicians valuable information – beyond just clinical risk factors – so that they can confidently make personalized treatment decisions.

"Although the reasons behind the need for decentralized testing are fundamentally different, it's clear that several markets would benefit from a localized processing solution."

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1. *TT Zuo et al., "Female breast cancer incidence and mortality in China, 2013", Thorac Cancer, 8, 214–218 (2017). PMID: 28296260.*
2. *F Cardoso et al., "70-gene signature as an aid to treatment decisions in early-stage breast cancer", N Engl J Med, 375, 717–729 (2016). PMID: 27557300.*

The Limits of Automation

Augmented intelligence for better prior authorization outcomes

By Navaneeth Nair, Vice President of Products at Infinx Healthcare, San Jose, USA

Several major health insurers across the USA have been implementing prior-authorization processes or some form of a laboratory benefits management program. These insurers are admitting that they lack the laboratory medicine expertise to determine medical necessity, so they are putting the responsibility back on the providers to minimize fraud and abuse within the industry. That move, in turn, is leading to more effort for already overworked staff members, who must handle the burdensome task of a seemingly endless number of manual insurance verifications and prior authorizations.

Many see completely automated solutions as the answer to this problem, but – despite all the advances in artificial intelligence (AI) – a machine simply can't do it all. AI exists to help humans make better decisions, not to automate 100 percent of a task. Decision-making, as it applies to the healthcare industry, still requires human intelligence and human empathy. As a result, providers should be looking to "augmented intelligence."

The American Medical Association says that "augmented intelligence" reflects the enhanced capabilities of human clinical decision-making coupled with AI's computational methods and systems. Make no mistake – we need AI in healthcare because the industry is swimming in data. As a result, the value proposition with the most potential is to provide a tool that can take the data, make sense of it, and present it in a way that allows people with knowledge and empathy to make the best decisions. The outcome very much needs to be a product of human determination.

The best outcomes in healthcare are the result of good intelligence and great execution. With advances in technology, AI is able to take administrative processes, such as prior authorization or revenue cycle management, off the plates of people who have more important jobs to do. Such systems can help us make better decisions while continuously learning from the data previous experiences have yielded.

In my opinion, digital labor will upend the healthcare processes – but in a positive manner. AI will accelerate current employee expertise, augment decision making, reduce manual processing costs and risks, increase consistency of output, and develop continuous self-learning processes. The best platforms to manage the healthcare revenue cycle will combine robotic automation, AI, and deep domain expertise – otherwise known as human intelligence – to assist practices with prior authorization, coding, and billing needs.

The robotic automation component is designed to handle the administrative "grunt work," which results in significant reductions in process cost with improved quality.

The AI component is designed to continuously learn and improve from all data and interactions to provide prescriptive insights for decision-making, while increasing process transparency. Notably, predictive models are inherently simple to build, but difficult to maintain. Why? Because none of our healthcare processes remain stable enough to use the data and patterns that are produced.

"Decision-making, as it applies to the healthcare industry, still requires human intelligence and human empathy."

Practices need a solution that seamlessly integrates the process and constantly accesses the latest and most relevant data. And that's why AI must be prescriptive and not just predictive; predicting the outcome without the ability to explain (black box AI) is limiting – particularly in healthcare, where we need to better understand machine rationale before applying it.

Lastly, the human component is required to make the decisions robotic automation and AI cannot. Only people with empathy and knowledge of each unique situation can tailor a patient's experience to their individual context and needs. Those practices seeking completely automated solutions for prior authorization or LBM programs should instead look to a solution that does not remove the human intelligence factor. Many general-purpose AI solutions are nothing more than spot analytics solutions branded as AI, which require significant investments with uncertain results. Someday, AI may evolve to the point of completely automating the prior authorization process – but, until that day, practices should look to incorporate human intelligence for better decision making and outcomes.

Cultivating Pathology's Future

Advocacy is the way forward for our profession

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

Advocating for the pathology profession and those working within it to ensure the protection of patients is an integral part of ASCP's mission. Although it's easy to sit on the sidelines and discuss what needs to be done, it's more difficult to put those words into action. Doing so requires not only intention and motivation, but informed engagement – we have to know what the issues are so we can work together to ensure positive outcomes. I'd like to take this opportunity to highlight some of our activities over the past year.

At home, we're in the early stages of the genetic diagnostic era. It's an exciting time for the profession, but it's also imperative that we provide accurate patient results while encouraging new technologies. Sometimes, these advances in diagnostics come by way of laboratory developed tests (LDTs) – diagnostics developed and validated by individuals within laboratories. In particular, molecular genetic tests – the results of which help predict disease or guide lifestyle choices – are commonly developed in-house, due to the low availability of commercial products. As such, ASCP and its members have a vested interest in their regulation. It is vital that the FDA strike the right balance in asserting its authority over the regulation of LDTs. The regulatory infrastructure adopted must be sufficient to safeguard the public health without being so burdensome that it impedes emerging technology. Recently, we wrote a letter to the FDA outlining our position on LDT regulation and offering our expertise as these policies are debated by legislatures, the FDA, and other interested parties.

Burnout, a feeling of emotional and mental exhaustion brought on by prolonged stress, is a very real occurrence today's laboratory. Pathologists, residents, and laboratory professionals play a vital role in healthcare and, as such, it's imperative to address their emotional and mental health. We recently completed a survey of our membership regarding job satisfaction, wellbeing, and burnout in the laboratory. Findings from our study will provide insight on how health care institutions can address these challenges and will inform ASCP's initiatives going forward.

Abroad, our goal is to create a sustainable presence in pathology and laboratory medicine around the world, which means we need to find solutions for the challenges we encounter. To address one challenge, HIV diagnosis, we're working with the US Centers for Disease Control and the President's Emergency Plan for AIDS Relief (PEPFAR) – and we've received over US$50 million to facilitate improvements in HIV testing in laboratories around the world. In addition, we're setting our sights on cancer diagnostics in low-resource settings. This includes performing site assessments, training, creation and support of online resources, and – perhaps most importantly – whole-slide image telepathology, which allows collaborating pathologists to consult on cases within 24 hours. Instead of weeks or even months, patients can now receive a diagnosis in days.

These are just a few of the issues ASCP is working on for the medical laboratory community at large. Advocating for the profession requires constant vigilance, but with that vigilance comes great rewards. No one will do this work for us; it's our responsibility to have an active hand in shaping our future. I'm proud ASCP is on the forefront of these efforts, and I look forward to working with you to create the future we desire.

THE SPICE OF LIFE

Precision medicine holds great promise – but if we don't improve diversity in genomic research, minority groups could be left behind

Precision medicine is an exciting new approach to disease treatment and prevention that tailors therapy to an individual's lifestyle, environment, and – most importantly – genetic background. As the push toward precision medicine picks up pace, one area of research is integral to its future success: genomics. Since the first human genome was sequenced in 2003, there has been an explosion in the number of genome-wide association studies (GWAS), with around 3,700 carried out to date (1). This ever-growing area of research has led to important discoveries about human health and behavior, including the identification of thousands of genetic risk variants and their biological function.

But precision medicine isn't a one-size-fits-all approach – in fact, it's often called by another name: "personalized medicine." Its wider success fundamentally relies upon the collection of genomic data from diverse and representative study populations whose genetic backgrounds form the basis of new targeted therapies. For example, a number of complex diseases, such as diabetes and coronary heart disease, are associated with multiple genetic variants and their interaction with social and environmental factors. The complex interaction of polygenic traits means that thousands of variants, each with a small influence on an individual's phenotype, combine to have a greater total effect – which may differ from one person to the next. Therefore, it's vital to characterize genetic variants from as many individuals as possible to ensure that potential therapies are applicable to everyone.

Although the National Institutes of Health (NIH) introduced a policy in 1993 that requires minority groups to be equally included as clinical research subjects (2), current evidence suggests that little has changed over the past 30 years. As a result, the field of genomics could be facing a large-scale diversity problem. Despite non-European ancestry groups' accounting for 40 percent of the total US population, not even two percent of the more than 10,000 cancer clinical trials since 1993 have included enough minority participants to satisfy the NIH's own diversity policy (3).

The consequences of this underrepresentation of non-European ancestry groups could be severe. A lack of diversity in genetic databases is predicted to lead to health disparities when precision medicine research is translated into clinical practice. Ultimately, this could render certain treatments unsuitable for and even dangerous to underrepresented groups.

But why is there such a considerable lack of diversity in genomic research? Is it a reluctance among minority groups to participate? Is there an element of scientific racism? Or is there a lack of effort from researchers to expand their study populations beyond the easily accessible European ancestry samples? We hear from two experts who open up about the diversity crisis and discuss how we can combat it to ensure that the future benefits of precision medicine are felt by all, regardless of ancestry.

GENOME-WIDE TO WORLDWIDE

A lack of geographic, ancestral, and demographic diversity in genome-wide association studies is threatening the representation of certain populations

By Melinda Mills

Years ago, when I was conducting a genome-wide association study (GWAS) on reproductive choice in relation to genetic factors, I noticed something startling. With a background in demography, I have always been interested in the structure of human populations, so as I was collecting the data for this particular research, I looked around the room at the people we were studying. And that's when alarm bells began to ring in my head about the diversity of our work – not only among the researchers, but also within our study populations. It was at this point that I decided we needed to investigate the level of diversity within genomic research more broadly.

To achieve highly targeted pharmaceuticals and personalized medicine, we first need to fully understand the specific mechanisms and functions of different loci. That's what GWAS aim to achieve by isolating single nucleotide polymorphisms and conducting downstream analyses to find the most appropriate clinical interventions; for example, screening to identify and target individuals who are most likely to develop a certain disease, so that they can minimize their risk. These genetic discoveries offer exciting medical possibilities – but their potential efficacy is dictated by the diversity of participants on whom discoveries are made. Increasing evidence for the omnigenic model suggests that a single complex trait is the product of all genes interacting with each other (4). Therefore, to gain the greatest returns from GWAS, it is vital to maximize the ancestral and geographic diversity of individuals studied.

Although the scientific contributions of GWAS have previously been assessed qualitatively, a systematic scientometric study into their impact has thus far been missing. And so, we investigated all 3,700 GWAS completed between 2005 and 2018, analyzing the demographics of study participants, sample sizes, genetic ancestry, and the geographical distribution of participant recruitment (1). Despite the absence of any empirical evidence to confirm it before our study, personal experience meant that we were aware of some striking aspects of the diversity of participants in this kind of research and the way that it was being conducted. For example, there seemed to be a concentration of subjects across only a few countries, and the data itself appeared highly selective.

But even though we had an idea about the lack of diversity that exists, the extremity of our results still came as a shock to us. We found that ancestry in genetic discovery is highly unequal and has been dominated by individuals of European ancestry, who account for 83.19 percent of participants across all GWAS. In contrast, 12.37 percent of participants are Asian, 1.96 percent are African American or Afro-Caribbean, 1.30 percent are Hispanic or Latin American, and just 0.30 percent are of African ancestry (see Figure 1). This heavy imbalance in ancestry groups used for GWAS is really concerning because, despite a surge in sample sizes, traits, and diseases studied, there is a massive under-representation of non-European ancestry groups. Because this type of research is often used as a basis for pharmaceutical development, the fact that it only covers a very narrow and specific population will result in drugs that are less relevant – and in some cases even detrimental – to the health of certain groups.

DIVERSE DISCOVERY

Typically, there are two stages to any GWAS – discovery and replication. The discovery phase involves the identification of hundreds of different loci related to a particular trait, such as type 2 diabetes or breast cancer. During the replication phase, the original results are applied to various different populations to test whether the loci match up. Although some people in the field argue that non-European groups are increasingly included in GWAS, we found that this was largely in the replication phase – to confirm the findings that had mostly been drawn from European ancestry groups – and not in the initial genetic discovery phase. To combat this, there needs to be a shift in the types of ancestry groups that are used in the discovery phase, something we can only achieve through larger sample sizes. There has been a considerable increase in the use of samples from certain populations, such as Japanese, South Korean, and Chinese, but we are yet to see huge increases in African samples.

Until now, much of the discussion surrounding genomic research has been centered on ancestral diversity, without considering the geographic locations from which participants are recruited. But geography is crucial; a large amount of epidemiological evidence shows that disease prevalence and life expectancy are strongly linked to the place where a person lives (5). We found that a staggering 72 percent of all discoveries have come from people who live in just three countries – 40 percent from the UK, 19 percent from the US, and 12 percent from Iceland. This is rather shocking when you consider that approximately 76 percent of the world's population resides in Africa.

The fact that so many participants come from Iceland is due to the presence of the headquarters for a large biopharmaceutical company called deCODE. Despite having a population of just 334,000, Icelandic participants represent 19.1 percent of all subjects included in genetic discoveries to date. Because every

country is unique in regard to its social, cultural, and economic background, as well as the specific disease profiles that are prevalent, the use of so many participants from one geographical area is concerning. Differences in alleles between regions caused by population stratification mean that it can be dangerous to draw so many conclusions from a single, distinctive group of people.

TELLING THE WHOLE STORY

When conducting a GWAS, researchers generally aim to obtain as much data as possible; however, when response rates are low, the resulting database may not be very representative of the population. For example, the UK Biobank is a long-term study investigating the contributions of genetic predisposition to the development of disease. But, in reality, it includes very few smokers, few people with high BMIs, and an overabundance of people of high socioeconomic status. Therefore, if we were to study smoking or other behaviors that are detrimental to health using the UK Biobank, we might wrongly conclude that certain genetic loci are protective or beneficial. In our study, we found that the most frequently studied people in GWAS are often older and more likely to be female (1). In regard to the over-representation of women, this could be a function of the traits that are being examined – such as breast cancer – but it could also be because men have a lower response rate to the studies themselves. Ideally, to tell the full story, we would need complete representation of individuals across all environments.

Not only is there an issue with the level of diversity among the participants of genomic research, but we also found a tightly knit group of researchers who dominate the ownership of very valuable genetic datasets. By holding richly phenotyped data that cover multiple diseases and traits, these people possess enormous power – and our social network analysis showed that the same core people consistently appear as authors of papers. What's more, of the more senior last author positions, 70 percent were occupied by men, which shows that men are more likely to be principal investigators and are over-represented in these powerful positions. On the other hand, women are relatively better represented as (more junior) first authors, despite still being in the minority at 44 percent.

"To gain thegreatest returns from GWAS, it is vital to maximize the ancestral and geographic diversity of individuals studied."

One way to tackle the dense web of interconnected authors is to rethink how we incentivize this type of research. The holders of large datasets understandably want to see a return on their

significant investments – but, as things stand, the only way to achieve this is to appear as an author on any papers that make use of their cohort. I think we need to start to value the use of these datasets in a different way and provide new incentives for their owners. Unfortunately, the waters are further muddied by the introduction of "direct-to-consumer" companies, many of whom analyze their data in-house and don't release it externally to researchers. It's striking that three of the top 10 most prominent GWAS authors all come from deCODE genetics, which is one of these commercial institutions.

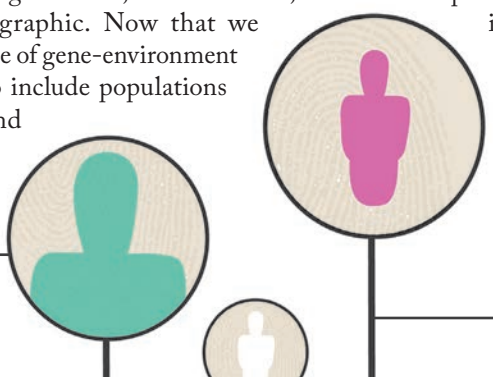
Interestingly, when we asked whether researchers of different genders tend to study different traits in GWAS, we discovered statistically significant results for two things. Women are more likely to study breast cancer, whereas men are more likely to study cardiovascular disease. This is interesting when you consider that, for many years, women's heart disease and heart attacks were misdiagnosed because symptoms are so different between men and women. A number of people have picked up on this, and some believe that it occurred because male doctors and researchers were focusing on the male system.

A QUESTION OF FUNDING?

The main reason for such a lack of diversity within the field is down to a lack of funding. US-based agencies – primarily the NIH – fund 85 percent of the research in question. Organizations in the UK, such as the Medical Research Council and the Wellcome Trust, also make up a large proportion of funding, whereas in Iceland, deCODE is the main source. These organizations specifically provide funds for data to be collected in those countries, explaining why 72 percent of findings emanate from them.

I think that researchers in the field are aware that they are looking largely at populations of European descent, but they might be surprised if they knew the exact figures. Some people might say, "We're looking at these basic biological and causal aspects, so it shouldn't really matter," but that doesn't work because we know that there are different allele frequencies between different populations.

It's one thing to identify this huge diversity problem within genomic research, but it's a whole lot harder to know how to tackle it effectively – not least because it's an issue that spans researchers, data providers, and national governments. One of the most important measures that we can take is to prioritize multiple types of diversity, including ancestral, environmental, geographic, and demographic. Now that we appreciate the importance of gene-environment interactions, we have to include populations that aren't healthy, and those that come from low socioeconomic backgrounds. To achieve this level of diversity on multiple fronts, I think people have to begin to recognize the impact that a lack of diversity has on research findings.



Commercial companies have started to become more agile, and our paper has already been used to actively market and promote more diverse samples. These companies have a responsibility in the US and the UK to drive greater diversity. On the other hand, within Africa, national science foundations are leading the way with initiatives to collect more data in the region. But one thing we must avoid is helicopter science, because concerns have been raised by some African scientists that data is merely collected from the region, then taken elsewhere. The African Genome Variation Project, funded by the NIH and the Wellcome Trust, is one initiative aiming to collect vital genetic information; however, it's unclear how much the community, researchers, and infrastructure in Africa are actually being developed. To achieve real expertise in these areas, we have to think on the ground about building networks so that we can really trust the data. We must help our colleagues in under-represented and under-resourced regions to conduct and publish their own research, rather than simply benefiting from the information they gather.

A different, more radical solution could be to impose funding sanctions and consequences when there are gaps in diversity. When carrying out our study, I contacted all of the science foundations involved and asked, "What is your diversity policy for researchers and study populations?" It was interesting to hear that some didn't have anything in place – something that has to change before we can make any kind of progress. We can talk about greater diversity all we want, but until measures are put in place to enforce it and sanctions are imposed when it's lacking, it will be difficult to achieve.

As things stand, not only are personalized medicine approaches going to be less suitable for minority groups in the future, but they could even be harmful. If we can't increase the amount of diversity in genomic research, we could end up exacerbating existing divisions. Basing personalized medicine on findings from a group made up of 83 percent European ancestry – and generally quite healthy – will only serve to reinforce inequalities. Steps have been made in the right direction but, to succeed, we need to adopt a unified approach that prioritizes multiple types of diversity, devise strategies to monitor diversity, call for local participant involvement, and reform incentive structures that include the role of authorship, data ownership, and access to results. Only then can we truly fulfil the immense potential of the genomic revolution for people across the globe.

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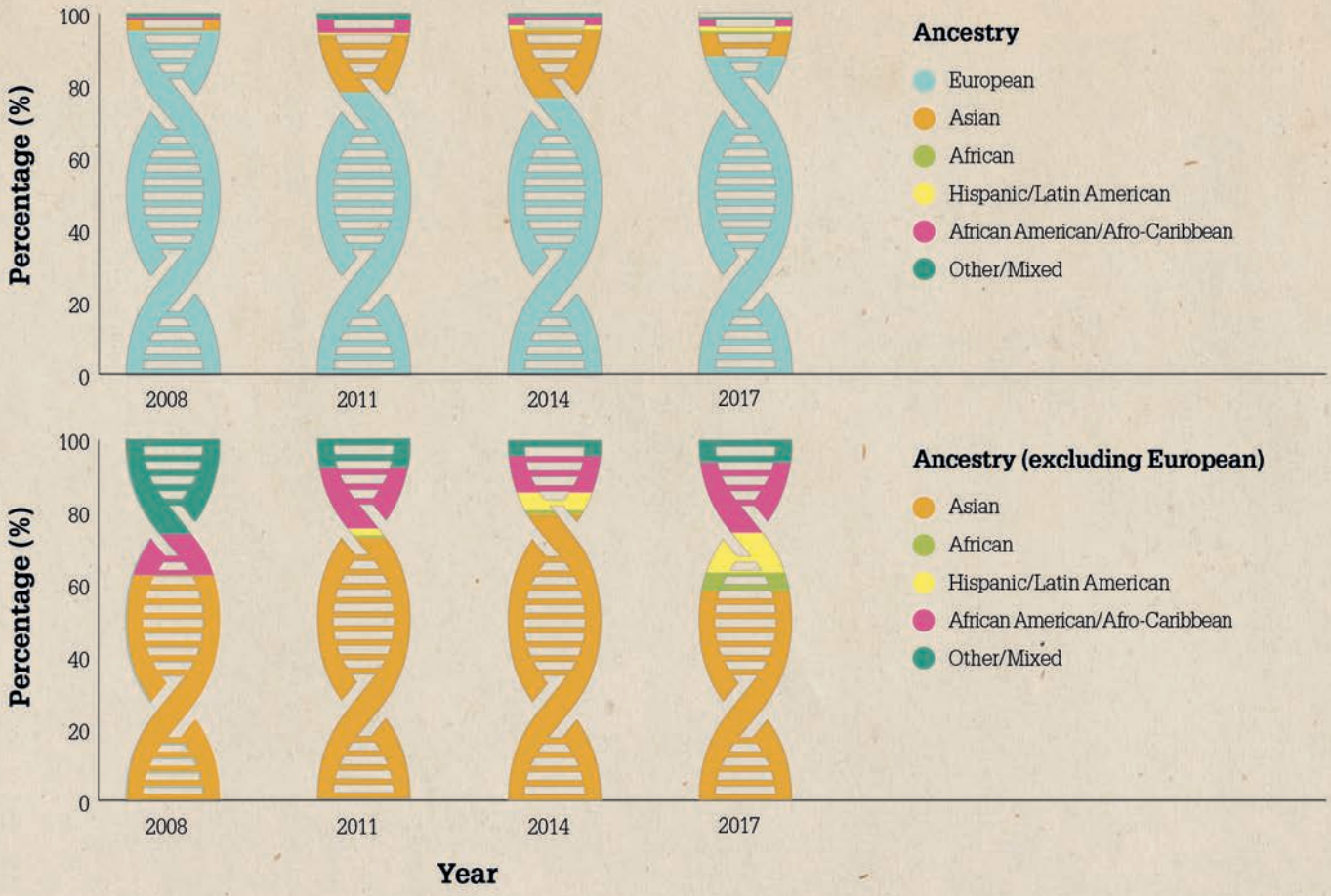


THE PRECISION MEDICINE CRISIS

The lack of diversity in cell lines is stifling the true potential of precision medicine

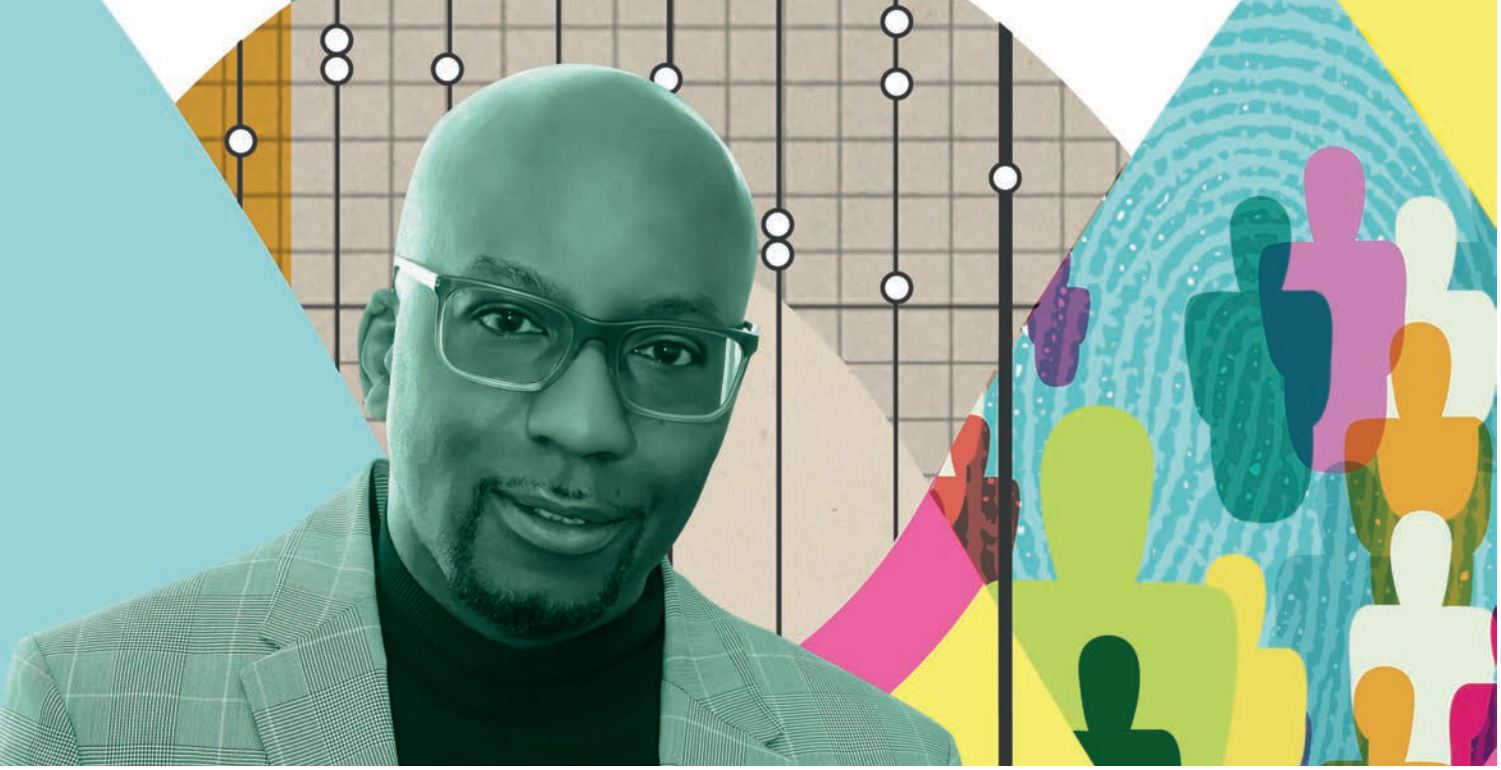
By Rick Kittles

As someone who conducts health disparities research, I know from personal experience how difficult it is to obtain diverse biospecimens. In my studies on prostate cancer, we commonly use cell lines as models to explore different pathways and test the effects of various treatments. But the problem with these cell lines is that there isn't adequate representation from different ancestry groups. In the US, African Americans have almost twice the incidence of prostate cancer as the white population – so why isn't the number of African American samples two times higher? Instead, they're overwhelmingly of European descent – in fact, there's almost a complete lack of cell lines of African American descent. It's essential to have representative cell lines from disparate populations if we want to study them effectively.

Not only that, but my colleagues and I also started to wonder whether the few cell lines that were labeled as African American actually contained that ancestry. We never felt completely comfortable or confident that the classification provided for these cell lines was adequate; that's why I wanted to investigate their origin in more detail.

Unfortunately, our results confirmed these fears. We characterized 15 commercial cell lines used to study prostate, breast, and cervical cancer based on their amount of West African, Native American, and European ancestry. After extracting and genotyping the DNA to identify ancestry-informative markers, we were able to determine the accuracy of their original ethnicity classification. Worryingly, although all of the cell lines previously classified as white/Caucasian were correct in their description (with a mean European ancestry of 97 percent), those previously classified as African American were not always accurate. Most notably, the cell line known as E006AA-hT – used for prostate cancer research – is classified as African American, but we found it to carry 92 percent European ancestry. In addition, there was high variance in other cell lines labeled as African American in terms of their true ancestry (6).

Although these results were shocking, they didn't come as a complete surprise to me because I had spent several years trying to get to the bottom of these misclassifications. For example,



I genotyped the E006AA cell line almost eight years ago and found that it was made up predominantly of white ancestry. At that point, some of my colleagues rightly stopped using that particular sample. However, for those who remained unconvinced, I decided to publish a study to demonstrate just how misleading the African American labeling really is. The concerning part is that there were federal National Institutes of Health (NIH) grants written that proposed to use the E006AA-hT cell line as a representative African American population, so those researchers will have wasted a lot of time and money. What's more, the numerous papers that have been published using E006AA-hT can no longer claim to represent African Americans.

HANDLING HETEROGENEITY

How did such a basic misclassification occur? That's a question for the individuals who developed the cell lines, but it essentially boils down to sloppy science – whether caused by a labeling error in the lab or misreporting of the original patient.

To prevent this kind of mistake from happening in the future, I believe that we need to implement stricter and more robust rules. Currently, there are no guidelines in place regarding how cell lines are classified or how they are sold to the public. For example, the company that sells E006AA-hT now has a disclaimer on their website to say that it might not be African American – but they are still labeling and marketing it that way!

Historically, researchers have encountered issues when it comes to including African American and Hispanic populations in their biomedical studies. African Americans form a macro-ethnic group. The bulk of our gene pool comes from West Africa, but there has been a high level of gene flow over time; now, some African Americans have a higher proportion of European ancestry, whereas others have more West African ancestry. This heterogeneity previously meant that it was too difficult for researchers to manage and account for the variance in genetic background. But now, with the help of ancestry-informative markers, we can control for high levels of diversity in a sophisticated way. Although there are thousands of these markers in the genome that allow us to distinguish between major geographic regions such as European, West African, Asian, and Native American, we found that only about 100 markers need to be genotyped to estimate ancestry with fairly high confidence levels. After that point, we don't learn too much more about ancestry by adding further markers, which is why we opted to use 105 such markers in our study.

For example, the Duffy null allele is almost 100 percent West African; it's present in the genome as protection from malaria and not seen in European and Asian individuals. Therefore, when Duffy null is present, you can say with high confidence levels that the person has some degree of African ancestry. By combining 105 of these ancestry-informative markers, we can take genetic heterogeneity into account and accurately characterize populations around the world. As a result, the issue of heterogeneity is no longer an excuse for researchers. If you're studying African American populations in terms of genetic risk and drug response, then it's crucial to take differences in genetic background into account.

THE DIVERSITY PROBLEM

In a general sense, there is nowhere near enough diversity in this area of research, and we need to be assertive and proactive in increasing the representation in our biospecimen samples. To rely on just two or three African American prostate cancer cell lines – and then find out that one of them isn't even African American – is a disservice to science. The obvious way to confront this issue is to increase representation in genomic research, but we must do so in a way that is robust and scientifically rigorous. Unfortunately, if we don't address

the diversity problem promptly, the impacts could be broad and the implications long-standing.

Cell lines are frequently used to test products and screen drugs. If all of the samples used for testing are of European ancestry, do we know that the drugs that we develop will benefit people of all ancestries? The simple answer is no – there's not enough genetic diversity in the cell lines to represent the broader population. Hundreds of millions of dollars have been funneled into drug discovery, but a huge proportion of the human population is simply missing from the screening phase.

Ultimately, if these drugs have a higher level of toxicity or lower efficacy in people who weren't represented in the screen, they could have deadly consequences. In some cases, we have already started to notice such effects. For example, the dosage algorithm for the anticoagulant warfarin was initially developed using genes common in European populations. Once that algorithm was applied to African American and Hispanic populations, these patients were treated inadequately. The dosage requirement for therapeutic anticoagulation is influenced by genetic variation, so the calculations were only relevant for individuals from the screening population.

This is not a problem we can tackle overnight. There's a history of racism in science that understandably dampens the enthusiasm of African Americans for this type of research. Stories such as that of Henrietta Lacks, whose cancer cells were cultured and immortalized without her consent or any compensation, and the Tuskegee syphilis experiment, where researchers knowingly failed to treat African American patients, do not engender confidence. Although those fears aren't as intense as they used to be, the lack of interest among the African American community is one of the reasons why we're at this point today.

MAKING A DIFFERENCE

To make strides toward greater equality in cell lines, I think there needs to be a strong push at multiple levels – from the federal government, to institutions, to the scientists, to colleges and universities, right down to schools where these issues are discussed. We need to educate the younger generation about the history of race issues in science – and encourage them to do something about it.

There has been disappointingly little effort from scientists to overturn the disparity in sample diversity. Despite conferences, conversations, and published papers on the topic, there is no clear, strategic plan yet to do anything about it. To be completely honest, I think a lot of scientists simply don't care enough. The majority of scientists and institutions are of European ancestry and would rather study the populations that are easiest to access.

If the correct steps are taken and people at multiple levels get on board, I believe we could turn things around within a single generation. For instance, there is a huge project in the US called "All of Us," which aims to recruit one million individuals for a population-based study by collecting their medical records and blood samples. It was initially called the Precision Medicine Initiative, but the name was changed to reflect the need for greater diversity within samples. Projects like this demonstrate that there is funding out there to encourage the engagement of African American institutions and populations. But that's just one project; the NIH and the federal government need to devise systematic and strategic plans to increase diversity going forward and invest in the required initiatives.

HOPES AND FEARS

I know that precision medicine will have enormous benefits and a huge impact in terms of improving health in the future. But my fear is that it won't help everyone. I don't care how great the science and technology is; if we continue to go down the route of only looking at homogeneous populations in the research phase, then the benefits of precision medicine aren't going to deliver on their promise.

With that in mind, I regularly make an effort to go out into the community to talk to African Americans about these issues. I am passionate about precision medicine, and I try to convey that excitement to the African American community. I tell people that it's not just a matter of throwing their arms up in the air; instead, they can actively participate in the process and be a part of the decision-making that affects them and their community.

From my own experience, I see a great response from African American people – they want to get involved and be part of the solution. My greatest hope is that there are enough institutions prepared to engage with people in a way that will increase diversity in samples for the future.

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In Practice

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The Integration Equation

Proposed pathologist guidelines for radiology consultations

By W. Dean Wallace and Robert Suh

When a patient is diagnosed with a lesion requiring further investigation, the diagnostic workup is frequently complex. It typically involves interaction between the initial clinician (usually a primary care physician), a specialist, one or more radiologists, and often several laboratory physicians, not to mention numerous support staff, nurses, physician assistants and laboratory technicians. In the setting of a teaching hospital, the environment can become even more complex as trainees in all of the involved departments are brought in as well. With a straightforward case – for example, a 4.5 cm spiculated lung mass discovered on screening chest CT scan, subsequently biopsied, and found to be adenocarcinoma – the issues may seem trivial; however, correlating the various ancillary imaging and laboratory studies may prove challenging, potentially leading to diagnostic delays or misinterpretations. The need to assemble all forms of imaging and laboratory information can be tedious and exhausting when the results are reported in different systems or under several different tabs in the electronic medical record (EMR).

At a Glance

- *Diagnostic workups can be complex and require the input of multiple medical specialists*
- *To optimize diagnostic processes and use of samples, pathologists and radiologists should work together*
- *When there are issues with a patient's biopsy, a pathologist's first port of call should be the radiologist*
- *Our role as members of the health care team is evolving – and by working closely with our colleagues, we stay relevant and can be most helpful for our patients*

Start a conversation

Discordance between radiology and pathology studies compounds these problems. As good practice, frequent verbal communications between pathologists and radiologists ensure that we recognize and minimize potential diagnostic confusion prior to issuing the pathology report. The radiologist-pathologist conversation may provide valuable feedback to the radiologist (because the pathologic findings may add to their understanding of imaging findings and improve interpretive skills), and to the pathologist (who may develop a better appreciation of the clinical question asked with the biopsy and provide a more relevant pathologic answer). A recent example on our service involved a right upper lobe (RUL) lung nodule that contained primarily fibroconnective tissue with pauci-cellular chronic inflammation, occasional mildly atypical pneumocytes, and prominent fragments of cartilage (see Figure 1A). Given the findings, we considered pulmonary hamartoma in the differential diagnosis. In our practice, we try to discuss all benign or negative biopsies with the radiologist. Specific to this case, the radiologist's (paraphrased) response was, "Well, I guess anything can happen, but it really looks like cancer and it doesn't have the expected features of a hamartoma. However, because of the location of the biopsy needle within the peripheral lung nodule, it's possible that cartilage could have been incidentally sampled from the chest wall (see Figure 1B)." With this additional verbal information, we cut deeper sections

"Both radiologists and pathologists need to be receptive to an open and collegial environment that encourages reflection and discussion of their findings."

into the biopsy tissue block and discovered a small focus of cells suspicious for non-small cell lung carcinoma (NSCLC; see figure 1c). Importantly, the radiologist was able to convey the degree of suspicion for malignancy much more thoroughly to the pathologist in direct conversation than in the biopsy requisition, which has only limited ability for nuanced communication.

When should a pathologist contact the radiologist? We propose the following situations:

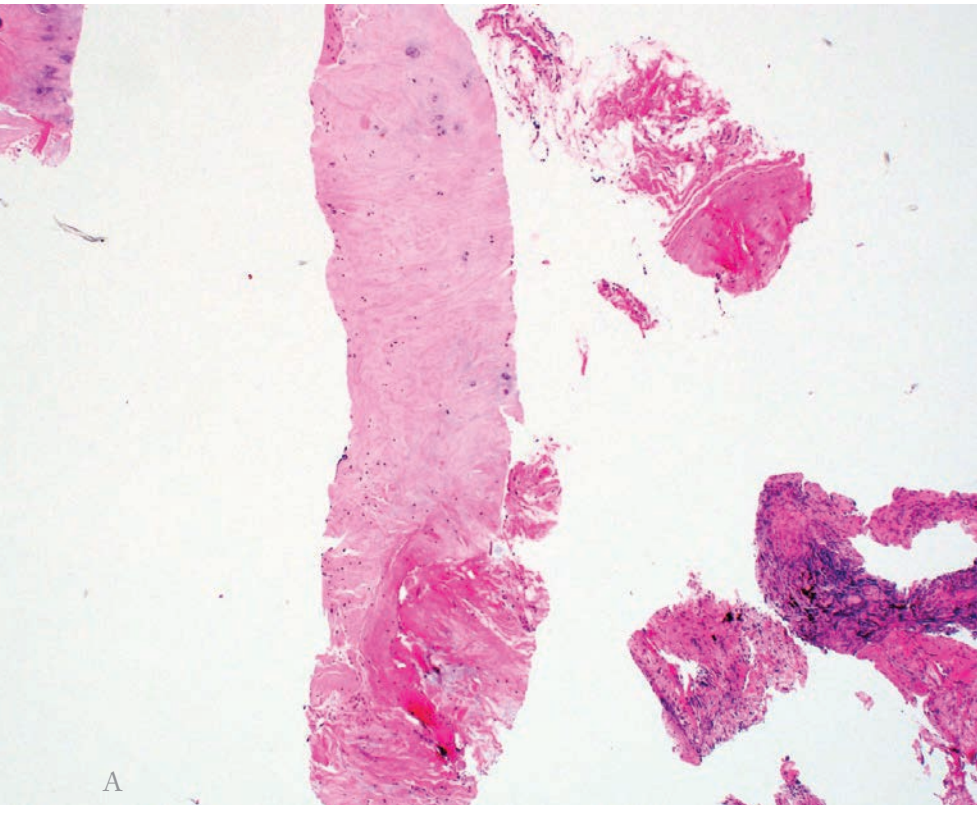
- negative/benign biopsy result,
- surprising/unexpected finding on the biopsy,
- clarification of specific requests for the biopsy, and
- insufficient material on the biopsy.

Negative or benign biopsy

We define a negative biopsy as one that "is negative for any pathologic process or contains only nonspecific findings." In this setting, sampling during the biopsy may have missed the intended lesion, or the findings may reflect a process that is not the radiographic lesion of concern (for instance, inflammation adjacent to a malignancy). Additionally, the biopsy may have been performed on an atypical or unusual radiographic presentation of a typically benign process with a lower level of suspicion for malignancy, such as an apical cap or rounded atelectasis. A discussion with the radiologist may help guide the diagnostic comment; it can also help inform the ordering clinician that the lesion was likely missed by sampling error or is a benign process (meaning that it can be followed without the urgent need for a repeat biopsy). Without an assured radiologic-pathologic correlation comment, the patient may be subjected to an additional, unnecessary needle biopsy or even a more invasive surgical biopsy.

Surprising or unexpected finding on the biopsy

There are at least two obvious advantages to reviewing unexpected findings with the radiologist. First, it serves as an excellent learning opportunity for the radiologist to get immediate follow-up on the biopsy they just performed; second, it can provide a clue that the findings might not necessarily be reflective of the lesion of concern. Furthermore, the discussion with the radiologist may provide very important context for the pathology findings. One recent example from our service was the discovery of papillary-type lung adenocarcinoma on a biopsy in a patient with a history of melanoma. The purpose of the biopsy was twofold: to confirm stage and to obtain material for molecular testing for the melanoma. The radiologist was surprised at the finding, but pointed out that the patient had numerous and bilateral rounded nodules that were still very suspicious for metastatic melanoma. With this insight, the pathology report included a diagnostic comment to indicate the biopsy finding might not reflect the overall radiology findings, and



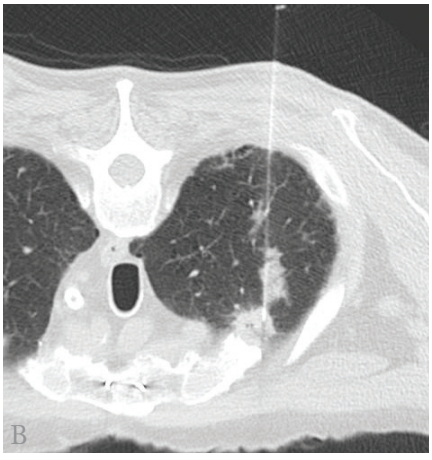
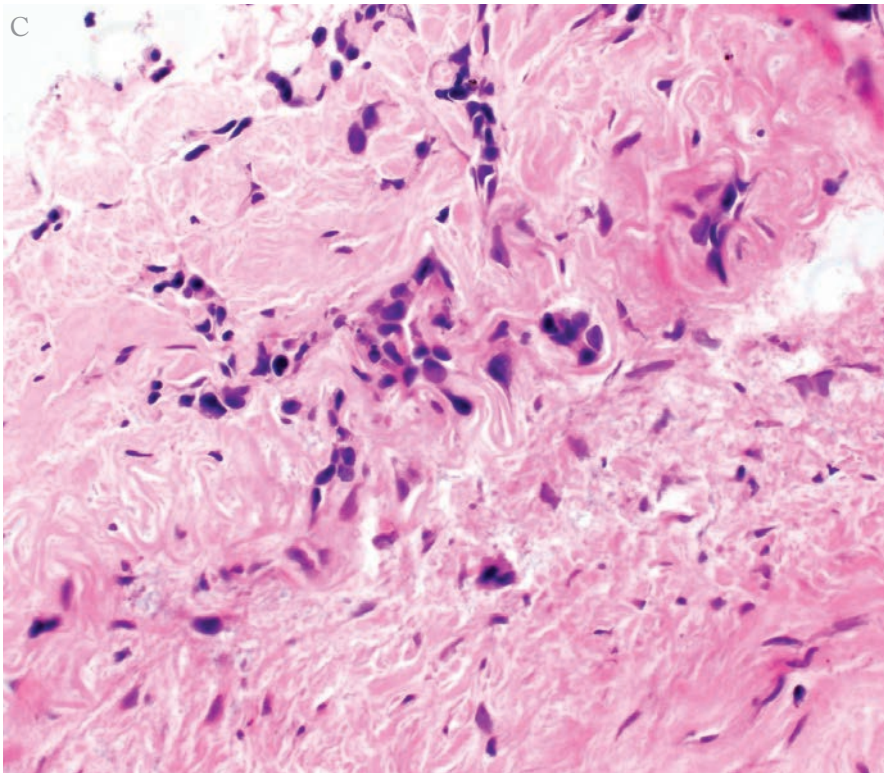


Figure 1. A. Biopsy of RUL lung nodule with prominent fragment of cartilage (possible hamartoma); H&E stain, original magnification 40x. B. Image from CT-guided biopsy demonstrates biopsy introducer cannula within the same spiculated RUL lung nodule (features not suggestive of hamartoma); note the close proximity of both the nodule and the biopsy cannula to the right first costochondral cartilage. C. Rare atypical cells found on deeper section (suspicious for NSCLC); H&E stain, original magnification 400x.



further sampling of other lesions might be necessary to confirm the suspicion of metastatic melanoma and obtain diagnostic tissue for ancillary studies.

Clarification of specific requests for the biopsy

The number of specialized studies that need to be performed on a small biopsy as standard of care continues to grow and significantly impacts the manner in which pathologists handle these small specimens. A biopsy may be performed as part of an initial workup or, if the patient has an established diagnosis, its purpose may be to obtain tissue for a specific test or clinical trial. The reason for the procedure should be available from the requisition or EMR – but, if not, the pathologist should contact the ordering physician or interventional radiologist to clarify the clinical question. In our practice, we usually contact the radiologist first. Why? The radiologist has just seen the patient and is usually well aware of the purpose of the biopsy.

They also tend to be easier to track down; there may be multiple oncologists in the EMR, and the oncologist we contact first may not be familiar with the reason for the biopsy. This issue is likely to be situational for different practice environments, and we encourage each pathology group to develop its own best practices for whom to contact with tissue handling questions.

Insufficient material from the biopsy

This problem occurs in every practice in the world. We must convey the finding of an inadequate biopsy to the procedural radiologists so that they can consider the particular circumstances of the biopsy. If the discovery is not explicitly communicated to the radiologist, they may not get this important feedback at all. In our experience, radiologists are very receptive to these discussions and appreciate the feedback.

Multiple reasons can account for insufficient or suboptimal biopsy material: the procedure may have been terminated early due to complications such as bleeding; an inexperienced trainee without sufficient guidance may have been involved; the adequacy evaluation by the cytotechnician may have been unrealistically generous, thus prematurely ending the procedure; or the tissue collected was adequate, but suboptimal handling in the laboratory resulted in loss of tissue at the grossing station or in the tissue processor. Without discussing the outcome of the biopsy, we lose the opportunity to understand and prevent similar problems in the future. Occasionally, the biopsy is suboptimal because the lesion is in an anatomically difficult location to sample with a needle biopsy. In this situation, the radiologist may recommend a surgical approach to further sampling if clinically indicated. (It is very unlikely for this suggestion to be made by the pathologist.) In this setting, input from the radiologist may save significant time and money.

For this collaborative paradigm to work, both radiologists and pathologists need to be receptive to an open and collegial environment that encourages reflection and discussion of their findings. This may challenge the initial diagnostic impression for either diagnostician; however, in our experience, the increase in collegiality from close and frequent interactions reinforces a shared sense of teamwork between radiologists and pathologists, creating a strong and respectful bond that allows for a little bit of ego bruising. In all areas of medicine, the diagnostic process increasingly involves more players using newer technologies, and the pathologist's role is changing. Technologies, such as point-of-care molecular testing or in vivo microscopy, have redefined – and will continue to redefine – the function of the pathologist in the diagnostic process of many diseases. Pathologists' ability to recognize our evolving role as just one part of the diagnostic team will enable us to interact effectively with our clinical colleagues and provide us with the best opportunity to optimize our value in the future.

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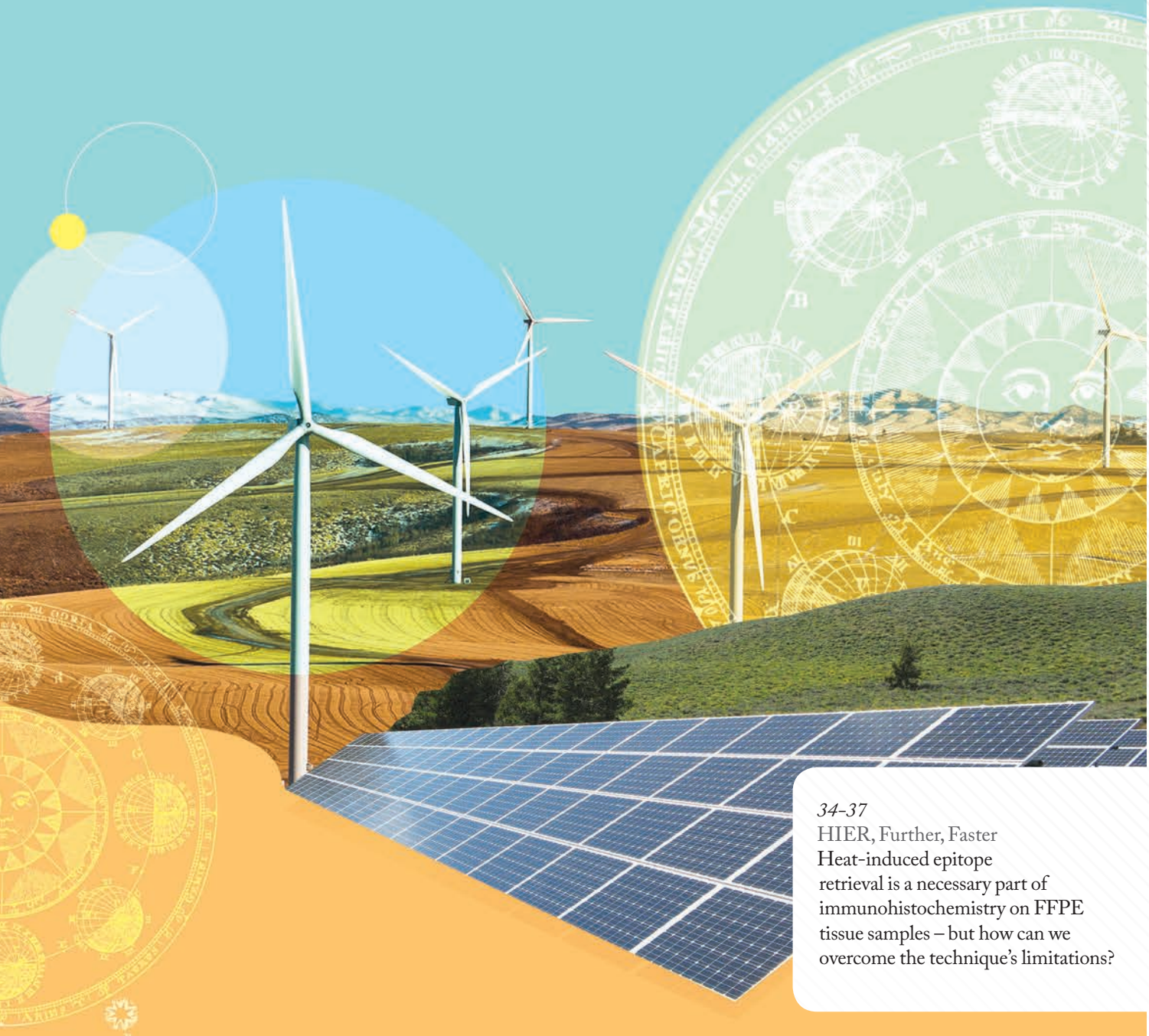

HIER, Further, Faster

Is hybrid power the next step in the evolution of automated heat-induced epitope retrieval?

By Jason Ramos and Spontaneous Russell

Since 1893, formalin has been the standard fixative for tissue processing in histopathology (1). It's certainly not the only fixative available but, so far, none have managed to supplant formalin in general use. Due to the chemical's superior preservation of morphological detail, criteria for pathological diagnoses have been established through the observation of formalin-fixed, paraffin-embedded (FFPE) tissue sections stained with hematoxylin and eosin (H&E). Formalin is a cross-linking type of fixative, meaning that it forms methylene bridges between tissue proteins (2,3). This cross-linking reaction adversely alters the proteins' structure, resulting in loss of antigenicity (4).

Although it was 1941 when Coons and colleagues published their groundbreaking work on immunofluorescence detection of antigens in frozen tissue (5), it took decades before the use of immunohistochemistry (IHC) in surgical pathology became routine. One reason for this lag was the absence of commercially available monoclonal antibodies. Over 30 years later, Kohler and Milstein published their seminal work (6) describing the generation of hybridomas to manufacture monoclonal antibodies "to order." Along with the development of more sensitive detection systems, hybridoma technology generated renewed interest in diagnostic IHC. But one hurdle to widespread adoption still remained; antigen detection via visibly tagged antibodies only worked well on frozen tissue sections with inferior morphological detail.

In 1991, Shi et al. overcame that hurdle with the development (7) of heat-induced epitope retrieval (HIER). By heating slides in a buffered solution, HIER critically facilitated the use of FFPE tissues for IHC, retaining the utility of existing morphologic diagnostic criteria. The new technique dramatically enriched the value of archival FFPE tissue blocks with known clinical follow-up data – creating a valuable resource for translational clinical research, basic research, and diagnostic protocol development that cannot easily be reproduced. With HIER, antigenicity could now be restored in FFPE tissue while still retaining the key morphologic features that correspond to the H&E-stained sections that form the basis of diagnostic histopathology. The incubation time with the primary antibody in the IHC protocol was also shortened to less than one hour for most antigens – a major improvement over the overnight incubations required to drive suboptimal interactions without HIER.

The complexity of the IHC protocol necessitates a properly trained, highly skilled staff to achieve accurate, consistent diagnoses. As we have increasingly realized IHC's enhanced diagnostic utility,

At a Glance

- *Heat-induced epitope retrieval (HIER) has made immunohistochemistry on FFPE tissue possible – but brings its own problems*
- *Manual HIER is time- and labor-intensive, but automating the process carries a capacity limit: the 30-slide barrier*
- *The sustained high heat requirement for HIER means that laboratory power supplies can only handle 30 slides at a time*
- *Hybrid power can provide a power boost during the heating process to overcome this limit*

histology laboratories have experienced a corresponding increase in demand. Automation, and the concomitant standardization and reduction of variability, allows laboratories to achieve the quality, reproducibility, and speed necessary to meet that increased IHC demand (8).

HIER we go

HIER, also known as antigen retrieval, is based upon biochemical studies suggesting that the cross-linking reaction between protein and formalin may be reversed by high-temperature heating or strong alkaline hydrolysis (2,3,9). The routine use of HIER prior to IHC has been shown to minimize inconsistency and standardize staining (10,11). The most critical aspects that influence the quality of HIER results are heating temperature, heating time, and the pH of the retrieval solution.

What exactly is HIER? It's the process of heating the slide-mounted specimen material in an antigen retrieval solution, followed by a cooling-off period. There is no universal solution for restoring all antigens, but the most commonly used solutions are citrate-, tris-, or EDTA-based (12,13). The pH of the HIER solution influences the IHC staining intensity significantly and is critical to the protocol's effectiveness for the specific antigen tested (14). Some antigens retrieve better in a lower pH solution, such as a citrate buffer, while others will retrieve better in a higher pH solution, such as a tris buffer. HIER at the appropriate pH allows the antigen to regain its natural shape, improving recognition and binding by its corresponding antibody – so the composition and the pH of retrieval buffers are critical for optimal retrieval, antibody binding, and subsequent staining.

HIER works by hydrolyzing the methylene bridge cross-links formed during the formalin fixation process (12,14–17). Breaking the formalin-induced methylene

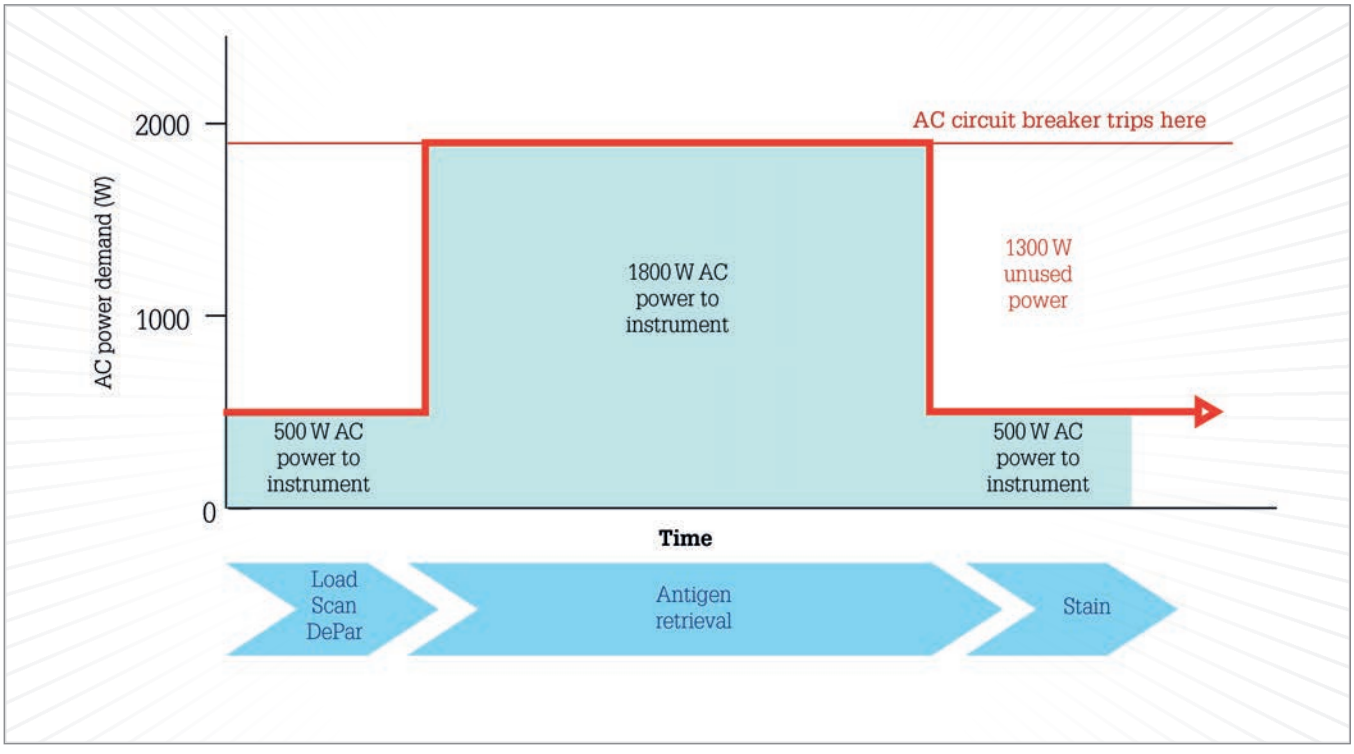

Figure 1: Power usage of current automated IHC staining platforms

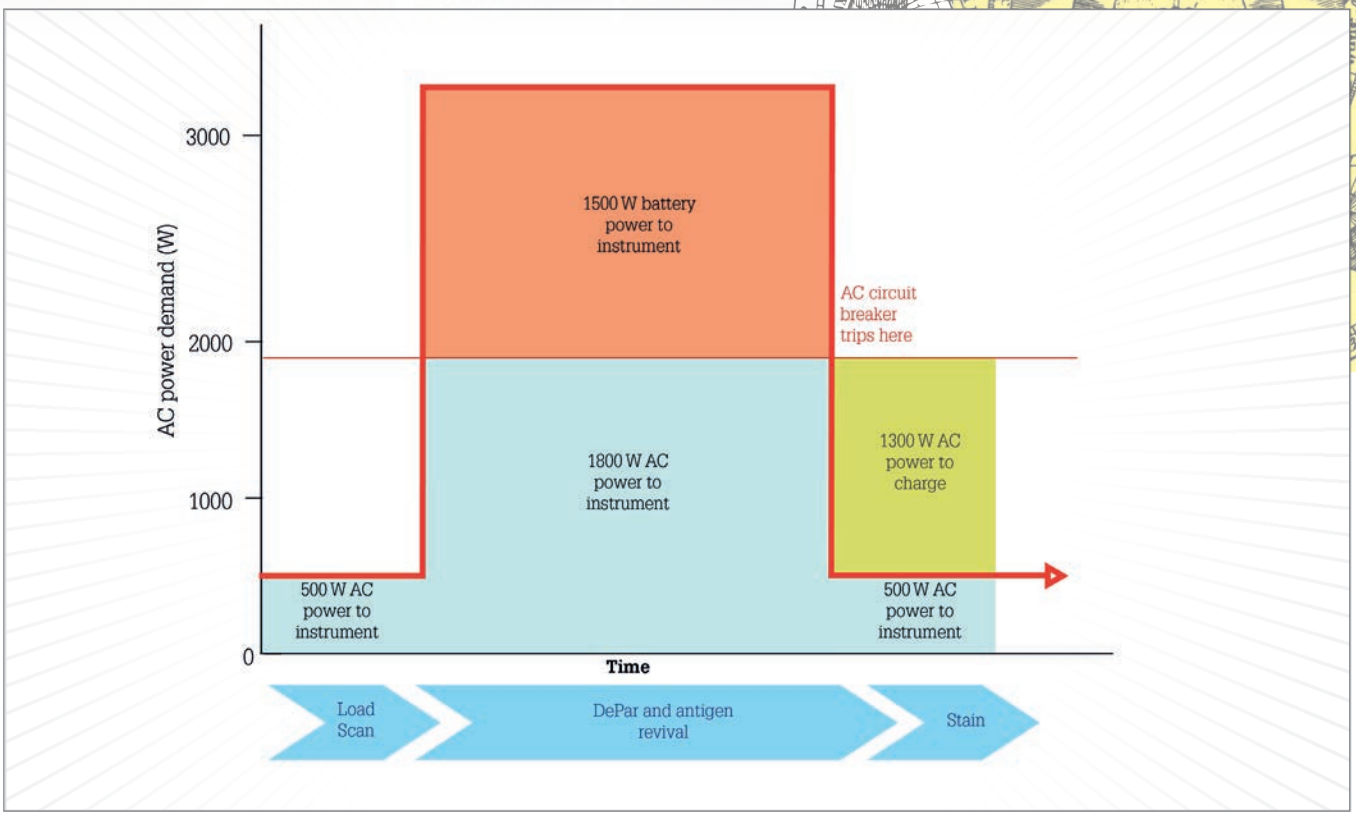

Figure 2: Power usage of automated IHC staining platform with hybrid lithium-ion power.

cross-links in the presence of the appropriate pH solution allows the fixed protein to undergo a series of conformational changes to restore, or partially restore, its native structure – allowing the antibody to better access and bind the antigen. The entire process is driven by heat (14); the methylene cross-links are hydrolyzed when their thermal energy threshold has been reached. The effectiveness of HIER is determined by heating time and temperature; the higher the temperature, the shorter the heating time needed to attain optimal results – but heating at a higher temperature for a shorter duration yields better staining results than heating at a lower temperature for a longer time (12).

There's no need for specialized heat sources – anything from a microwave oven to a fully automated IHC stainer will work – but, of course, some perform better than others. Laboratory pressure cookers eliminate the irregular heating and temperature variation inherent to devices like steamers and microwave ovens (12,13,16), but the best solution to inconsistency problems is an automated IHC staining platform and online heat retrieval techniques. Automated platforms standardize protocol and reduce the inter-user variability seen with manual deparaffinization, HIER, and IHC staining processes. Online processes are more reproducible, less damaging to tissue sections, and save a great deal of hands-on technician time.

Beyond the 30-slide barrier

Over the past few decades, the adoption of HIER as a standard IHC enhancement technique has revolutionized the use of IHC as a diagnostic tool for FFPE tissue examination (18). However, to date, the mechanical requirements of HIER protocols have constrained the maximum performance features of automated IHC staining instruments, limiting their throughput capabilities.

Because HIER involves applying continuous high temperatures and specially formulated buffers to FFPE tissue on glass microscope slides, automated IHC instruments that support on-board HIER commonly use under-slide heaters to indirectly apply sustained heat (8). The inefficient thermal conductivity of microscope slide glass, combined with the rapid heating and sustained temperature requirements of HIER, necessitates the use of powerful heaters – and, when more than 30 slides are simultaneously undergoing HIER,

those heaters can exceed the electrical power available from standard laboratory circuits (see Figure 1). The average lab wall outlet has a maximum power draw of 1,800 W – so, to remain beneath that threshold, automated IHC staining platforms are designed to use no more than 30 under-slide heaters in parallel.

Many IHC laboratories prefer the workflow advantages and consistency of automated staining, including on-board automation of the HIER process. The downside is the "30-slide barrier," which impacts the lab's overall daily slide throughput – leaving them with the choice to either purchase and accommodate additional machines or switch to a more labor-intensive and error-prone manual protocol. Ultimately, we need a better solution – one that allows automation without the capacity limitations of existing processes.

In a recent article, Schwedler and Basiji outline a way to deliver more power to the HIER process – the point at which energy demand typically exceeds availability (19). Their approach uses a rechargeable lithium-ion battery to augment the available wall power and boost parallel slide processing capability by 60 percent (see Figure 2). Following the HIER process, the excess energy available from the wall outlet (shaded green in Figure 1) is used to completely recharge the battery before the next run. In the event of a power outage, the battery can even serve as an electrical backup to prevent the loss of samples.

This kind of hybrid power technology will allow clinical and research laboratories to maximize throughput and consistency without the need for additional staff. Overall, the technology not only saves time and cost, but also improves patient care through faster turnaround times and enhanced diagnostic accuracy. With ever-increasing throughput and performance demands placed upon diagnostic laboratories to offset rising healthcare costs – not to mention expectations of accurate, consistent, high-quality staining results – laboratories must, in turn, demand maximum efficiency from IHC. To maximize return from a single automated platform, rather than needing to purchase and deploy several, we'll need to turn to innovative technology. Integrating hybrid power systems into the next generation of automated IHC staining platforms will allow laboratories to meet and even exceed throughput and performance demands while maintaining the quality of their results.

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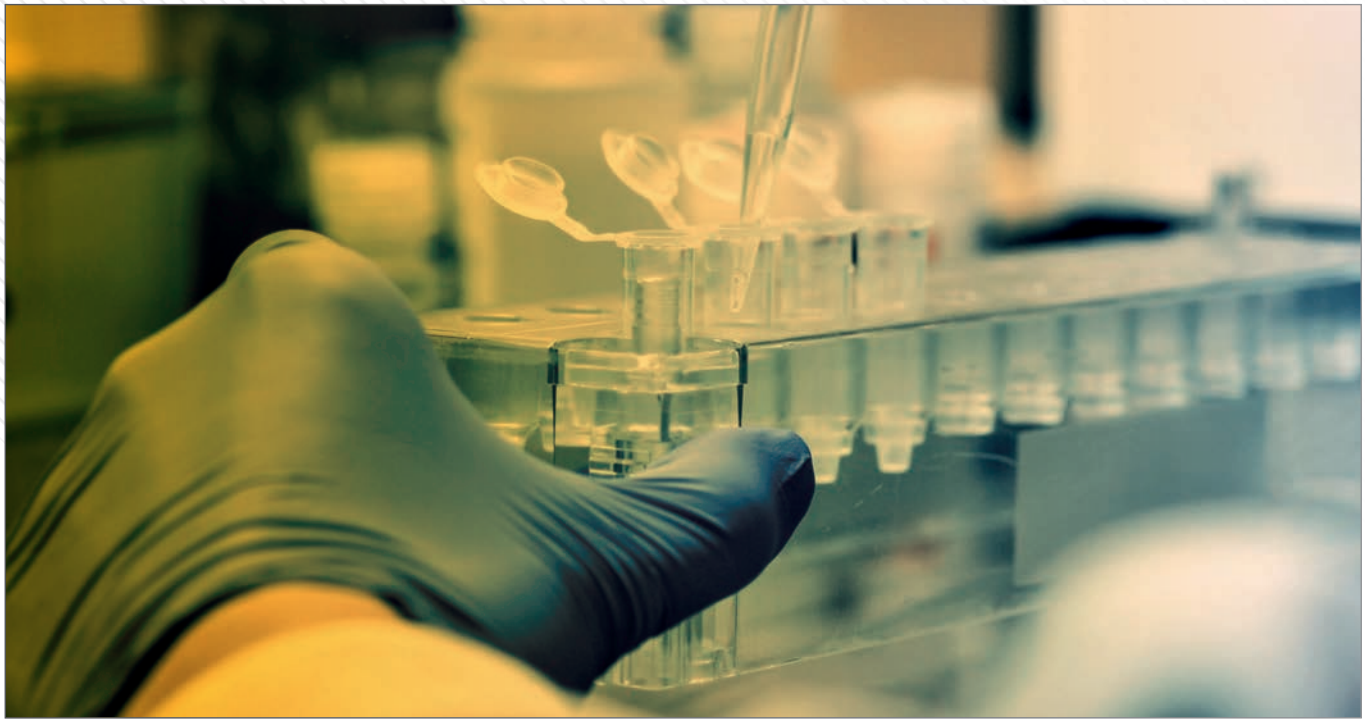

Automating Lab Inspection Readiness: The Next Great Challenge for Pathology Laboratories

July 17, 2019
1pm EDT / 6pm BST

Is your lab ready for inspection? If not, how much time – and how much work – would it take to get there?

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The Evolution of a Lab Hero

What exactly is a pathologists' assistant – and how do we bring real value to the medical laboratory?

By Jesse McCoy

Medical laboratory professionals are at the heart of the laboratory and at the diagnostic crux of healthcare. I am a part of the medical laboratory professional team; I am a pathologists' assistant (PA). It has been my honor and privilege to serve patients and fellow healthcare professionals alongside pathologists for over a decade. In that time, I have watched our profession become an integral role within the healthcare team as the "unsung heroes" of the lab (1).

My first synoptic report

My journey as a PA has been less than traditional. In fact, it began in an elementary school gym. I can still smell the freshly polyurethaned floor as I perused the annual school science fair exhibits. My own submission wasn't particularly innovative or award-winning; however, I found it both fascinating and exquisite. You see, I had stumbled upon a model brain at the local hobby store – one that could be dissected and colored – and decided to feature it in my science fair submission. The model was accompanied by a nine-year-old's version of a synoptic report correlating anatomy with neurologic function, albeit in a very rudimentary way. I recall being mesmerized by this anatomic structure: its splendor, beauty, and complex functionality. It was then I knew I wanted to be… a brain surgeon.

Fast-forward many years through high school, with university decisions looming. I faced an inner dilemma between my technical and creative ability as an artist and my passion and intrigue for the biological sciences. Sadly, neurosurgery didn't make the cut – but I was able to find an acceptable marriage by attending the Rochester Institute of Technology, from which I graduated with a degree in medical illustration. My initial post-undergraduate years of employment were as a full-time, in-house, contract biomedical illustrator and animator at Pfizer Global Research and Development, where I developed content for clinical trial patients, clinicians, and researchers. Although rewarding, the work was very much removed from both the patient experience and the pathology that deeply intrigued me – a disconnect that weighed heavily on my creative juices.

But, as fate would have it, the ever-changing dynamics of the biopharma industry caused my entire creative services team to be "reassigned." This left me out of a job and, out of desperation, I ended up taking a position as a technical illustrator at Dominion Nuclear Power Plant. I spent my days illustrating turbines and regulatory commission datasets which, although important, was less than fulfilling. But it did make me realize that I needed to get back to the drawing board and reconnect with the passion that so deeply influenced my undergraduate studies. Those curiously blissful moments of dissecting a human cadaver in gross anatomy and investigating the disease mechanisms behind said cadaver's demise was what drove my research.

Finding a new path

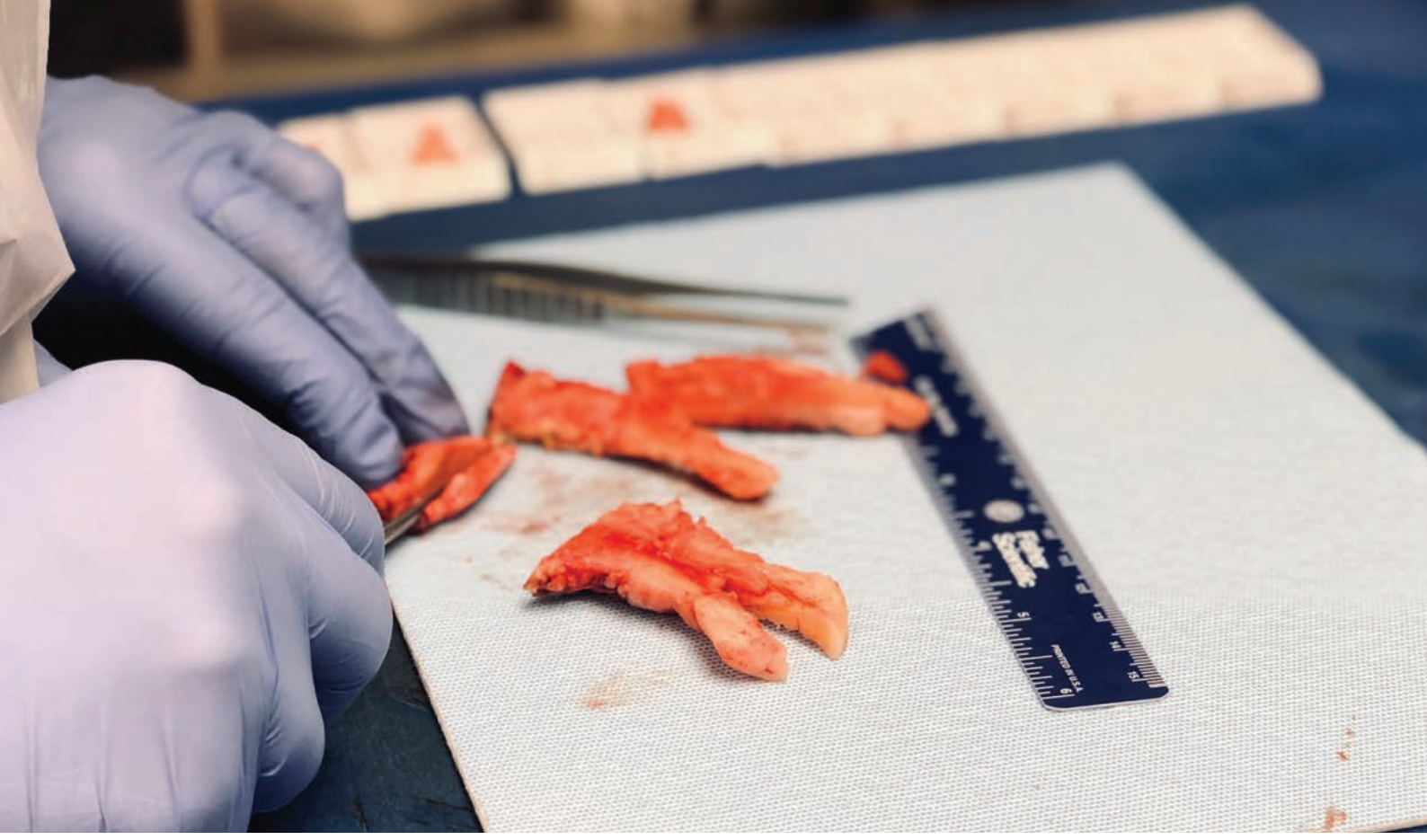
Thanks to Dogpile (an Internet metasearch engine), the keywords "human dissection" + "pathology" + "master's degree" pointed me in the direction of a profession I hadn't even heard of: the pathologists' assistant. It offered a career leveraging my technical ability and passion for biomedical sciences, with the added prospect of being able to focus exclusively on dissection while nevertheless serving patients and the healthcare community. A perfect match!

As a Connecticut native, Quinnipiac University – one of eleven NAACLS-accredited "PathA" training programs (2) – was in my backyard. Without hesitation, I applied and was accepted into the class of 2007. PA school was intense and certainly not for the faint of heart. Our first year was entirely didactic. Courses were stretched out over a 12-hour span, Monday through Friday (and even Saturdays during the summer), so days on campus were long. Sleepless nights ensued as my classmates and I scoured endless pages of notes from courses such as Human Microscopic Anatomy, Basic Human Pathology, Clinical Pathology, Laboratory Management, and Embryology.

The second year consisted of intensive clinical rotations in places like Yale University School of Medicine, the Connecticut State Medical Examiner's Office, Hartford Hospital, the VA medical center in West Haven, Crouse Hospital in Syracuse, and many more. We trained alongside residents and other PA students. Our preceptors, to whom I am eternally grateful (thank you all for your patience and commitment to the profession) served as models for how to be successful behind the gross bench and in the autopsy suite. Overall, the Quinnipiac program prepared me with "comprehensive knowledge in the

At a Glance

- *Pathologists' assistants play an integral role in the laboratory medicine team*
- *Their backgrounds are often non-traditional, ranging from medical illustrators to mosquito supervisors*
- *Such diversity brings with it versatility and a creative approach to problem-solving*
- *Volunteering is a great outlet for laboratory medicine professionals, including PAs, and can lead to new opportunities for professional development*



practice and operations of the anatomic pathology laboratory" (3).

Upon graduation, I sat for the American Society for Clinical Pathology (ASCP) Board of Certification and passed. I was now a bona fide, ASCP-certified PA – I was a PA (ASCP)cm.

The next step – a job

As a resident of Connecticut, I was warned that Quinnipiac's presence caused the market there to be somewhat saturated – so it would be difficult to obtain employment locally. This didn't deter me. I wrote letters to every hospital in the state that didn't have PAs, offering my services as an eager and emerging PA. Much to my professional satisfaction, I was offered a position at my birthplace, the William W. Backus Hospital, with University Medical Group (later University Pathologists, LLC).

This first job out of school was one of evolution. For several years I served as not only the PA, but also the histology supervisor. You see, the scope of practice of a PA is vast, as I quickly discovered during my time at Backus. Grossing surgical specimens, prosecting autopsies, accessioning, cutting frozens, specimen photography, intraoperative consultations for specimen adequacy, negotiating service contracts, participating in annual reviews, managing chemical inventory – you name it, I did it, in collaboration with an excellent team of pathologists and medical laboratory professionals.

After a transition to a new and equally diverse role at Kent Hospital, where I again served as both PA and technical histology supervisor, I finally felt I had the experience to spread my wings and leave Connecticut in 2015. I relocated to southeastern Virginia, where I initially worked at Bon Secours Maryview for a year and then moved to a position close to my home. To this day, I am employed at Chesapeake Regional Medical Center with Hampton Roads Pathology.

Making our mark

What sets those who choose the PA profession apart is our variety and versatility. My professional evolution highlights the infinite variability among our journeys to becoming PAs. In fact, medical illustration wasn't the only unconventional first career I encountered in PA-dom; this eccentricity is a common thread among PAs, with previous professions including: boar laboratory technician for artificial insemination, professional dancer at Walt Disney World, Spanish translator, and mosquito colony research tender. Certainly, there are those who follow the natural progression within the lab – histotechs, cytotechs, or clinical laboratory scientist (according to an informal Facebook pathologists' assistant group poll and discussion). But this is precisely what makes us unique – the vast diversity of experience we bring to the proverbial grossing bench.

The versatility we offer relates to job responsibility (supervisory versus non-), type (community hospital versus academic), and genre (surgical versus autopsy). In my humble opinion, we are not just pathologists' assistants despite our official job titles; in actuality, we bridge the gap between all aspects of the preanalytical, analytical, and post-analytical stages for every patient who comes through the door of our laboratory. Our scope of practice is beyond what I

can describe through my own personal experiences but, to say the very least, we are "academically and practically trained to provide accurate and timely processing of a variety of laboratory specimens" and, as such, we are "key partners in assisting the pathologist to arrive at a pathologic diagnosis (4)."

Aside from my day job grossing, I have never been particularly satisfied with the status quo; I have always sought ways to keep my creative juices flowing. As a result, I have taken advantage of every opportunity to serve the profession – and I've found it amazingly rewarding. I have teamed up with both the ASCP and the American Association for Pathologists' Assistants (AAPA), working on a vast array of programs and projects. Shortly after graduating from Quinnipiac, I applied to serve as an ASCP Career Ambassador, which really served as a catalyst for my volunteer roles within the organization. With a significant workforce shortage looming over the laboratory, ambassadors visited area high schools to present on careers in the laboratory. I happened to have access to the Yale University autopsy organ teaching collection, which was a huge hit with the students. This experience evolved into a role on the Council of Laboratory Professionals, where I currently serve as the Immediate Past Chair (2018–19). I now also serve as a Member-At-Large on the Commission on Membership (2019–21). These roles have given me the opportunity to keep my finger on the pulse of our profession and stay closely in touch with our members – the entire medical laboratory professional team. I am deeply committed to ASCP's mantra: we are indeed stronger together.

In 2012, the AAPA embarked on a journey to create the "Grossing Guidelines," more officially known as the "AAPA Macroscopic Examination Guidelines: Utilization of the CAP Cancer Protocols at the Surgical Gross Bench." As a classically trained medical illustrator, I was invited to be a part of this immense project – and it is with pride and satisfaction that I now fulfil the role of Art Director/Illustration Liaison and contributing illustrator on this wonderful practice aid and teaching tool. The Grossing Guidelines aim to lead the entire pathology community through the macroscopic examination of cancer resection specimens. What a labor of love and commitment – and a true marriage between my passions and professions as a medical illustrator and pathologists' assistant.

Words of wisdom

If I had a message for all PAs out there, it would be to value your amazing career opportunity and be the best you can be. Pathologists, value your PAs; we have much to offer. And to the rock-star medical laboratory team: leverage what you may already have in your lab toolkit and look to the PA, a multifaceted part of your team.

My message for all laboratory medicine professionals, from phlebotomist to pathologist, is this: get out there and do something great! Your professional value goes far beyond the walls of a hospital – for instance, with volunteer roles that are critical to our field as well as to your growth and development. Why keep those unique qualities we bring to the grossing bench to ourselves when we can be a part of a diverse team for the greater good of our healthcare profession? Volunteerism has pushed my career forward in more ways than I can describe, allowing me to network with a vast group of medical laboratory professionals and participate in challenging – yet rewarding – projects. I've soared farther than I could have ever imagined, and I'm sure the best is yet to come.

I'm telling my story in response to an editorial in a previous issue of The Pathologist, in which my colleagues and I were described as the "unsung heroes of the lab (1)." That editorial called upon us to tell our stories as non-pathologist laboratory professionals. If I had only one goal in doing so, it would be to inspire all of you to truly be lab heroes. I am an ordinary person, with unusual but simple beginnings, who has embraced the journey. I challenge every reader to commit to some form of volunteerism – something that gets you one step closer to becoming the best you can be. Your patients deserve a better you. They deserve a lab hero.

Jesse McCoy is a Pathologists' Assistant for Hampton Roads Pathology at Chesapeake Regional Medical Center, Chesapeake, USA.

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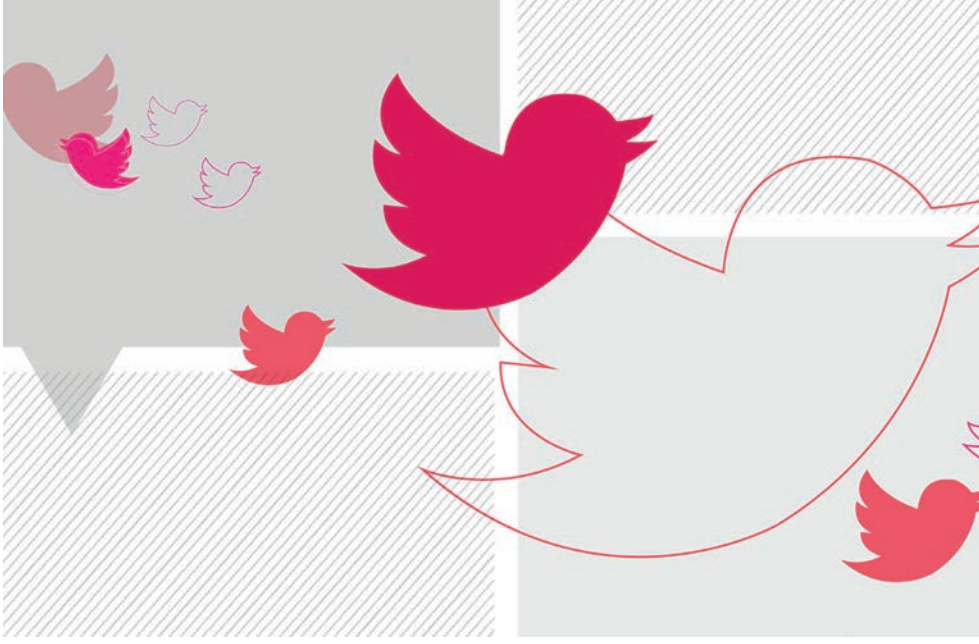


#MedEd Goes Social

The winners of a grassroots award for Twitter-based pathology education speak out

By Michael Schubert

Like medicine itself, medical education is moving into a futuristic reality. We now have online forums for case presentations, simulated patients to help us learn, and even computers that can assist us in diagnostic decision-making. But not every advance comes from the top down; some educational approaches are rapidly – and perhaps unexpectedly – gaining ground. Chief among those is the use of social media, which many pathologists and laboratory medicine professionals now cite as a valuable learning tool.

In fact, social media is so popular for disseminating information that a group of "tweeple" – the Twitter community's term for themselves – got together to establish a grassroots award for pathology education via social media: the Educational Pathology Tweet Award, or #PathTweetAward. Twitter users who create educational tweets for others are encouraged to use the hashtag so that they become more visible to the learning community, as well as to the judges who select the best of the best. And the award has certainly had a significant impact. In its inaugural year, two prizes were awarded to trainees for their outstanding education tweets, and two further prizes were given to pathologists in the open category. We spoke to the winners – Tiffany M. Graham, Mariam Molani, Raul Gonzalez, and Angel Panizo – to learn more about their tweets and their views on the future of medical education.

At a Glance

- *Social media is a part of the revolution taking place in medical education today*
- *The pathology and laboratory medicine community has found social media, especially Twitter, a valuable place for grassroots learning*
- *A community of such professionals on Twitter has established an educational pathology tweet award to recognize educational posts*
- *Here, the winners of the inaugural prizes share their thoughts on #SoMe and #MedEd*

Winner (Trainee)	Tiffany M. Graham
Twitter Handle	@HeartPathology
Winning Tweet	tp.txp.to/award1

Tell us a bit about yourself and your path to pathology…

For a quick whirlwind tour of myself: I grew up in the mountains of North Carolina and graduated with a Bachelor of Science degree in biochemistry from East Carolina University. I then attended American University of the Caribbean School of Medicine in St. Maarten, which afforded me the opportunity to complete one year of my clinical training at a hospital in London and several elective rotations at various prestigious hospitals in the United States.

Being exposed to such diversity in both patient populations and healthcare systems, learning more about how disease affects people and how we can help treat them, was fascinating to me. It was not until my fourth year of medical school, while in the process of narrowing down "what I wanted to be," that I even considered pathology as a career option. I had always enjoyed learning pathology, but did not realize exactly what it entailed until I completed an elective rotation. I distinctly remember the moment I decided that pathology was the career for me. I walked into the grossing room/histology lab and saw the words "Pathology Rules" written in the form of neutrophils with hyperlobated nuclei. It made me giddy to see that others shared my nerdy sense of humor!

Fast-forward four years: I am now finishing up my fourth year of anatomical and clinical pathology residency at the University of Alabama at Birmingham and will be completing my fellowship training in gastrointestinal and hepatobiliary pathology at the Medical University of South Carolina in Charlton. After that… exploring the job market!

What inspired your interest in education?

Ironically, I used to have a huge fear

of public speaking. It was after a lot of coaxing from my anatomy professor at medical school that I agreed to be the sole anatomy tutor for the upcoming class of 200+ students. I was terrified, but quickly realized how much I enjoyed sharing my knowledge with others. I was even more pleased that they seemed to really appreciate my teaching style and notes. Since then, I jump at the opportunity to teach others. I'm honored that my hard work is being recognized; I was awarded the Jay M. McDonald Award for Excellence in Laboratory Medicine Presentation in 2017, the Outstanding Trainee Teaching Award for Multidisciplinary and Medical Student Education in 2018, and now the #PathTweetAward.

How do you use social media and the Internet for educational purposes?

I first started using social media for educational purposes while in medical school. During that time, I blogged about my experience as a means to stay connected with friends and family back home. However, I soon became flooded with questions from people all around the world (mostly medical students or those interested in becoming a doctor) who had somehow stumbled upon my website. Most of these questions were trivial: "Do you have any tips for how to study?" "What are the hours like in the hospital?" "What resources do you recommend so I can prepare for [insert rotation/class]?" Although there are a few published resources that discuss these issues, many can only be answered by conversing with someone who has already gone through the process. Thus, I viewed this as an opportunity to share various tips, tricks, and study notes on a larger scale.

Being in residency now (and in the process of studying for board exams), I decided to take a similar approach by creating a "study blog" (IHeartPathology.net) dedicated to those who "heart," or love, pathology. I designed the website to serve as a centralized source of information from which I could quickly reference material during sign-out, prior to being on call, or when starting a new rotation. Much of the content posted is geared toward sharing the "bread and butter" information commonly seen in clinical practice. It is great for pathology residents, but anyone who loves pathology and wants to learn more about it can use the website as a free resource.

When I heard that many pathologists use Twitter, I decided I would give it a shot and started to share my study notes there. Since winning the #PathTweetAward, more people are cognizant that Twitter is becoming a big deal and that it's a great way to collaborate with other pathologists. I like that it brings pathologists out from behind the scenes and emphasizes our prominent role in patient care. I think social media is just one tool we can use to help change the slightly skewed stereotype of a pathologist (very smart; socially awkward; "hates people") and may entice more medical students to consider pathology.

Tell us about your educational tweet…

This is an example of a high-yield summary created after I reviewed an excellent presentation created by Richard DeMay regarding the foundations of cytology. This infographic exemplifies how 20 slides can be summarized into a single concise review. I find lecture slides to be a great study tool; they are often used by residents in lieu of a textbook as their "ground zero."

What are the qualities of a good educational presentation?

I think it's important to acknowledge that everyone learns differently. There is no one right way to study. Personally, I am a "visual" or "hands-on" learner. I struggle to retain the same amount of information using traditional study methods, such as reading text, as I do when that information is presented pictorially. For me, creating infographics and mind maps allows me to easily visualize the key points and appreciate the delicate interrelationships between entities. This has been tremendous for solidifying my pathology knowledge base and bridging the gap between what the textbooks say and what we actually see at the microscope. Regardless of one's learning style, I think it is critical to never lose sight of the "big picture." To learn (and teach) a topic, there must be a solid foundation upon which to build.

Lecture slides can be a great study tool and are often used in lieu of a textbook. However, given this medium's static nature (the lectures themselves are not often recorded), its educational benefit is highly dependent upon the quality of the presentation slides. Additionally, it can be easy to lose sight of the relationships between various diseases if structure and organization is lacking. Keeping in mind that others will be referencing the material secondhand, there are quite a few things one can include in the content to make it "better."

1. Overview and summary slides. These are helpful whenever there is a topic change as it keeps things in perspective for the reader. Creating a mind map first helps to establish a hierarchy and show the big picture. Adding on the details as you study allows you to appreciate the subtleties between various entities.
2. Emphasis on the key point you want to get across. This can be done via a variety of methods: bold, italics, underlining, highlighting, colorful text, using different fonts, circling something, using arrows, and so on.
3. Labels for all [histology] images.

As they say, a picture is worth a thousand words – but what happens when the picture comes along with zero words? The reader can only guess what you are trying to illustrate. It's important to remember that we, as pathologists, view histology on a daily basis. However, to someone trying to learn this new material, having things spelled out is always nice.

4. Keep it simple. Yes, we know you have a big brain. Does that mean you have to purposely use big words to prove it? No! The best presentations are the ones that help explain difficult concepts by relating them to everyday scenarios. Relatability = memorability.
5. Narrative. Keep in mind that there is a big difference between giving an oral presentation and providing slides/material for review. Someone reading the content should have access to the same information as someone who was at the presentation. This narrative can be put in the comments section of a slide set or included in the main text box.

What is your best advice on educating via social media?

Don't be afraid to post about something you find interesting – or any time you learn something new. You may think that everyone else already knows it, but chances are that someone else struggles with the same concept or may have additional insight that helps further your understanding. Social media is not about trying to get a zillion likes or followers. It's about creating connections with colleagues, gaining new perspectives, refreshing your knowledge on infrequently seen entities and, most importantly, sharing your knowledge in the hope that you learn something new in return.

I have been blown away by the amount of support and encouragement from my fellow pathology "tweeples." Knowing that my charts and website helps others encourages me to continue producing and maintaining them. It is certainly rewarding to know my hard work is appreciated!

Winner (Open)	Raul S. Gonzalez
Twitter Handle	@RaulSGonzalezMD
Winning Tweet	tp.txp.to/award2

I became interested in pathology during medical school. I had the opportunity to shadow several physicians, and the pace of pathology clicked with me. I liked being able to take my time, stare at a slide, pull down a textbook, and really give thought to difficult or interesting cases. My interest in education probably also stems from this aspect of my personality – if I am pondering something, I want to share my thoughts and incorporate the experience of others. I believe education is at its best when it's two-sided in that way. Like many tweeting pathologists, I was introduced to social media via Jerad Gardner (@JMGardnerMD). We met while we were both in training and his passion for social media made me decide to jump in.

Tell us about your educational tweet…

I chose to create a tweetorial after seeing Sanjay Mukhopadhyay (@smlungpathguy)'s excellent tweetorials on lung disease. I have experience with diagnosing, researching, and lecturing about gastroenteropancreatic neuroendocrine neoplasms, so I felt that topic would be the best fit for my first tweetorial. What I most wanted to impart upon my colleagues was how to approach these neoplasms, making sure to use the correct terminology and workup, and also that they must consider the importance of site of origin.

A tweetorial is, as the name implies, a tutorial in tweet form. Because a single tweet has a limited amount of available characters, it can only dive so far into a topic. String a bunch of them together in a coherent narrative, though, and you've basically got a lecture or a review article. I have only created one so far, but I think that it succeeded due to my efforts to make the tweets clear, cohesive, conversational, and supported with good references and photographs. I do plan to create new tweetorials in the future, as time allows – they're not something to rush! My upcoming tweetorials will focus a little more on clinical aspects of disease; although I composed my first imagining other pathologists as the target audience, much of the positive feedback I received came from patients with neuroendocrine tumors, so I will endeavor to craft future tweetorials to suit their needs as well.

What is your best advice on educating via social media?

One thing that always helps me is making sure I teach myself first. Any time I'm about to post a case, I first write what I know off the top of my head, then double-check to make sure I am including all of the correct information. By doing this, I've found new twists on old ideas and corrected mistaken notions I had. Even more importantly, it has kept me from spreading inaccurate information. It takes extra time, but it's definitely worth it.

Runner-Up (Trainee)	Mariam Molani
Twitter Handle	@drmarmolani
Winning Tweet	tp.txp.to/award3

I am a second year anatomic and clinical pathology resident at the University of Nebraska Medical Center. I grew up in Louisiana and went to medical school in Kansas City, where I completed a dual degree program with a simultaneous MBA in healthcare leadership. When I was in my third year of medical school, I struggled to find a specialty that called to me – but once I completed an elective rotation in pathology, I fell in love with the field because it was visual, cerebral, diverse, and challenging.

I have always wanted to become an educator, and I became fascinated with social media as a teaching tool after an interactive presentation on Twitter medical education in one of my MBA classes. Although many of my classmates labeled social media a professional faux pas, I saw immense educational potential through free platforms that offered unlimited information sharing and instantaneous communication with people around the world. I became very active online and started my own personal #MedEd social media accounts, and my first year of residency, I started a pioneer social media #MedEd account for my residency program.

Tell us about your educational tweet…

My mesothelioma flash card is part of a larger series of digital drawings I make to review various diseases and tumors. I sketch them on my iPad because they are easy to edit, organize, and – best of all – share. I tweeted a photo of my notes with the idea that digital flashcards might be a helpful study tool for other residents as well. I did not anticipate the interest that others would have in my sketch, or the overwhelming support of the Twitter pathology community for online trainee medical education!

Creating and sharing my digital notes was a very fulfilling experience not only because it might have helped other trainees, but also because I learned a lot in the process. Some experienced pathologists suggested the addition of new markers that I had not included in my table; others pointed out additional clarifying information about the malignancy. It was a collaborative social and educational experience – all while scrolling!

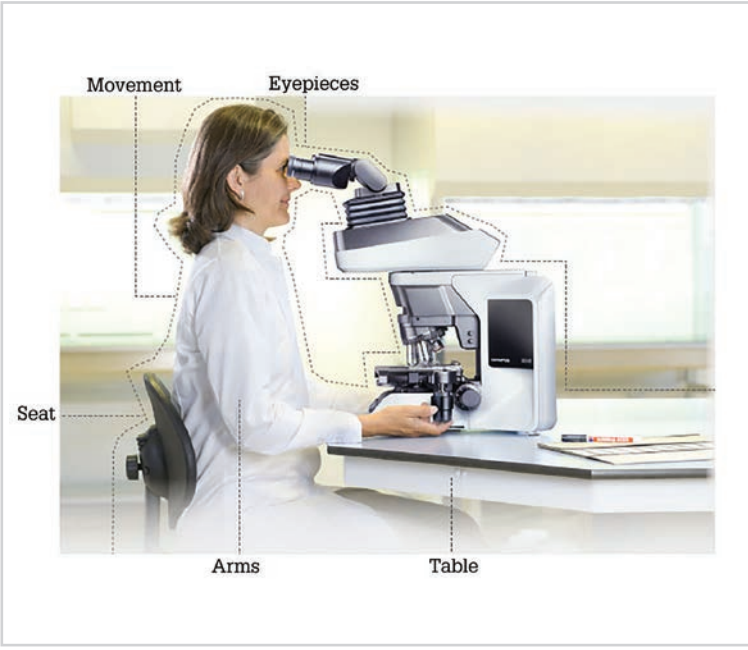
What is your best advice on educating via social media?

Step away from the PowerPoint! Adapt to your audience and take advantage of new and exciting resources to optimize your educational experience. I love it when I go to a lecture and the lecturer says, "Pull out your phones and tablets! Let's use a new app to learn today's subject!" This kind of approach changes passive learning into an interactive experience. I say: don't be afraid of change. Jump on innovative platforms like livestreaming, videos, chats, applications, and cutting-edge software to keep learning hands-on, visually stimulating, and dynamic.

Runner-Up (Open)	Angel Panizo
Twitter Handle	@angelpanizo1
Winning Tweet	tp.txp.to/award4

Routine Microscopy: Improving Productivity Through Better Ergonomics

Working in an ergonomically designed environment helps to prevent injuries and contributes to increased productivity. When it comes to microscopy, ergonomics is particularly important, because the nature of the work puts unusually specific constraints on the operator's posture. Many professionals working in research, clinical, and industrial settings regularly work with microscopes. However, there are certain job roles, such as in pathology, where microscopy forms a significant part of a person's daily activities—sometimes taking up more than 50 percent of their working hours. This "routine microscopy" poses additional challenges to prevent injuries. In response to the specific requirements for routine microscopy, dedicated microscopes have been developed that address the needs of these users. Specific features that are not normally present on conventional microscopes help ensure that these users remain comfortable during long periods of work.



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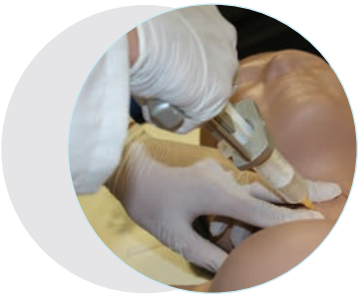

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Title: Where We Are and Where We Are Going – The Winding Road of Cancer Immunotherapy Biomarkers

Dr. Darragh McArt, Sonrai Analytics, N. Ireland
Title: Data Integration Driving Analytics for Modern Day Healthcare

Shiralee Lubke, Northern Health, Australia
Title: "Against The Trend – Moving From Private to Public"

Grahame Grieve, Health Intersections Pty Ltd, Australia
Title: FHIR: Transforming the Pathology Business Relationship

Dr. Louise Harewood, Precision Medicine Centre, N. Ireland
Title: "Cancer Genomics: A Precision Medicine Centre Perspective"

Dr. Jonathan Liu, University of Washington, USA
Title: Nondestructive 3D Pathology with Open-top Light-sheet Microscopy for Precision Medicine

Prof. Stephen Fox, Peter MacCallum Cancer Centre, Australia
Title: Using ctDNA for Precision Cancer Medicine: Is This The Future?

Dr. Anant Madabhushi, Case Western Reserve University, USA.
Title: Artificial Intelligence and Computational Pathology: Implications for Precision Medicine

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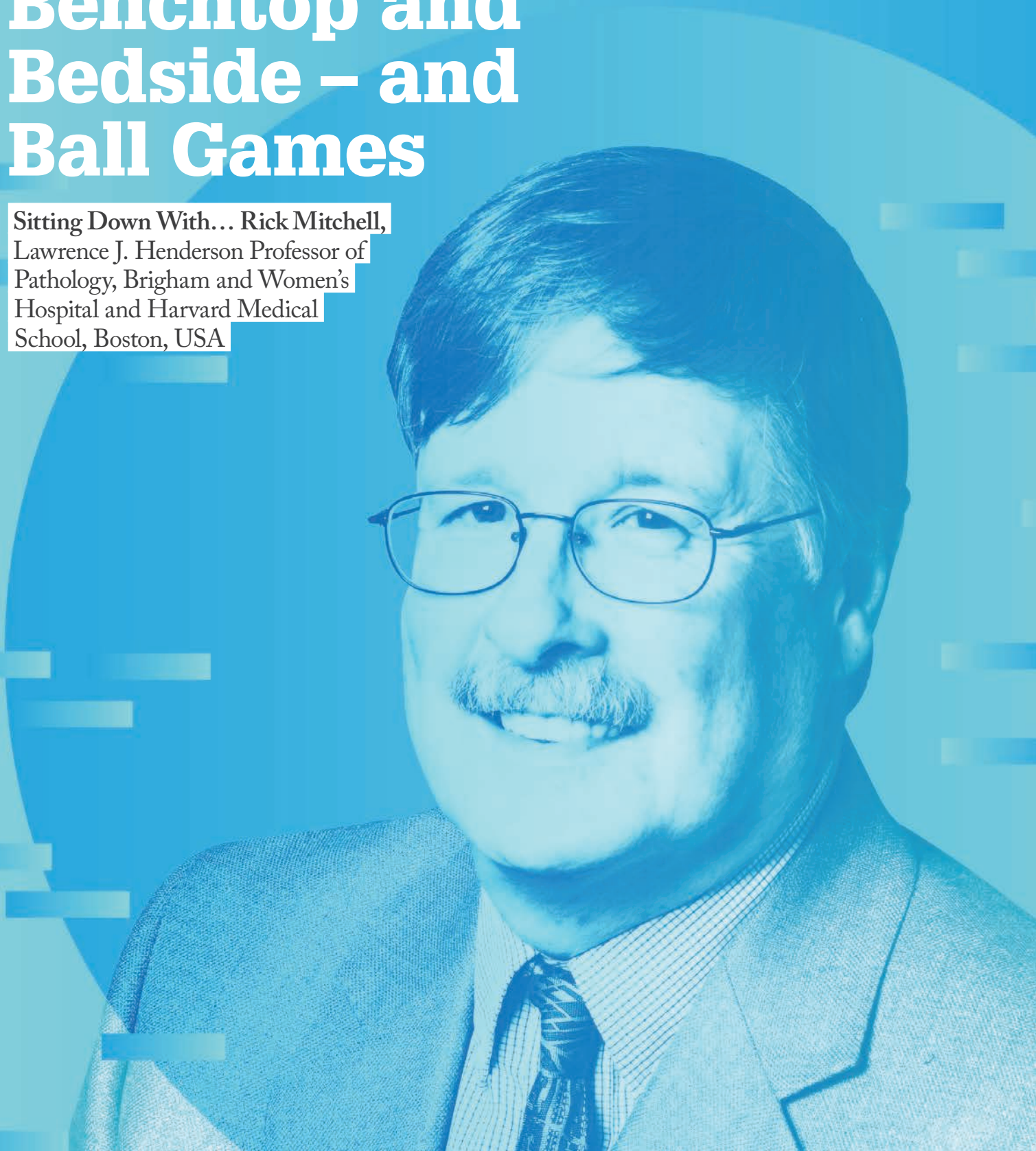

What inspired you to pursue pathology as a career?

Actually, I was very much on the fence. I always wanted to focus on basic research applicable to human disease; I figured that would be the best way to maximize the contributions I would make to humanity (so idealistic!). That's why I originally attended graduate school and earned a PhD in immunology. At the end of that process, however, getting the MD degree also seemed fairly important in moving the clinical-translational needle – so I headed off to medical school, where I found that treating patients was actually pretty interesting. At the same time, four years of medical school had buttressed my convictions that the exploration of disease mechanisms was what really excited me. In that regard, pathology offered a great opportunity to interweave basic research and patient care in a way that emphasized pathogenesis, as well as the excitement of the scientific sleuthing that comes during the diagnostic workup.

As luck would have it, my residency advisor was the late Ramzi Cotran, Chair of Pathology at Brigham and Women's Hospital. After listening to me for a while, he suggested that I just do a medicine internship to get the idea "out of my system." He predicted I'd be back within six months of starting internship, begging him to let me do a pathology residency… and he was right – but I think the year of medicine helped me to become a better pathologist. It certainly made me appreciate how the practice of pathology has allowed me to be a competitive researcher and an expert in a diagnostic area – and also have time to teach – and get home to coach my kids' sports teams.

What's the most interesting thing you've learned in your career?

Perhaps the most amazing thing I've come to appreciate is that the human body works reasonably well much more often than it doesn't. Our daily routine in the hospital focuses on disease, and autopsies clearly don't happen without a death, so as physicians we tend to lose track of the marvelous, resilient, homeostatic mechanisms that keep most of us ticking. In many ways, our bodies are over-engineered, with lots of tissue redundancy, regenerative capacity, and built-in fail-safes… and, perhaps even more remarkably, the entire structure is self-assembling and self-maintaining!

I think the most unexpected thing I've encountered is how incredibly complex the adaptive immune system seems to be. Yes, it has to have remarkable plasticity – and yes, it's in a constant war against an incredibly diverse (and clever, and mutating) microbial world – and, most remarkably of all, everything had to develop through natural selection. Still, I'm not sure that, if one were to think about designing this de novo, it would look anything like it does now.

How are novel technologies changing the face of pathology?

Just as immunohistochemistry and cytogenetics became widely used tools for pathologic diagnosis, the same will happen with molecular diagnostics and with digital and computational pathology. Training programs are already educating residents to understand genomic data and, for subspecialty diagnosis, clinicians will expect the pathologist to have integrated genetic analysis into the final sign-out. I'm doubtful that every slide will eventually be scanned and read on a computer screen, but I do believe that we will increasingly embrace specialized application suites that can take on tedious tasks, such as counting mitoses or enumerating tumor-infiltrating lymphocytes. Image analysis and artificial intelligence algorithms will also represent a terrific growth opportunity for budding researchers in pathology. And, to make sense of the data deluge, we will need to work with (and importantly, educate) computational wizards. As pathologists, we may not become expert in all of those areas, but we do need to understand their indications (and limitations) and be comfortable in applying them in patient diagnosis.

"Follow what you love doing, and the rest somehow works out."

How do you balance your many tasks with a personal life?

My wife would probably say that I still haven't figured out the perfect balance. There are many late nights and some endless meetings that take me away more than we'd like. However, I work at trying to be present when I am home. Although I may prep for a lecture or read papers, I rarely answer emails in the evening or weekends, and I try to stay off the computer. We have a weekly date night and enjoy movies, concerts, plays, and eating out. When we're on vacation, I make it a point to stay off the Internet, even if it means a horrendous backlog when we get back.

Actually, being a pathologist gave me the latitude to pursue other things that a clinician (with live patients) might not have the opportunity to do. Consequently, I was able to coach baseball, soccer, and basketball with the kids and take on a bunch of home improvement projects. In retrospect, having those outside activities probably helped to keep me sane. A sense of humor also helps!

If I could go back and give my younger self one piece of advice, I'd say, "Do it the same way. Follow what you love doing, and the rest somehow works out."

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