JANUARY/FEBRUARY 2020 # 62

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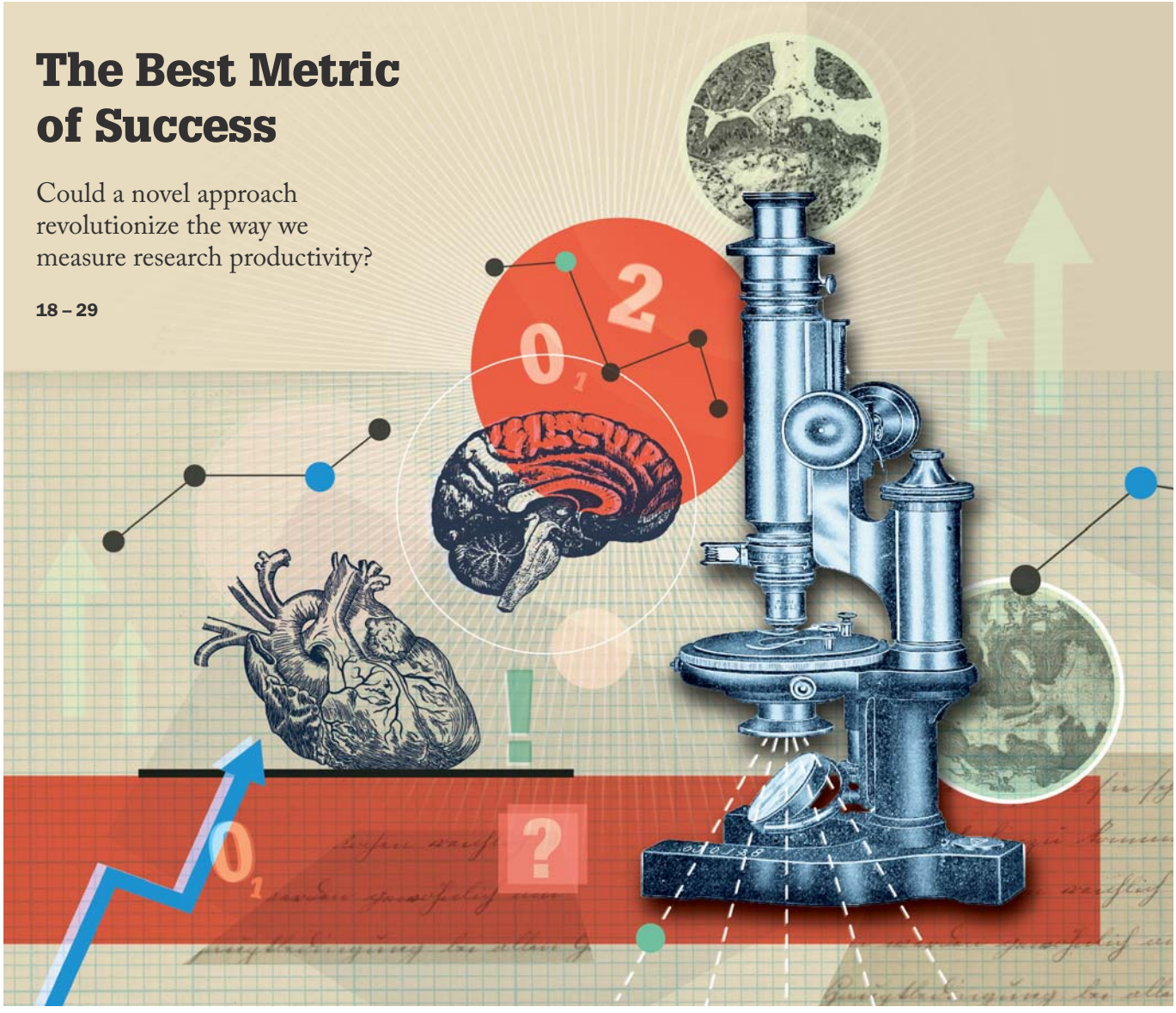

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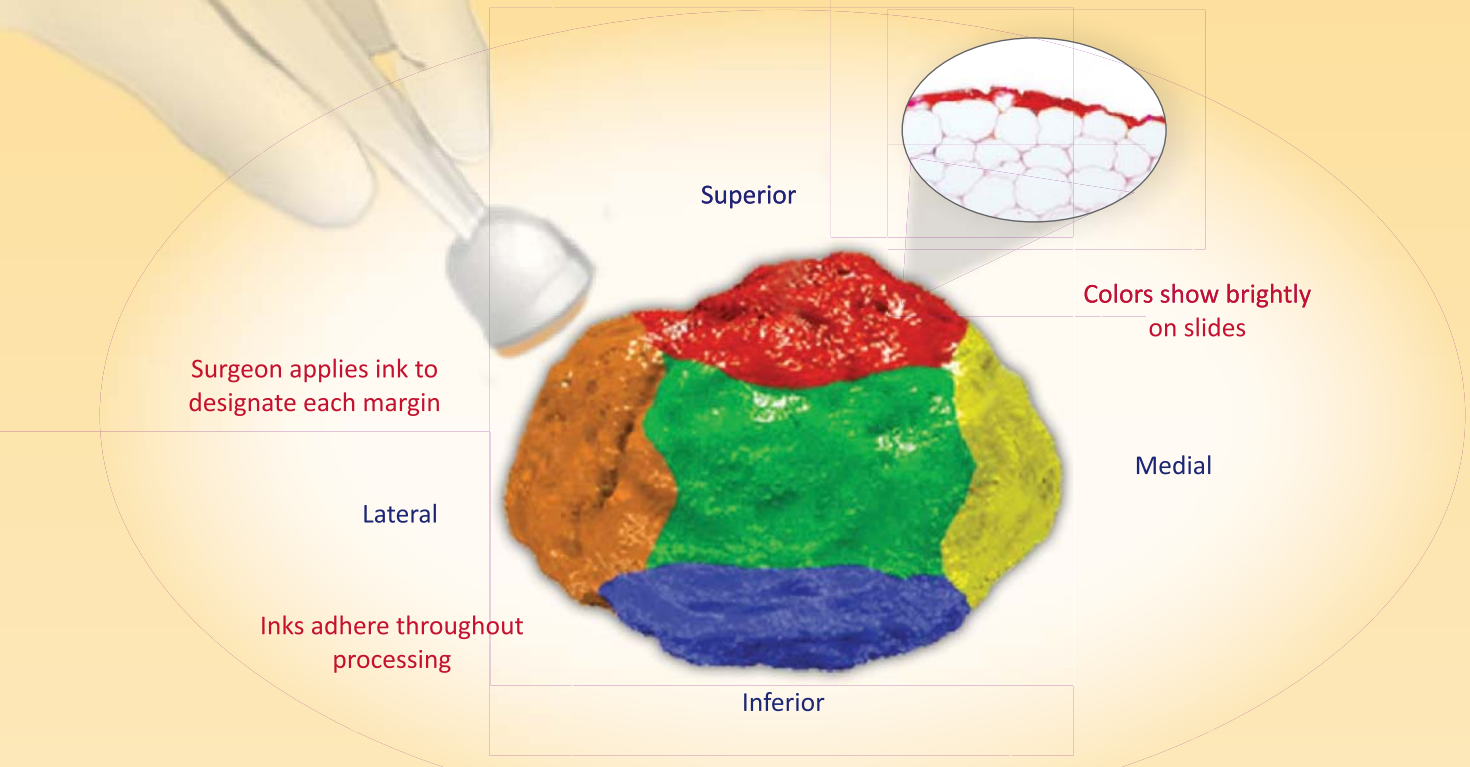

Pathology Receives Specimens With Margins Clearly Marked by the Surgeon

In cancer surgery, the single most important predictor of local recurrence is the tissue margins.[1] Research shows discordance rates as high as 52% in the identification of specimen margins.[2,3] Re-excision rates exceed 20% in breast surgery.[4] Use of Vector Surgical's MarginMarker can result in:

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- Improved cosmesis[6,8]

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VECTOR™ SURGICAL

USCAP 109th Annual Meeting | Los Angeles, CA | Feb. 29-Mar. 5
BC[3] (Breast Cancer Coordinated Care) | Washington, D.C. | Feb. 27-29
SSO 2020 - International Conference on Surgical Cancer Care | Boston, MA | Mar. 25-28

 References: (1) Dooley, W.C. and Parker, J. "Understanding the Mechanisms Creating False Positive Lumpectomy Margins." *American Journal of Surgery* 190 (2005): 606-608. (2) Britton, P.D.; Sonoda, L.I.; Yamamoto, A.K.; Koo, B.; Soh, E.; and Goud, A. "Breast Surgical Specimen Radiographs: How Reliable Are They?" *European Journal of Radiology* 79 (2011): 245-249. (3) Molina, M.A.; Snell, S.; Franceschi, D.; Jorda, M.; Gomez, C.; Moffat, F.L.; Powell, J.; and Avisar, E. "Breast Specimen Orientation." *Annals of Surgical Oncology* 16 (2009): 285-288. (4) McCahill, L.E.; Single, R.M.; Aiello Bowles, E.J.; Feigelson, H.S.; James, T.A.; Barney, T.; Engel, J.M.; and Onitilo, A.A. "Variability in Reexcision Following Breast Conservation Surgery." *Journal of the American Medical Association* 307.5 (2012): 467-475. (5) Singh, M.; Singh, G.; Hogan, K.T.; Atkins, K.A.; and Schroen, A.T. "The Effect of Intraoperative Specimen Inking on Lumpectomy Re-excision Rates." *World Journal of Surgical Oncology* 8.4 (2010). (6) Landercasper, J.; Attai, D.; Atisha, D.; Beitsch, P., Bosserman, L.; Boughey, J.; Carter, J.; Edge, S.; Feldman, S.; Froman, J.; Greenberg, C.; Kaufman, C.; Morrow, M.; Pockaj, B.; Silverstein, M.; Solin, L.; Staley, A.; Vicini, F.; Wilke, L.; Yang, W.; & Cody III, H. "Toolbox to Reduce Lumpectomy Reoperations and Improve Cosmetic Outcome in Breast Cancer Patients: The American Society of Breast Surgeons Consensus Conference." *Annals of Surgical Oncology* 22.10 (2015): 3174-3183. (7) Lovrics, P.J.; Cornacchi, S. D.; Farrokhyar, F.; Garnett, A.; Chen, V.; Franic, S.; and Simunovic, M. "The Relationship Between Surgical Factors and Margin Status After Breast-Conservation Surgery for Early Stage Breast Cancer." *The American Journal of Surgery* 197.6 (2009): 740-746. (8) Gibson, G. R.; Lesnikoski, B.A.; Yoo, J.; Mott, L.A.; Cady, B.; Barth, R.J. Jr. "A Comparison of Ink-Directed and Traditional Whole-Cavity Re-Excision for Breast Lumpectomy Specimens with Positive Margins." *Annals of Surgical Oncology* 8.9 (2001): 693-704. (9) Gage, I.; Schnitt, S.J.; Nixon, A.J.; Silver, B.; Recht, A.; Troyan, S.L.; Eberlein, T.; Love, S.M.; Gelman, R.; Harris, J.R.; and Connolly, J.L. "Pathologic Margin Involvement and the Risk of Recurrence in Patients Treated with Breast-Conserving Therapy." *Cancer* 78.9 (1996): 1921-1928. (10) Menes, T.S.; Tartter, P.I.; Bleiweiss, I.; Godbold, J.H.; Estabrook, A.; and Smith, S.R. "The Consequence of Multiple Re-excisions to Obtain Clear Lumpectomy Margins in Breast Cancer Patients." *Annals of Surgical Oncology* 12.11 (2005): 881-885.

Five Years and Counting

How has laboratory medicine changed since we first appeared on the scene?

Welcome to another year of The Pathologist! Some of you may know that we recently celebrated the five-year anniversary of our publication and, with that in mind, I've been browsing through previous issues of The Pathologist to find out what the hot topics were in the good ol' days.

I was not at all surprised to recall that our first-ever issue featured digital pathology. A quote from the article: "Uptake of the technology is growing, but only slowly." From where I stand, at the start of 2020, the digital transition is now anything but slow. Laboratories around the world are opting for fully digital workflows; some have already implemented them, whereas others plan to do so this year. Even areas with limited resources are beginning to place their trust in digital pathology as a way to expand the scope of their abilities. Where will the technology go next? No one knows for sure – but artificial intelligence appears to be a smart bet.

Many of you will remember our cover feature from December 2014, and its (almost famous) headline – "The Last Respite of the Socially Inept?" – which directly quoted one doctor's scathing opinion of pathology. In the article, students, trainees, and pathologists tackled common stereotypes (not to mention some less common ones. Where did survey respondents get the idea that pathologists like to collect roadkill and pigeon claws?!). Five years on, has anything changed? Students still report negative reactions to their interest in pathology; many regions still report staffing shortages and hiring difficulties; members of the public (and sometimes even other doctors) are often unaware of the laboratory's important role in their health.

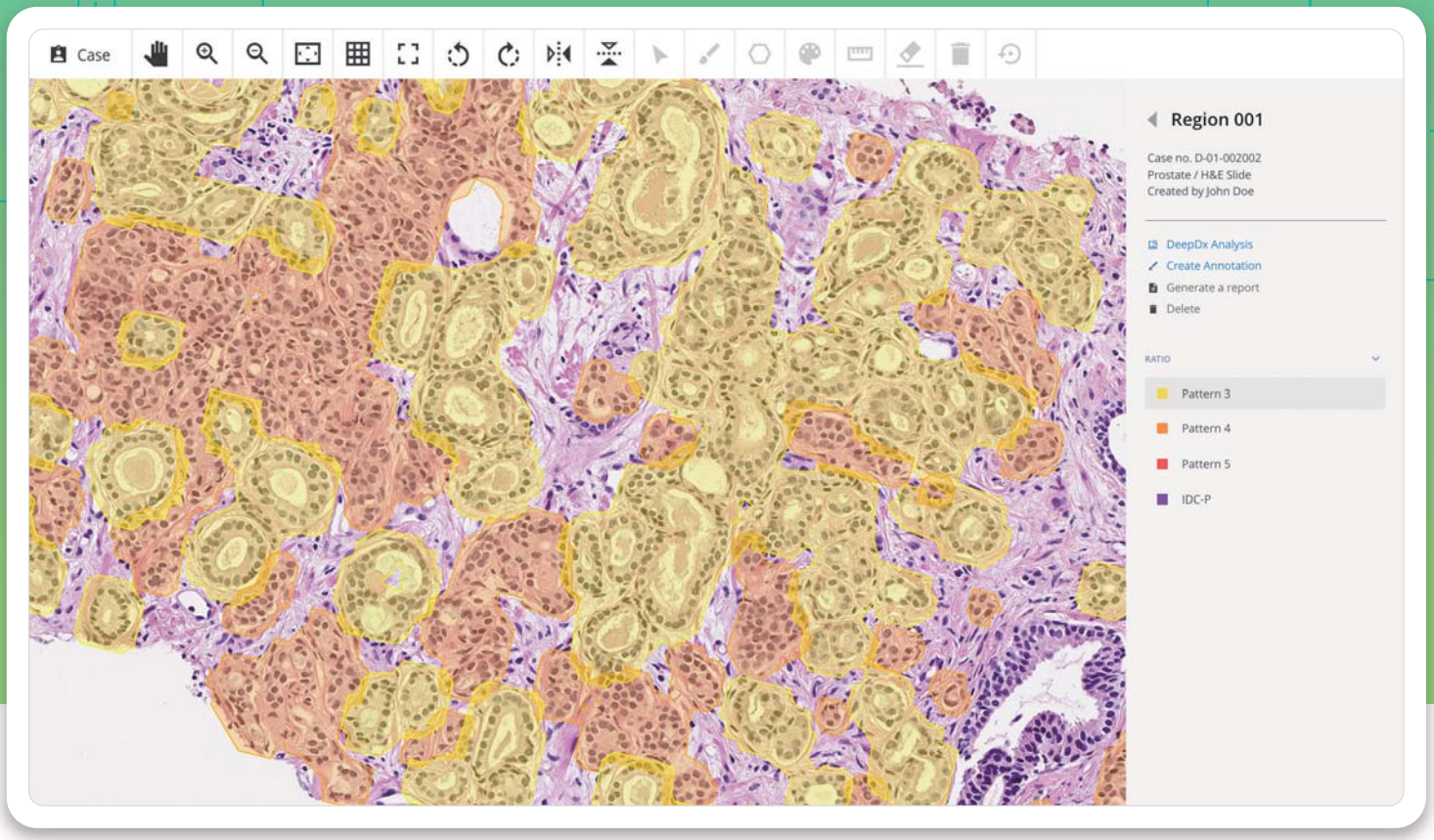
Do you remember what the landscape of pathology looked like five years ago – or even 10 or 20? How has your career progressed over those years? What has changed and what has stayed the same? If you'd like to share your views with us, please feel free to email edit@thepathologist.com (or drop us a line on social media – another phenomenon that has seen huge growth in recent years). We'd love to hear from you!

Michael Schubert
Editor

Contents

We welcome you to visit our booth 728 at USCAP 2020 for more information.

DeepDx-Prostate, What's the Gleason score?



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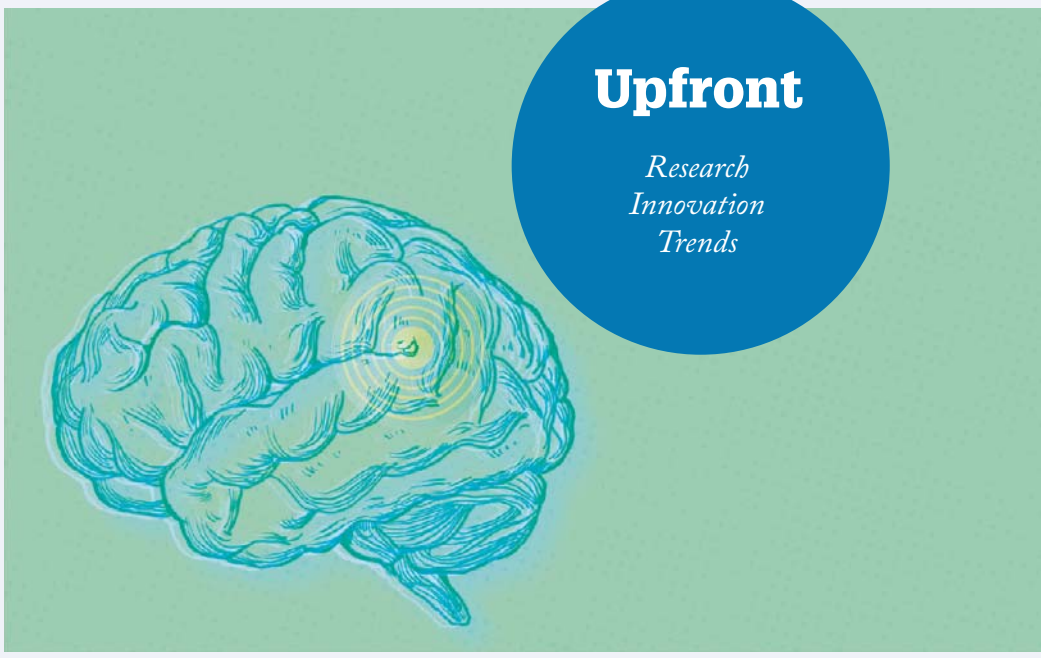


Upfront

Research
Innovation
Trends

Predicting Prognosis in Glioblastoma

The link between cfDNA concentration and progression-free survival for GBM patients

Glioblastoma multiforme (GBM) is the most common primary brain tumor in adults – and the deadliest. Only five to 10 percent of patients survive longer than five years. Predicting prognosis can be particularly difficult because surgical procedures are complicated and invasive, a challenge exacerbated by the tumor's heterogeneity. But now, a team from the Abramson Cancer Center of the University of Pennsylvania have found that patients with a higher concentration of circulating free DNA (cfDNA) have shorter progression-free survival. Senior author Erica Carpenter believes this underlines the potential utility of liquid biopsy for monitoring brain tumors.

"The assumption in the field is that cfDNA in the peripheral blood is unlikely to be reflective of the tumor microenvironment, which is largely protected by the blood-brain barrier," she explains. "That's why we were surprised to find a significant association between pre-therapy plasma cfDNA concentration and clinical outcome." In a study of 42 patients with newly diagnosed GBM, 28 had a lower cfDNA concentration than the average of the group – and those patients had a median progression-free survival time of 9.5 months. That's almost double the median 4.9 month progression-free survival time of the 14 patients whose cfDNA concentration was above the group average (1).

The team also discovered genetic mutations in over half of the liquid biopsies – but there was no overlap with the genetic information from solid tissue biopsies. "The mutations detected in plasma, but not tissue, could be an indication of the spatial molecular heterogeneity of the tumor tissue. In other words, the mutational profile of the tumor differs depending on the location of the biopsy tissue," says Carpenter. This signals a bright future for liquid biopsy in GBM diagnosis. "The combination of liquid biopsy with DNA analysis of the tissue biopsy could improve sensitivity when detecting mutations. A more comprehensive view of the tumor's molecular profile will enable us to select more effective treatment combinations." The next step? A larger follow-up study to confirm the findings and hopefully kickstart more personalized treatment for these devastating tumors.

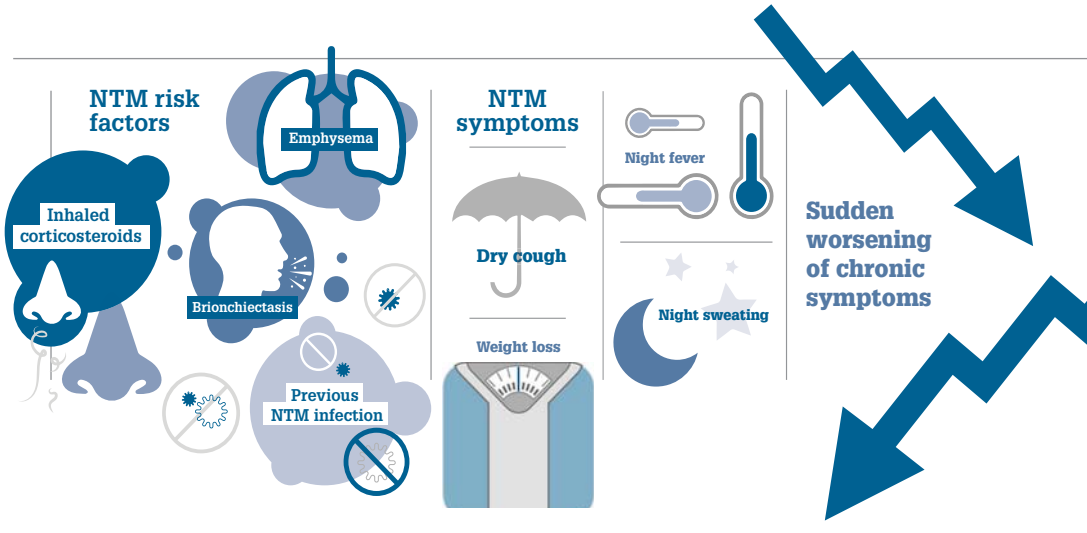
Reference

1. *SJ Badley et al., Clin Cancer Res, [Epub ahead of print] (2019). PMID: 31666247.*

INFOGRAPHIC

Non-Tuberculous Mycobacteria

An under-acknowledged lung infection by the numbers.



A QUESTION OF QUALITY

How can we deliver quality assurance for point-of-care tests across the board?

Point-of-care-testing (POCT) promises a simple, accessible, cost-effective alternative to laboratory testing. But many resource-limited areas lack guidelines for quality assurance – so how can we ensure that POCT everywhere conforms to the same standards? This International Pathology Day, we posed this question to a panel of experts…

Charles van Heyningen, Former International Advisor at the Royal College of Pathologists

POCTs need to be as user-friendly as possible, but complex enough to address quality issues. New technologies often have internal quality control systems built in, and even some of the simple bedside or self-monitoring tests allow you to run quality checks more readily than ever, removing the need for complex laboratory backup systems.

Tahir Pillay, Professor & Chair in the Department of Chemical Pathology and Head of Pathology at the University of Pretoria

Cost and complexity are the main barriers to accessibility. Many UK hospitals have established POCT committees and coordinators; laboratories act as a central point for deployment and quality assurance, with a fixed schedule of auditing and incident recording to maintain quality. Low-resource countries have not yet reached this level of best practice.

Lieutenant Emma Hutley, Defence Medical Services, Joint Hospital Group South East

It's important to determine exactly what you're asking of the test – how is it going to change the management of the patient or outbreak? How it will inform patient flow and management? Many POCTs use the ASSURED criteria: availability, sensitivity, specificity, user-friendliness, robust, reliable, equipment-free, and deliverable.

Wale Atoyebi, Consultant Hematologist at Oxford University Hospitals NHS Foundation Trust

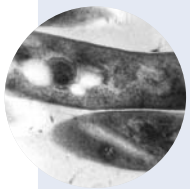
Resource-limited countries don't have the infrastructure to undertake processes that are established in developed countries. The main concern is the audit trail and who is managing the process. The simplicity of POCTs can sometimes mean that people grow lax in their procedures – so we must be vigilant.

Watch the entire panel discussion on demand at tp.txp.to/Webinar/POCT

TB Triage

A new triage test for active tuberculosis answers the WHO's call for blood-based diagnostics

Over 10 million people have active tuberculosis (ATB) globally – but laboratory testing is expensive and sputum-based testing is slow and inaccurate. After the World Health Organization (WHO) called for a greater focus on blood-based tests, a collaborative team have developed an ultrasensitive, multiplexed triage test that analyzes the levels of four proteins in the blood. With 86 percent sensitivity and 69 percent specificity, the test could become a point-of-care diagnostic that costs just US$2 and provides results in 30 minutes.

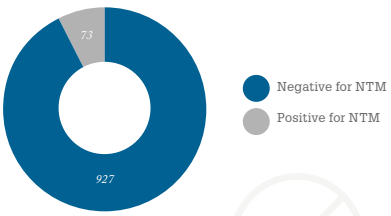


David Walt of the Wyss Institute hopes the test will lower the barrier to care in low-resource settings. "Once we improve the sensitivity and specificity to meet WHO standards, we will deploy the test in clinics and hospitals in the developing world before introducing it to more rural settings," he explains. The new test can detect different strains of ATB and its results are not affected by HIV infection status.

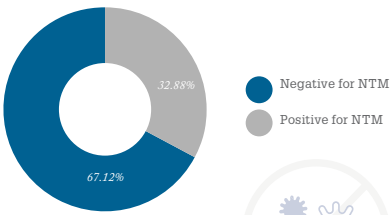
Reference

1. *R Ahmad et al., Sci Transl Med, 11, 515 (2019). PMID: 31645455.*

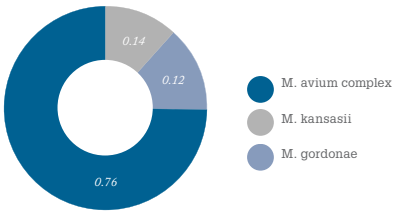
1,000 patients
tested for NTM



Cultures from
NTM patients



Most common
NTM species

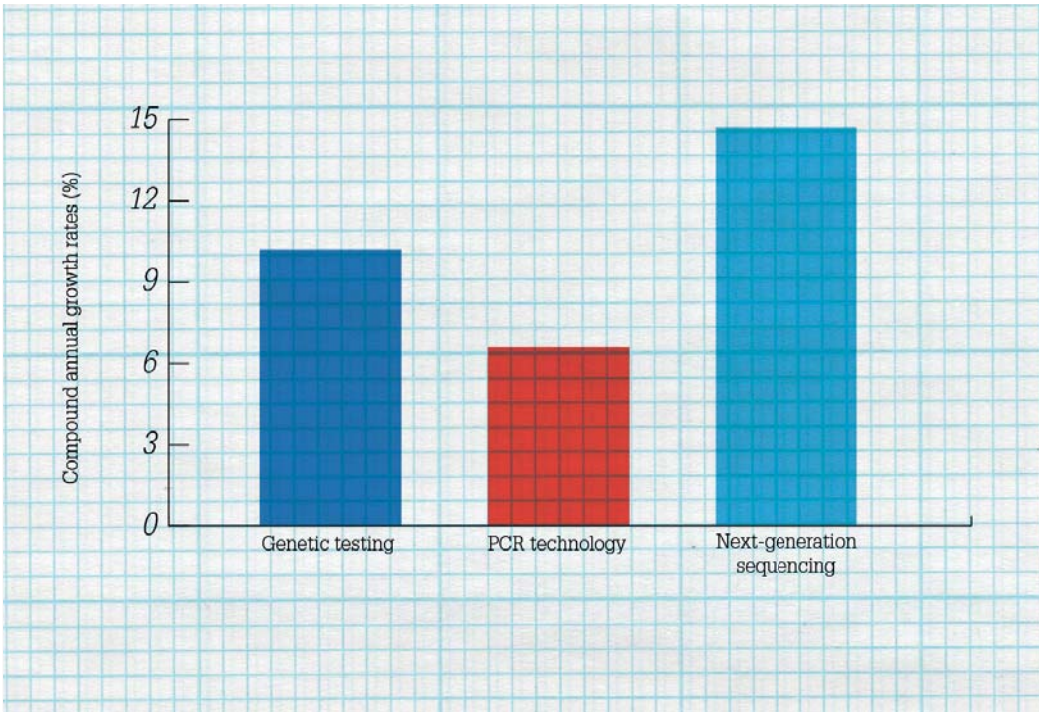


Molecular Diagnostics on the Rise

Genetic disorders and infectious diseases will bolster global molecular diagnostics over the next five years

What's the fastest-growing field in the laboratory medicine industry? If you ask five different people, you may well get five different answers – but one thing is for sure: there is an escalating demand for competent and accurate diagnostic methods. And for those who desire the most precise and personalized medicine possible, molecular diagnostics are key. velit diam vitae.

The expansion of the molecular pathology industry won't be solely down to patient demand, though. Market researchers have also seen widespread product acceptance for applications including infection identification, patient stratification, drug regimen selection and therapeutic monitoring, and more. Because any error in diagnosis or treatment can have severe repercussions, pathologists and laboratory medicine professionals need accurate, safe, and dependable diagnostic tools – and this is where molecular diagnostics has the opportunity to shine.



Molecular diagnostics in 2024

Genetic disorders and infectious diseases must be diagnosed early and accurately, not only to provide efficient treatment, but also because late detection can give rise to further complications. In terms of the reliability and rapid response time required for early intervention, traditional diagnostic approaches fall significantly short. As a result, the molecular diagnostics market is expecting significant growth (1).

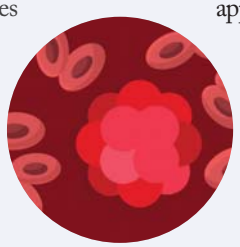
Reference

1. *S Ugalmugale (2018). Available at: https://bit.ly/2Dgtq71.*

Cancer Trap

Synthetic cancer traps could be the future of early diagnosis – but how do they work?

A new synthetic scaffold could help with the early detection of recurrence and metastasis in cancer patients. The device – readily accessible underneath the skin – functions as a metastatic niche to attract circulating cancer cells. "Analysis of collected cells indicates unique cancer cell properties at metastatic sites relative to the primary tumor, or cells in circulation," says Lonnie Shea, Professor of Bioengineering at the University of Michigan and senior author of the paper (1).

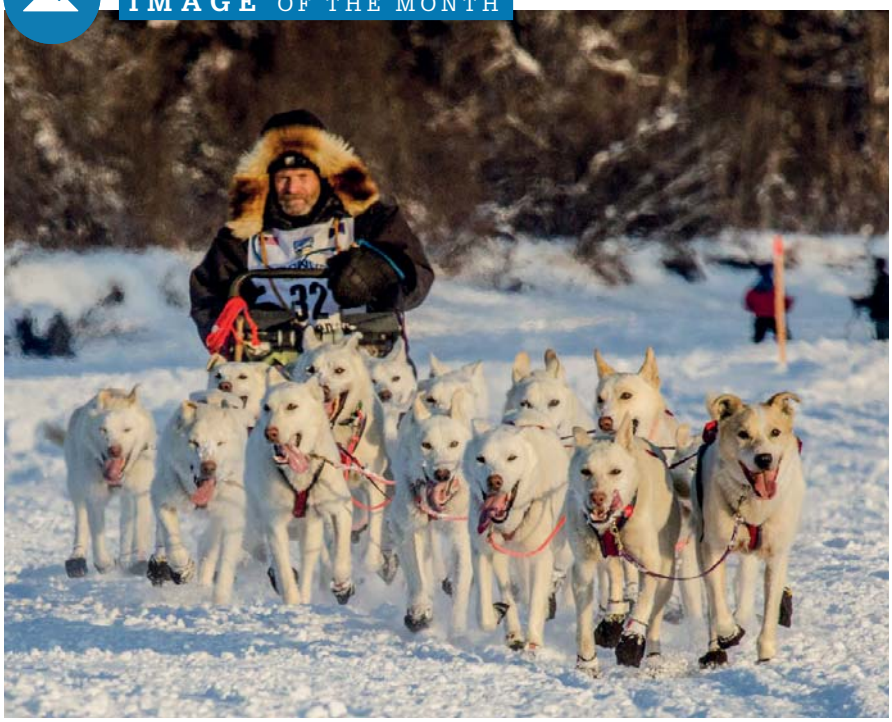


Biopsies of the scaffolds in mouse models revealed 635 cancer cell genes, 10 of which helped to identify whether or not the cancer had begun to spread. "Liquid biopsy has shown promise for monitoring disease, but our approach is distinct because it captures tumor cells that have left the vasculature," explains Shea. The cancer traps are attractive when compared with invasive biopsies – and Shea sees a future in which sensors continuously monitor the implant in high-risk patients.

Reference

1. *RS Oakes et al., Cancer Res, [Epub ahead of print] (2019). PMID: 31662327.*

IMAGE OF THE MONTH



The Master Musher

Jim Lanier enjoyed a successful 33-year career in pathology – but he now spends his time sled dog racing across Alaska! Here he is leading his pack up the Yentna River in the Iditarod 2018.

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

QUOTE of the month

"I think people sometimes want permission to say there's no answer. Sometimes, when you write that a case cannot be determined as a definitive entity (or even benign versus malignant), it makes them feel better. They can say, 'We're all stuck and we don't know what it is.' But our clinical colleagues don't always understand that; there is always a clinician or a surgeon who thinks we can just send the case to somebody who does know. You have to teach clinicians that there isn't an answer for everything."

Christopher D.M. Fletcher

Mutation Detective

A new tool could predict whether cancer patients will benefit from immunotherapy

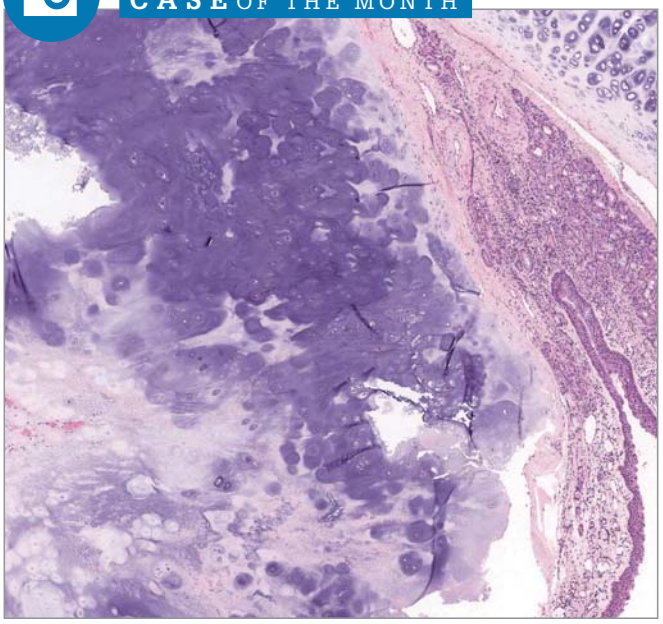
Nonsense mutations in the DNA disrupt protein synthesis and can lead to hereditary diseases and cancer. The human immune system generally recognizes and remove these nonsense mutations in a process called nonsense-mediated mRNA decay (NMD) – but new research shows that NMD can actually result in greater disease severity, especially in cancer patients, where NMD may prevent tumor cells from being exposed to the immune system (1).

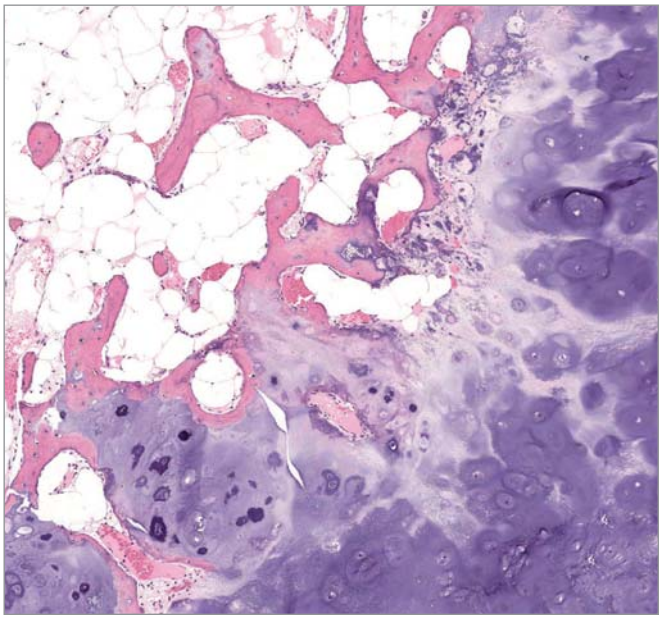
Using a machine learning approach, one research team created a tool called NMDetective that describes every possible nonsense mutation – and then used it to analyze thousands of genetic variants leading to hereditary diseases. "We think that pharmacological NMD inhibition could potentially treat the symptoms of various genetic diseases," explains Fran Supek, senior author of the research. By analyzing a tumor's mutations, the NMDetective algorithm can provide insight into how a patient is likely to respond to immunotherapy, enabling more personalized treatment.

Reference

1. *RR Lindeboom et al., Nat Genet, 51, 1645 (2019). PMID: 31659324.*

CASE OF THE MONTH





A 71-year-old female presented with an incidental osseous nasal septum mass. The mass was completely excised via endoscopic septectomy.

What is the diagnosis?

a) Chondroblastic osteosarcoma
b) Osteochondroma
c) Low-grade chondrosarcoma
d) Enchondroma

Answer to last issue's Case of the Month…

d) Sclerosing polycystic adenosis

Sclerosing polycystic adenosis (SPA) is a rare, benign lesion that typically involves the parotid gland and resembles sclerosing adenosis/fibrocystic change of the breast (1,2). The lesion is well circumscribed with a thick, fibrous capsule. There is an epithelial proliferation that contains a variety of structures including nests, ducts, acini, and cystic structures surrounded by fibrosis (1–3). The cytoplasm has characteristic PAS-positive eosinophilic granules (1,3). Differential diagnosis includes pleomorphic adenoma (PA), salivary duct carcinoma, and chronic sclerosing sialadenitis (3,4). In contrast to SPA, PA typically demonstrates a chondromyxoid matrix and lacks prominent cytoplasmic eosinophilic granules (4). Salivary duct carcinoma demonstrates cellular pleomorphism, mitoses, comedonecrosis, and an infiltrative growth pattern not seen in SPA (4). Chronic sclerosing sialadenitis does have a prominent fibrotic component, but lacks a cystic component and typically involves the submandibular gland with a prominent inflammatory component (3).

Submitted by Emily R. McMullen and Jonathan B. McHugh, University of Michigan, Ann Arbor, USA.

References

1. *F Petersson, Head Neck Pathol, 7, S97 (2013). PMID: 23821217.*
2. *DR Gnepp, Head Neck Pathol, 8, 42 (2014). PMID: 24595421.*
3. *CA Eliot et al., Head Neck Pathol, 6, 247 (2012). PMID: 22183766.*
4. *S Manojlović et al., Pathol Res Pract, 210, 342 (2014). PMID: 24636837.*

To register your guess, please go to http://tp.txp.to/0120/case-of-the-month
We will reveal the answer in next month's issue!

Case of the Month is curated by Anamarija M. Perry, University of Michigan, USA.

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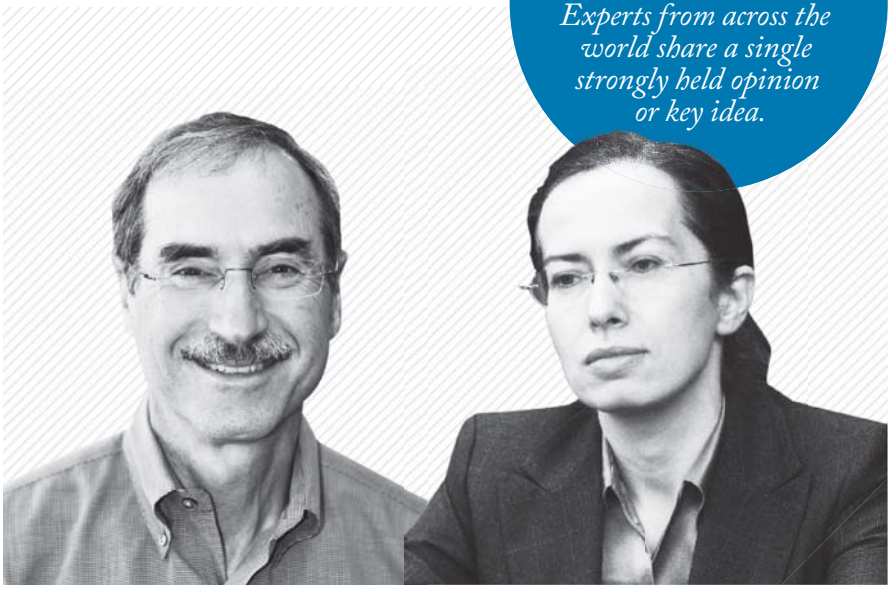
In My View

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

Which Assay for Atezolizumab?

A response to "Welcome To Our Kitchen," by David Rimm

Emina Torlakovic, Division Head of Hematopathology in the Department of Pathology, University of Saskatchewan and Saskatchewan Health Authority, Saskatoon, Saskatchewan, Canada, and Allen M. Gown, Founder and Senior Pathologist at PhenoPath Laboratories, Seattle, Washington, USA



We read, with great interest, David Rimm's comments regarding the FDA-approved Roche Ventana PD-L1 (SP142-based) assay, which is intended to determine triple-negative breast cancer patients' eligibility for treatment with the immune checkpoint inhibitor drug atezolizumab. Rimm makes very serious allegations regarding this immunohistochemistry (IHC) assay and serious allegations regarding IHC assays in general. We would like to share our views on relevant general concepts regarding IHC methodology and quality assurance, as well our response to some specific comments made regarding the FDA-approved Roche Ventana PD-L1 (SP142) assay.

Rimm states, "It's the (IHC) protocol – not the recipe – that leads to a high level of reproducibility." Some IHC protocols may be more robust and easier to reproduce; however, it is not the protocol alone that leads to reproducibility. The other important component is the readout, which is mostly done by pathologists with or without image analysis (1). Such readouts may not be highly reproducible – an issue that applies not only to IHC scoring, but also all areas of pathology practice. Reproducibility depends on the complexity of the task and the nature of the readout's subject. Some readouts require more training and experience, whereas others are intuitive and simple. Nonetheless, more training and experience will lead to more reproducible results.

The reproducibility of the IHC assay also depends upon how tightly controlled the other components are. For many IHC assays, preanalytical conditions must be monitored and controlled to achieve reproducibility. Quality assurance measures for instruments, reagents, and operator training could also have a major impact. Therefore, the multiparametric nature of IHC assays and each parameter's impact on total assay reproducibility cannot be forgotten. The "total test approach" Clive Taylor introduced to IHC methodology definitely applies to its reproducibility and is even more relevant today, in the era of precision medicine, than before (2).

Another statement with which we take issue is that the developers of the FDA-approved companion diagnostic assays have "relegated pathologists to the role of short-order cook." Most pathologists are not directly involved in IHC assay development and do not participate in the validation of IHC laboratory-derived tests (LDTs). Even medical directors of IHC laboratories may not be applying sound principles of validation for any given use of the assay. Those who do understand that validation for predictive assays may be complex and costly, and that there is a growing need to ensure that predictive assays are properly clinically validated (3–5). When using an FDA-approved kit, the IHC laboratory must only verify the assay, which is much easier. One way or the other, the pathologists receive IHC-stained slides to perform a readout and interpretation – their usual starting point. Pathologists are rarely involved with the "cooking" phase of IHC assays. Indeed, less cooking is generally better for both laboratories and pathologists.

We also disagree with Rimm's assertion that IHC laboratories "create our own tests […] rather than use a kit, so that we know exactly what is in each component of the assay." LDTs are employed for numerous reasons, usually because there is no other choice or because the FDA-approved assay kits are perceived as too expensive. From the standpoint of laboratory accuracy and reproducibility, the published data (for instance, from the NordiQC QA program) clearly demonstrate the superior performance of FDA-approved assay kits (6). Furthermore, LDT protocols can vary widely between laboratories, yielding poor inter-laboratory reproducibility. This is in direct contrast to FDA-approved

assays, which are far more reproducible from laboratory to laboratory. Importantly, pathologists do not necessarily know what is in an LDT assay – even one that is run in their laboratory – given the proprietary nature of certain reagents and the closed nature of many auto-stainers.

The tissue tools laboratories use to determine the performance characteristics of an LDT IHC assay can vary widely in their ability to provide information on analytical sensitivity or reproducibility. FDA requirements for industry often far exceed those for LDTs when it comes to providing evidence about performance. For most assays, pathology laboratories can perform validation studies in which "gold standard" positive and negative controls are employed, usually looking for the assay's ability to detect expression of a cell-specific marker. We have not yet achieved standardization of such controls – a requirement recently emphasized by an ad hoc international expert group (7). In biomarkers such as PD-L1, which predict response to a specific therapy in a specific subset of patients treated with a specific drug, laboratories cannot validate the assays – only verify them.

And why is Rimm so exercised about this "limitation" of the Roche Ventana PD-L1 (SP142) assay? The situation is identical with the FDA approved 28-8, 22C3, and SP263-based PD-L1 assays from various vendors, all using specific instruments. Only clinical trial studies can serve as true gold standards for the clinical validation of predictive biomarkers. We have no better benchmark than clinical outcomes, even when the assay is not 100 percent predictive of that outcome. The next best thing to verification of a clinically qualified biomarker is having pathologists use this exact clinically validated biomarker as a "designated gold standard" (or reference standard) for a specific purpose when setting up an LDT IHC assay with the same purpose – a practice referred to as "diagnostic validation" or "indirect clinical validation" (5). It is therefore critical to understand that it is not possible to design a "better LDT" – that is, an LDT that would be better for its specific purpose than the one approved by the FDA (based on the clinical trial evidence) – without the clinical trial. Furthermore, it is difficult (if not impossible) to harmonize LDT performance to the level that some FDA kits have achieved.

"The 'total test approach' Clive Taylor introduced to IHC methodology definitely applies to its reproducibility and is even more relevant today, in the era of precision medicine, than before."

We would also like to comment on the specific allegations regarding the Roche Ventana PD-L1 SP142 Assay. The first is that the readout of the latter has been shown to be non-reproducible "… between the 13 or 25 pathologists participating in statistically powered, prospective studies done in the real world." Readout agreement between pathologists is poor for many scoring systems that are still clinically applied (such as Gleason grading), but it improves with education and training (8). We agree that PD-L1 testing has introduced another level of complexity in IHC readout for pathologists. Poor readout results are a real obstacle only if they continue to be poor after proper education and training. There is no evidence of this in the published literature. The question Rimm asks – "What will happen when thousands of pathologists around the world are expected to read this assay?" – is a good one. We do need more education and training – and we believe pathologists accept that continuing medical education is important. As we are well aware, specialty certification does not ensure proficiency in any skill or task, including reading the IHC-stained slides of predictive assays.

The second allegation is that the assay is less sensitive than another that also detects PD-L1. It may be true that tumor cells are stained to a lesser degree with the SP142-based IHC assay, but the opposite is true of immune cells, which appear to be "overstained"; but it seems the intent of the assay was lower analytical sensitivity for tumor cells and higher analytical sensitivity for inflammatory cells – a goal that was achieved. Most importantly, this is not a universal PD-L1 IHC assay. The purpose of the assay should always be considered when its performance is judged. Any use of the assay beyond the purpose for which it was qualified should be considered "off-label" and should be validated before use in clinical practice.

Thus, the most significant mistake in Rimm's analysis is his confusion between analytic sensitivity and specificity and diagnostic sensitivity and specificity. It is not possible to make direct assumptions of one from the other. In the case of PD-L1 detection using the Roche Ventana PD-L1 (SP142) assay, Rimm is correct that this antibody has decreased sensitivity when assessing PD-L1 on tumor cells in tissue sections, but not on inflammatory cells. However, the assay's analytic sensitivity for PD-L1 detection on tumor cells is not relevant to the assay's diagnostic sensitivity for most purposes for which the kit was approved. The assay's diagnostic power appears high, and PD-L1 expression in

the immune cell population of triple-negative breast cancers remains the best predictor of clinical response to atezolizumab combined with nab-paclitaxel (9).

The Roche Ventana PD-L1 (SP142) assay has been designed to highlight and favor signaling on immune cells and, to these two observers, it does a great job. We have been trained to do readout for this SP142 IHC assay in triple-negative breast cancer (TNBC), and we find it both simple and highly reproducible, paralleling the assessment of this assay in a study (not cited by Rimm) involving six pathologists and three sites (10). Indeed, in our opinion, the readout with the Roche Ventana PD-L1 (SP142) assay is far easier and more reproducible than any of the other PD-L1 assays. Rimm's motivation to harmonize this assay (designed to highlight PD-L1-positive immune cells in TNBC) with one that is designed to identify PD-L1-positive lung cancer tumor cells flies in the face of logic and good laboratory practices. These other PD-L1 assays have not been shown in any clinical trials to be predictive of response to immunotherapy in TNBC, and it would be irresponsible to replace the Roche Ventana PD-L1 (SP142) assay with one of the other FDA-approved PD-L1 kits or with an ad hoc LDT. Although an LDT that has not been clinically validated might show excellent signal-to-noise ratio and produce aesthetically excellent results, it may nevertheless fail at its main purpose – that is, to accurately predict a patient's response to atezolizumab.

This article has been abbreviated to fit the available space. Please see the full article and references at: http://tp.txp.to/atezolizumab.

Come Together

Why is interdisciplinary teamwork important in patient care?

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

It feels like a long time ago that I graduated from a prestigious orthopedic pathology fellowship at New York's Hospital for Joint Diseases (now NYU Langone Orthopedic Hospital). I had a great time working with my mentor, German Steiner, and occasionally attending the old New York Bone Club with internationally recognized orthopedic pathologists, including Peter Bullough, Howard Dorfman, and Michael Klein. It was a privilege to work with these old-school gentlemen – but not just because we became friends; the Bone Club is also the place where I learned how important it is to work as a team with my clinical colleagues.

I remember Samuel Kenan, an orthopedic oncology surgeon who did an orthopedic pathology fellowship with German Steiner. He regularly came to the frozen room during surgery to discuss the case with pathologists. I found out that was a great way to get all the clinical information – we could ask him any questions we had and he could do the same to us. It definitely helped us to come up with the best possible answers for each patient. From that time on, wherever I went, I tried to form good relationships with my clinical colleagues – and, over time, it worked wonders.

These relationships can't be formed overnight, though. Each time I moved to a new institution, I had to start building an orthopedic pathology service from scratch. Both times, though – at the University of California Davis and at Loyola University Chicago – I found a great team of knowledgeable, intelligent, and friendly colleagues in musculoskeletal radiology and orthopedic oncology surgery. I follow "Jaffe's triangle," a concept first published by Henry Jaffe in 1958, in which the orthopedic surgeon, the radiologist, and the pathologist all share their points of view on a bone lesion to form a rational diagnosis.

This approach is especially important in bone sarcoma teamwork. In most cases, the pathology team receives only small fragments of bone – a challenging diagnostic puzzle unless you can correlate the samples with radiological and clinical findings. For example, differentiation between enchondroma and low-grade chondrosarcoma is not always possible on a histological level. However, if you combine histology with tumor size and local behavior, you can come up with a more definitive diagnosis. If, for instance, I see that the tumor involves bone cortex, my diagnosis will favor low-grade chondrosarcoma over enchondroma – a distinction I would not be able to make without radiological and clinical correlation. It's cases like this that showcase the importance of an interdisciplinary, collegial approach to diagnosis.

By building the trust and respect of your clinical colleagues, you create a foundation that will serve you well in your clinical work. Interdisciplinary teamwork not only helps you in daily practice, but also has a positive impact on patient care. By combining all the information in a timely, friendly manner, you and your team will provide faster and more accurate answers for your patients. After years of working in this way, I see only positives to an interdisciplinary approach to patient care – and I've built successful orthopedic pathology practices and made many friends along the way.

The Laboratory: Critical to Sports

How pathology and laboratory medicine support elite athletes

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

Elite athletes from all over the globe will travel to Tokyo to compete in the 2020 Summer Olympics. Try to imagine more than 10,000 athletes, all of whom have been training most of their lives for that very moment. They've spent hours practicing and perfecting their skills. They've sacrificed time with family and friends to pursue their goals. They've dedicated their bodies and minds to their talent. And now, they're almost there – at the apex of sporting events. Those weeks in July and August represent the culmination of their sport, and each participant is eager to take home the gold – to be deemed the world's best.

But they couldn't have gotten there without the medical laboratory.

Just as it is a cornerstone of healthcare, the laboratory is a cornerstone of fair athletic competition. In the late 1960s, when drug-testing Olympic athletes became standard, the International Olympic Committee mandated that host cities have medical laboratories that could accurately analyze and detect any trace of performance-enhancing drugs. Now, the World Anti-Doping Agency (WADA) leads the charge in ensuring that athletes are not using such drugs to improve their performance. Through these years, the laboratory has provided necessary and accurate testing.

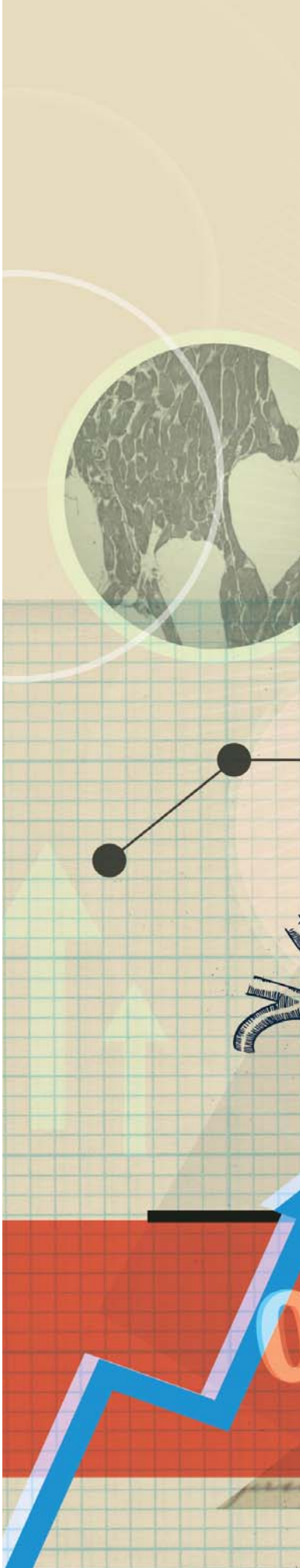
Since the early 2000s, the prevalence of doping scandals at the Olympics has risen, and we've seen multiple athletes caught up in them. As recently as this past December, WADA banned Russia from participating in the Olympic Games altogether for the next four years because of accusations that their athletes are using illegal performance drugs. Scandals like these take a toll on the public's trust – trust that the athletes they cheer on are upstanding in their sport. Trust that all those involved have the integrity of the sport foremost in their minds. Trust that the international sporting community is keeping a sharp eye on regulations around performance-enhancing substances and on the athletes or coaches or trainers who may attempt to bend or break the rules.

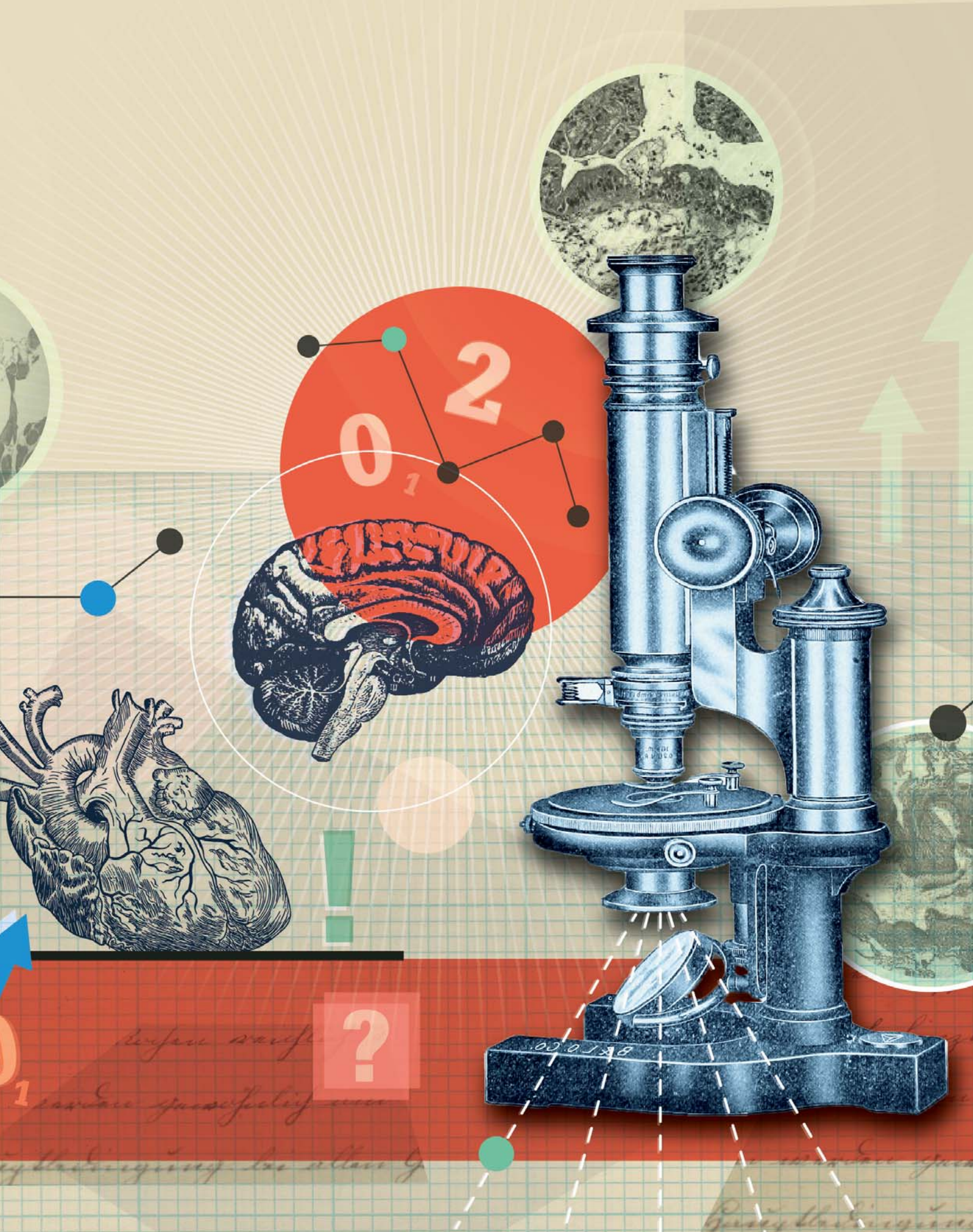
But what the public has always trusted – and should always trust – is the fact that the medical laboratory is there to support these athletes and keep the integrity of the sport intact. As new drugs come onto the scene, the laboratory continually upgrades its technology and practices so that no athlete will have an unfair advantage over others. The laboratory is the first line of defense in creating an even playing field.

So, this summer, when you tune in to watch your preferred Olympic sport, know that, as pathologists and laboratory scientists, your profession played an important part in these Olympic games. Your profession will have a hand in these athletes' successes. It is our community that safeguards these Olympic Games and other international sporting events from the unfair edge stemming from banned substances, providing the foundation for good sportsmanship worldwide.

THE BEST METRIC OF SUCCESS

Contributions to academia are often evaluated by grant dollars alone – but this oversimplifies a complex system. Could USCAP's Annual Meeting abstracts provide the conditions for a next-generation assessment of research productivity that uses freely available data?

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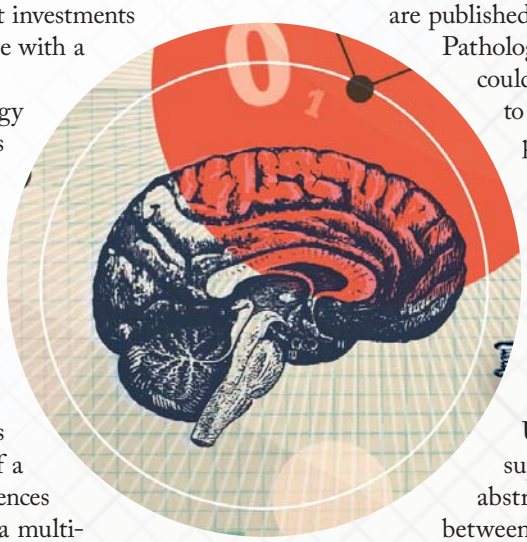
Funding for clinical research has fallen over the past decade – to the point where the National Institutes for Health now provides more money for basic and translational research than it does for clinical research (1). There's no getting away from this new fiscal reality, which is why it is now best to encourage research that is inexpensive and high impact, maximizing the returns from finite resources. But, to achieve this, it is first crucial to establish a thorough and effective way to measure research output. All too often, the productivity of a researcher is assessed by the amount of grant money they receive; however, this metric alone is restrictive – and often inappropriate.

Evaluating research based solely on grant money received conflates institutional funding – an important factor in its own right – with researcher funding, a metric that is only loosely tied to academic impact. The number of publications combined with research productivity per grant dollar might be a more useful metric of research output than grant dollars alone. Just think about the process of evaluating the efficacy of a particular medical treatment. A million-dollar treatment is not necessarily better than an alternative that costs US$100 – or one that costs nothing. Treatment efficacy is not directly proportional to its cost. Nor is the cost of scientific research necessarily proportional to its impact. In terms of return on investment for the funders of clinical research, high-impact, low-cost investments are obviously more attractive than those with a low impact, but a high cost.

Clinical and basic research in pathology is no different. Academic contributions in some institutions are assessed by grant dollars alone simply for ease and because other measures are not readily available. Other common metrics include the number of publications and the h-index, a number proportional to the square root of the number of publications. One of the main issues with these approaches is that they inevitably treat all authors of a given publication as equals, despite differences in the value added by contributors to a multi-author publication.



A new alternative

What if there were a better way to measure academic productivity in pathology research? The United States and Canadian Academy of Pathology (USCAP) Annual Meeting is the largest global gathering of pathologists, attracting over 4,700 attendees from across the world during its 107th iteration in 2018 (2). The conference is also home to the largest number of on-site scientific abstract presentations in anatomic, clinical, and molecular diagnostic pathology. After the meeting, all presented abstracts are published in USCAP's official journal, Modern Pathology. We believe that USCAP abstracts could provide an alternative metric by which to gauge both an individual's impact on the pathology community and the strength of individual institutions.

To test and demonstrate the efficacy of using USCAP abstracts as a metric of research productivity, we undertook an in-depth systematic review to uncover the most prolific researchers and to paint a picture of current research trends in the field. Using data from Modern Pathology supplemental issues (4), we retrieved all abstracts from USCAP Annual Meetings between 2015 and 2018.

Our data-mining approach enabled us to extract each abstract's ID number, title, subspecialty, author(s), number of authors, author affiliation, and number of affiliations. After writing these abstract data – along with analysis codes – into a single tab-separated file, our extensive dataset was complete. The final product contained all of the details from 8,621 abstracts – out of a total 8,683 published between 2015 and 2018 – that could be parsed and extracted. Any parse

What makes using USCAP abstracts as a productivity metric attractive?

- abstracts are presented at – and published in – one place, so there is no need to develop a metric to compare different academic venues (journals, conferences, websites, and so on)
- abstracts are reviewed in a blinded fashion
- leading institutions are well-represented and there is a good deal of data for comparison to the world's best
- conference abstracts are an entry point for researchers
- USCAP abstracts are often the basis of manuscripts published in pathology journals (3)

Top Authors Overall						
Rank	Author	Total	Last Author	First Author	NFNLA	WCS
1	L. Jeffrey Medeiros	93	4	0	89	48.5
2	Jeffrey S. Ross	82	55	10	17	93.5
3	Jonathan Epstein	75	40	1	34	60
4	N. Volkan Adsay	74	42	1	31	60.5
5	Michelle Reid	67	12	9	46	62
6	Siraj Ali	63	2	4	57	42.5
7	Julia A. Elvin	59	2	7	50	48
8	Philip M. Stephens	59	4	0	55	31.5
9	Jason L. Hornick	57	14	0	43	35.5
10	Vikram Deshpande	56	31	1	24	46
11	Liang Cheng	52	17	3	32	42
12	Alyssa Krasinskas	51	7	0	44	29
13	Victor Reuter	50	9	0	41	29.5
14	Robert Soslow	48	11	2	35	34.5
15	Russell Broaddus	45	19	3	23	39.5
16	Adeboye O. Osunkoya	45	29	0	16	37
17	Cynthia Cohen	45	12	0	33	28.5
18	Mark Routbort	45	2	0	43	23.5
19	Brian Robinson	44	5	9	30	47
20	Andrew Bellizzi	44	32	6	6	53
21	Lynette Sholl	44	17	1	26	33
22	C. Blake Gilks	43	10	4	29	36.5
23	Britta Weigelt	43	11	2	30	32
24	Stefan Pambuccian	43	10	2	31	31.5
25	Esther Oliva	42	19	0	23	30.5
26	Sean R. Williamson	41	6	8	27	43.5
27	Bahar Memis	41	0	6	35	35.5
28	Samson W. Fine	41	3	1	37	24.5
29	Momin T. Siddiqui	41	19	0	22	30
30	Marc Ladany	41	8	0	33	24.5
31	Satish Tickoo	41	5	0	36	23
32	Brooke E. Howitt	40	13	7	20	44
33	Shimin Hu	40	18	0	22	29
34	Victor Prieto	40	7	0	33	23.5
35	Ming Zhou	39	14	3	22	34
36	Hikmat Al-Ahmadie	39	9	3	27	31.5
37	Rajyalakshmi Luthra	39	7	0	32	23
38	Anuradha Gopalan	38	4	3	31	28.5
39	James Suh	38	2	2	34	25
40	Minghao Zhong	38	32	0	6	35

Table 1. A list of the top authors in the study period by total abstract count. An extended table containing the top 50 authors can be found in the online article at tp.txp.to/thebestmetric.

How did we do it?

Because the data is available in PDF form on the Modern Pathology website (tp.txp.to/ModernPathology), we serially read all files with a custom pre-processor program – written in Python – and converted them to text (5). The PDFs of scientific papers are typically formatted in two columns, so we "de-columned" the text using custom code to avoid formatting irregularities caused by figures and tables, and then used the logic-based text parser (LBTP) program to obtain the information we needed.

LBTP extracted each abstract "head" and further processed it using an algorithm to obtain the abstract, ID number, title, category, author(s), number of authors, affiliation(s), and number of affiliations. These components were written into a tab-separated (.csv) file.

We then used LibreOffice Calc to examine the .csv file and iteratively refine the extraction algorithm, followed by custom programs to generate an author list and an institution list. The author list tabulated author position both generally and in relation to the abstract category, producing two tables: an unweighted authorship table and one that weighted first authors x3, last authors x1, and non-first, non-last authors (NFNLA) x0.5. The institution list was categorized into i. country of origin, ii. state or province, iii. institution, and iv. other (uncategorized).

Both lists faced a unique issue – that of similar names. Author surnames were grouped together ("lumped") if the name was deemed infrequent. Institution names were purged of nonspecific words such as "university," "medical," or even "the" to create names consisting of unique words (e.g., "Yale" or "Toronto") so that similar names could be lumped. In this way, "Yale University" and "Yale School of Medicine" could be considered the same institution. Each affiliation was counted only once per abstract, even if multiple authors claimed the same affiliation.

"IT IS WIDELY ACCEPTED THAT NOT ALL ABSTRACT AUTHORSHIPS HOLD THE SAME ACADEMIC VALUE – EVEN WHEN PRESENTED AT THE SAME CONFERENCE"

failures are suspected to be related to the PDF formatting, and those that could not be extracted at all had either been classed by Modern Pathology as "previously published" or "withdrawn." A random audit of 700 extracted abstracts showed that 99% were processed correctly by the LBTP – an estimated error of only 1 percent.

Prolific publishing

By subspecialty, the largest number of abstracts presented at USCAP Annual Meetings over the four years in question came from genitourinary pathology, with a total of 1,001. This is closely followed by gastrointestinal pathology with 919, whereas the subspecialty with the fewest abstracts was infectious disease (see Figure 1). The median number of authors per abstract is five (see Figure 2). We also looked at the number of authors with a given number of abstracts and, as expected, this figure declined steadily as abstract number increased.

Digging a little deeper into the data, we then identified individual authors and arranged them by the total number of abstracts on which they appear as an author (see Table 1). This process delivers an overview of the most productive authors across the whole field based solely on raw abstract count. However, it is widely accepted that not all abstract authorships hold the same academic value – even when presented at the same conference. For example, the 10th author in an abstract with 20 authors is unlikely to have put in the same amount of work as the senior author – and even less than the first author. On the other hand, in an abstract of just two authors, it is entirely plausible that equal effort was contributed by both. That isn't to say that a large, multi-author publication can't be contributed to equally; rather, the issue is that, under

Sorted by Weighted Composite Score (WCS)						
Rank	Author	Total	Last Author	First Author	NFNLA	WCS
1	Jeffrey S. Ross	82	55	10	17	93.5
2	Michelle Reid	67	12	9	46	62
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8	Brian Robinson	44	5	9	30	47
9	Vikram Deshpande	56	31	1	24	46
10	Rondell Graham	35	8	9	18	44
11	Brooke E. Howitt	40	13	7	20	44
12	Sean R. Williamson	41	5	8	27	43.5
13	Bin Xu	26	0	12	14	43
14	Siraj Ali	63	2	4	57	42.5
15	Liang Cheng	52	17	3	32	42
16	Chengquan Zhao	30	23	6	1	41.5
17	Zaibo Li	32	10	8	14	41
18	Sounak Gupta	19	0	12	7	39.5
19	Russell Broaddus	45	19	3	23	39.5
20	Anne Mills	30	17	6	7	38.5
21	Adeboye O. Osunkoya	45	29	0	16	37
22	C. Blake Gilks	43	10	4	29	36.5
23	Thaer Khoury	14	3	11	0	36
24	Lisa Rooper	14	2	11	1	35.5
25	Prashant Bavi	16	0	11	5	35.5
26	Aaron M. Udager	28	3	8	17	35.5
27	Bahar Memis	41	0	6	35	35.5
28	Jason L. Hornick	57	14	0	43	35.5
29	Eman Abdulfatah	20	0	10	10	35
30	Gregor Krings	28	7	7	14	35
31	Minghao Zhong	38	32	0	6	35
32	Lindsay Alpert	19	0	10	9	34.5
33	Robert Soslow	48	11	2	35	34.5
34	Andres Matoso	24	9	7	8	34
35	Raul S. Gonzalez	31	17	4	10	34
36	Ming Zhou	39	14	3	22	34
37	Lynette Sholl	44	17	1	26	33
38	Takashi Muraki	20	0	9	11	32.5
39	Rifat Mannan	20	0	9	11	32.5
40	Cristina R. Antonescu	37	18	2	17	32.5

Table 2. A list of the top authors in the study period by weighted composite score (WCS). An extended table containing the top 50 authors can be found in the online article at tp.txp.to/thebestmetric.

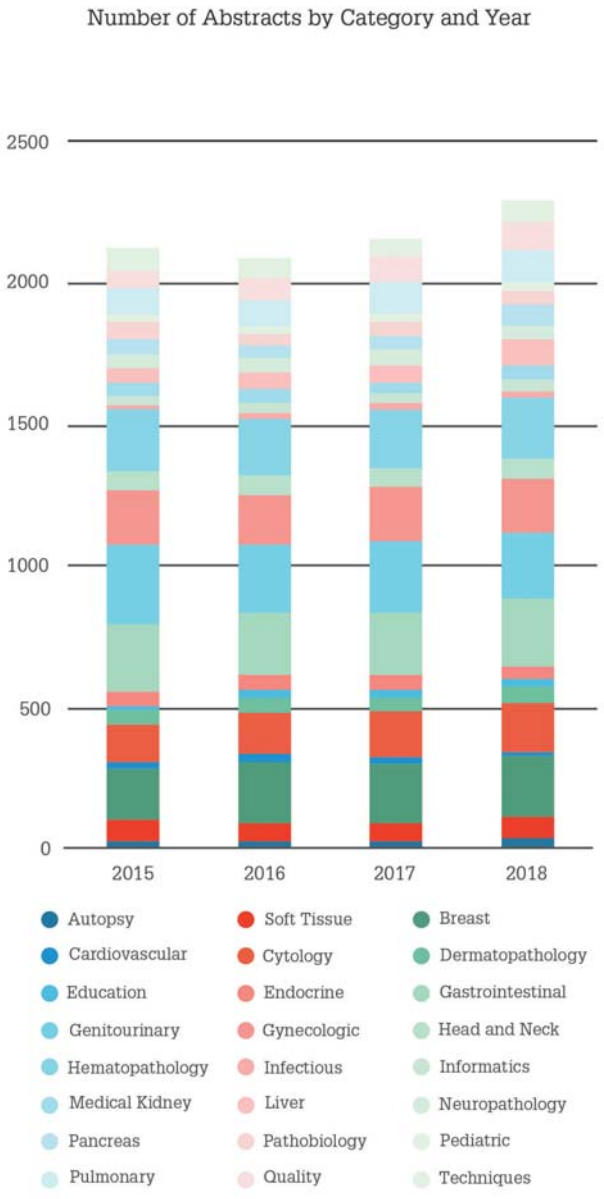


Figure 1. Number of abstracts published in each subspecialty by year of publication.

the current system, there is no indication as to the amount of work offered by each individual on the author list. And that makes further analysis into author contributions difficult; the author list only allows us to guess contributions based on what might be typical.

In an attempt to adjust the most active researchers (according to raw abstract count) for their relative contribution to different abstracts, we created a subset of the data in which different values were applied depending on a given person's position in the author list. Our weighted composition score (WCS) assigned first author abstracts a value of 3, last author abstracts 1, and non-first, non-last authorships (NFNLA) 0.5. Interestingly, the top 50 authors according to the WCS differ from those based on total abstract count (see Table 2) – and only 28 authors appear on both lists.

A class of their own

One of the main issues with relying on a simple abstract count to quantify the productivity of authors is that it doesn't reveal the budding researchers who deserve further opportunities. Neither does it identify previously productive researchers who have been struggling and might benefit from assistance. But how can we change such a deeply ingrained routine in academic publishing? Some have proposed that authors should be placed in contribution categories, such as "primary author," "contributing author," and "supervisory author," rather than creating one indiscriminate list (6). Perhaps a hybrid model would be an amicable solution: authors could provide a list – as is customary – as well as placing individuals into contribution categories at the time of submission.

This "category approach" to authorship would allow individuals to be in more than one tier; for example, an author could be in both the primary and supervisory categories. They would also allow each category to be occupied by multiple authors to indicate when primary or supervisory authorship is shared. Ideally, contributions should be captured in a more granular fashion to allow further analysis, revealing any "honorary authorships" that don't meet the International Committee of Medical Journal Editors guidelines for authorship or "ghost authorships" that leave certain contributors unacknowledged.

First to last

It is interesting to note that, at USCAP's Annual Meeting, authors can appear on an unlimited number of abstracts in a given year. There is a three-abstract limit on the number of times someone can be a first author in a particular year, but nobody in the top 100 authors hits this cap. Notably,

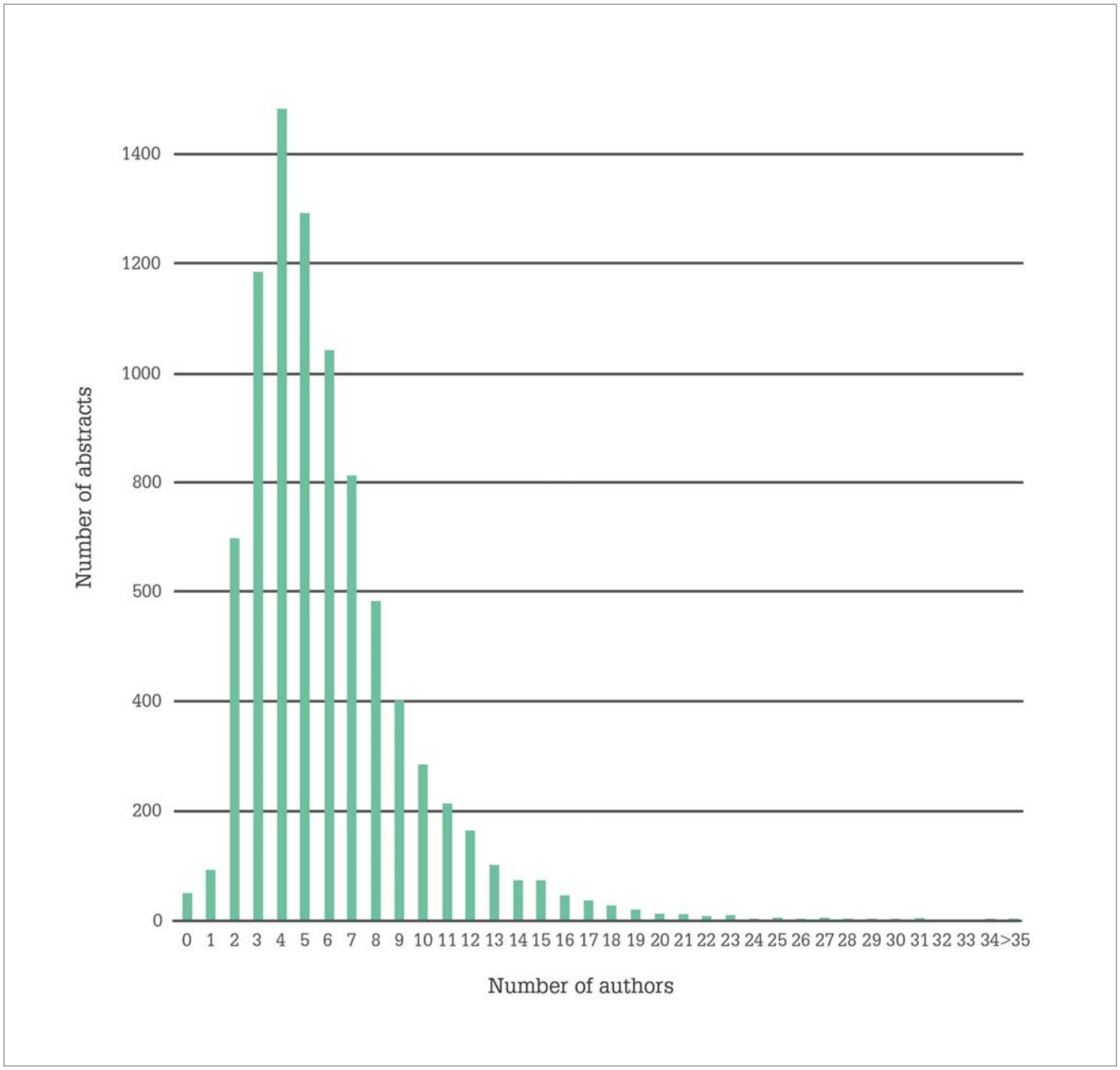


Figure 2. Number of abstracts published by the number of people listed as authors.

the European Society of Pathologists' rules for their yearly congress restrict individuals to a maximum of five abstract authorships, regardless of authorship type.

In our top 100 author list, the average total authorships over the four years is 38.4, the average number of last authorships is 11.1, the average number of first authorships is 2.2, and the average number of NFNLAs is 25.2. The predominant authorship among our top 100 publishers was therefore the NFNLA category. Because researchers are naturally keen to do whatever it takes to get ahead, these findings are in keeping with the idea that administrators focus principally on the total number of authorships. In other words, the sheer volume of a

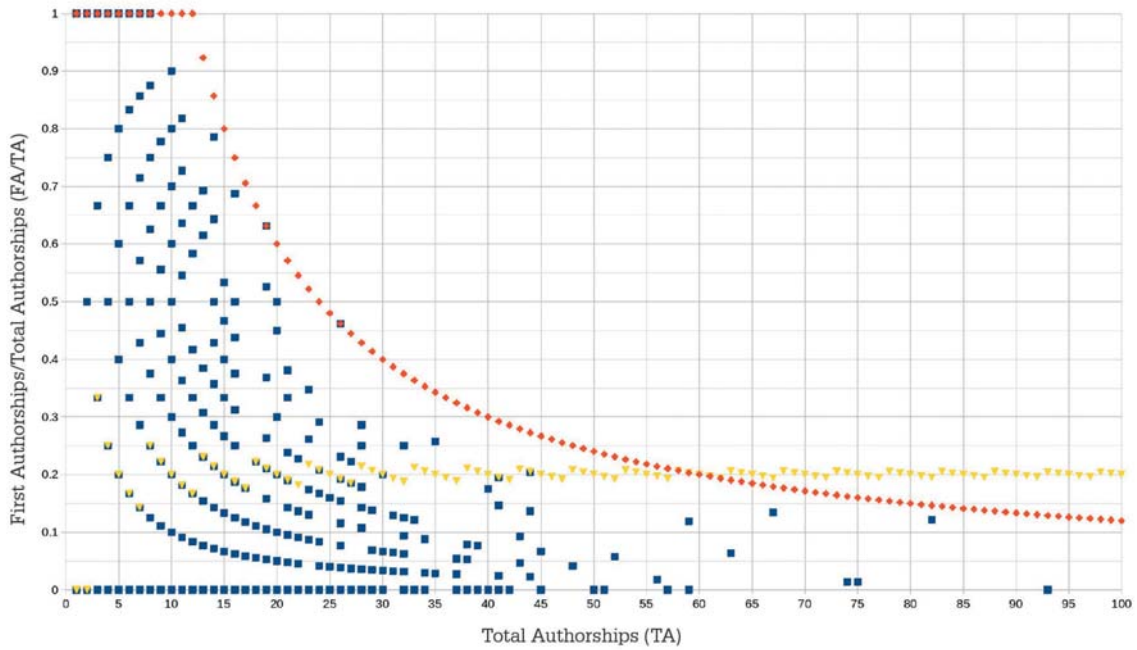


Figure 3. First author distribution plot. Blue markers represent one or more authors. All ~20,019 authors are shown; however, many authors are represented by one marker. The red markers are the maximal allowable FA/TA. USCAP does not allow more than 3 first authorships per year. The yellow markers show the expected FA/TA for the thought experiment.

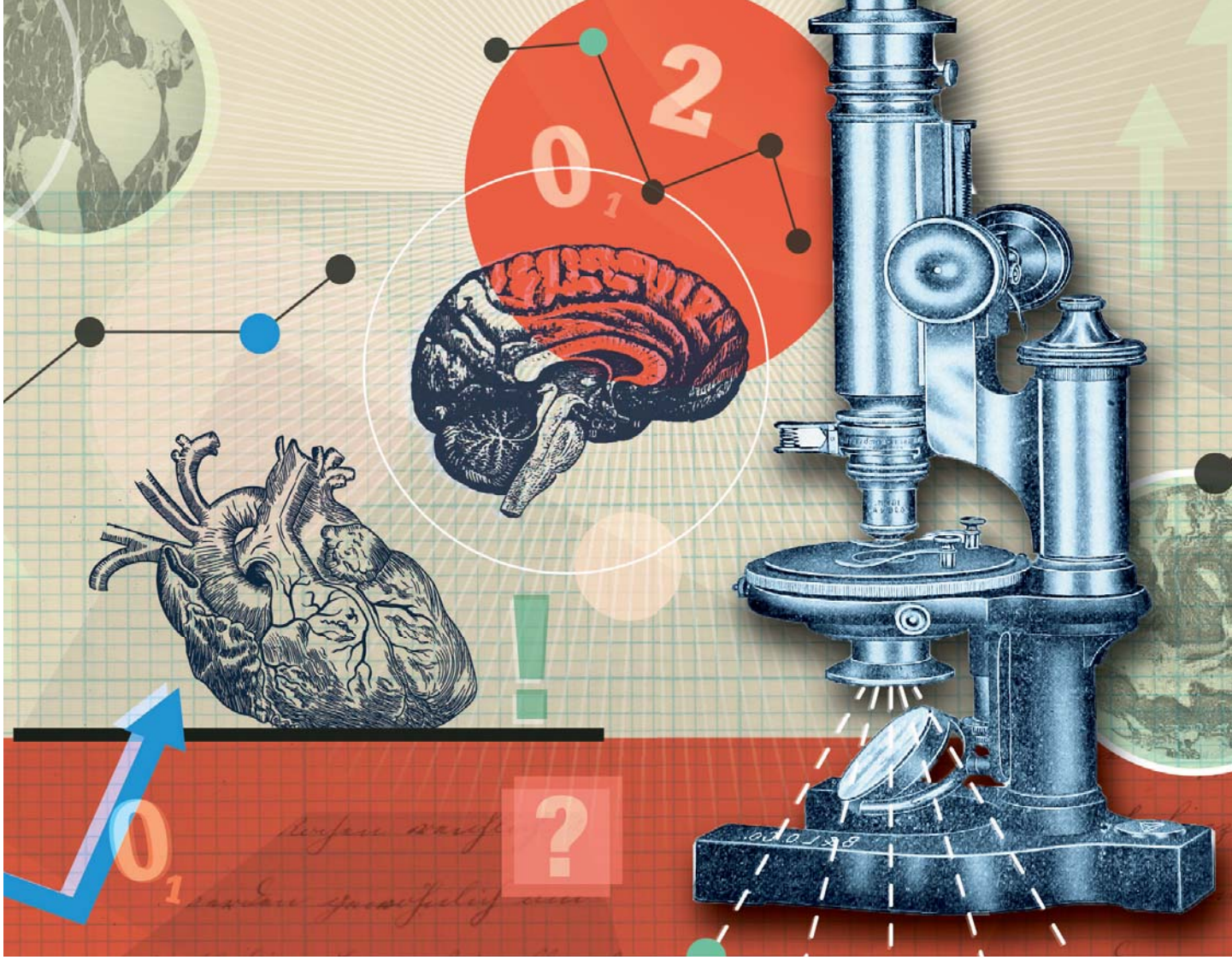
"THE SHEER VOLUME OF A RESEARCHER'S WORK IS CURRENTLY THE KEY ACADEMIC METRIC."

researcher's work is currently the key academic metric.

We believe that a metric with a built-in disincentive for "honorary authorships" might be desirable to prevent anyone appearing as an author who hasn't pulled their weight. For example, the academic value assigned to the authors in a category, such as NFNLA or supervisory authors, could be divided by the total number of authors in that category. We want to investigate this type of weighting scheme for different authors further.

Because we found that the median number of authors on a given abstract is five (see Figure 2), hypothetically, if we assume that authorship is random, we would expect authors with multiple abstracts to have a first authorship to total authorship ratio of 0.2. To test whether this was the case, we generated a first author distribution plot (see Figure 3) and calculated the average first author to total author (FA/TA) ratio.

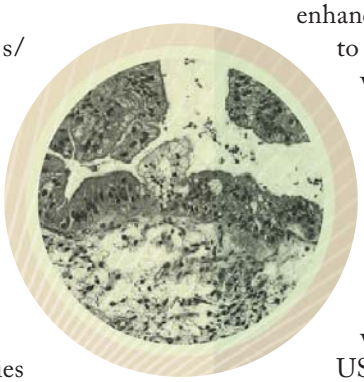
As mentioned above, in our list of the top 100 authors, the average number of first authorships is 2.2 and the average number of total authorships is 38, giving an average FA/TA ratio of 0.057. Therefore, there must be a subgroup with a high FA/TA ratio – so, to identify those individuals who appear as first author more often, we extracted a new author list with a FA/TA ratio over 0.30 (see Table 3, available online at tp.txp.to/thebestmetric). The traditional thinking is that those with a high FA/TA ratio are residents, fellows, or junior staff and up-and-coming researchers. Is this group a collection of future top performers? Or are they keen but under-resourced researchers who haven't been given the right opportunities? Perhaps even senior researchers keen on occupying first authorship positions? We suspect it is a mix of the above, although the latter is unlikely because few individuals in this group are names that most pathologists would readily identify.



Unique insights

Pathology has many different branches/subspecialty areas that should not be compared directly. Therefore, we mapped out the top authors according to total abstract count broken down by subspecialty (see Table 4, available online at tp.txp.to/thebestmetric). These top ranked authors showed little crossover across the 24 (subspecialty) categories, pointing to a high degree of subspecialization. It is obvious that USCAP is a collection of smaller communities with a rich overlap. As a result, USCAP's blinded review policy is laudable because it enhances objectivity in the assessment of abstracts in the smaller subspecialty groups, where researchers often know each other. In the evaluation process, multiple raters score each abstract in a blinded fashion.

The raw abstract score – and variation among raters – could be an interesting metric of quality itself, if it were ever released. It would help move the discussion around academic contributions beyond merely counting authorships, enhance transparency, and allow pathologists to revisit past discoveries to uncover whether highly rated abstracts from years ago were genuinely high-impact or just highly rated at the time.



As expected for an American and Canadian conference, when we arranged the abstracts by country of origin, we found that the majority were (very unevenly) associated with these two locations (see Figure 4). The US was involved in for 80.1 percent of abstracts and Canada 5.4 percent. In the four-year period assessed, 1,079 abstracts (12.5 percent), were associated with two or more countries. The MD Anderson Cancer Center is the most prolific institution, accounting for 365 of the abstracts in our dataset. This is closely followed by the Memorial Sloan Kettering Cancer Center, Mayo Clinic, and Brigham and Women's Hospital, each with over 300 abstracts (see Table 5, available online attp.txp.to/thebestmetric).

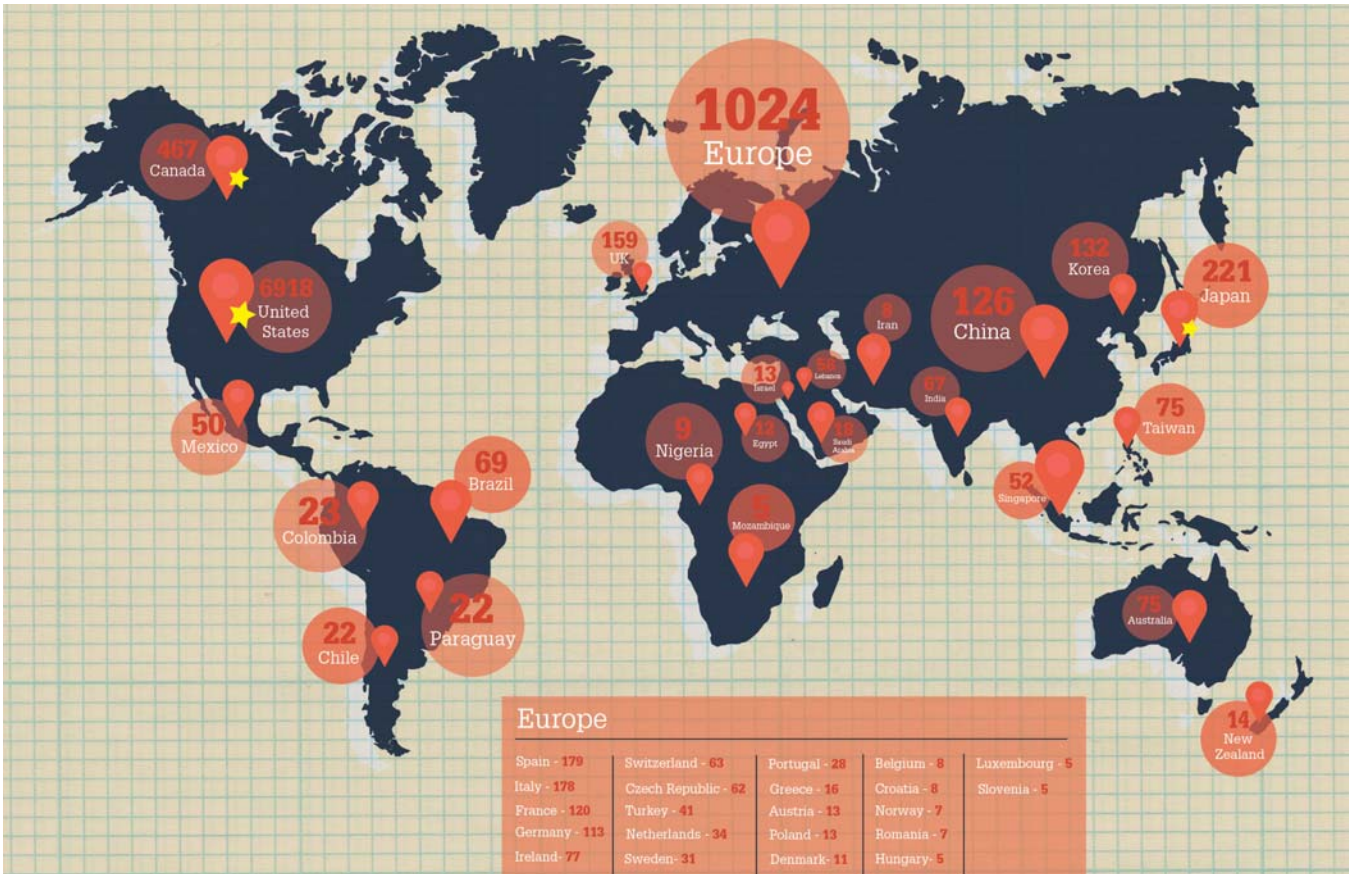


Figure 4. World map showing number of abstracts according to their country of origin. The top three countries by abstract count are marked with stars.

Necessary limitations

No analysis is free of limitations – and that includes this work. The first point at which issues arise is during parsing, when the algorithm improperly parses approximately 1 percent of abstracts – meaning that, especially when examining individual authors, its results should be used with caution.

The name lumping algorithm may lead to false matches. Individuals with the same first name and an uncommon last name – say, "Joe E. Skule" and "Joe B. Skule" – will both be lumped together under "Joe Skule." On the other hand, individuals with common last names will not be lumped, so the system considers "John D. Wang" and "John D.R. Wang" to be different individuals. This can result in an artificially inflated number of authors, with an artificially diminished level of credit to the individual. Unfortunately, there is no way to definitively separate authors with exactly the same name – and the problem increases when using data prior to 2015, when meeting abstracts listed only last name and first initial. The ideal solution would be for meetings such as USCAP to require a unique author identifier, such as an ORCiD ID.

Institution lumping also presents problems – for instance, that it does not capture variant word orders, so "Brigham and Women's" is not considered the same affiliation as "Women's & Brigham." Nor does it capture abbreviations, so an author from "MSKCC" would not be lumped with one from "Memorial Sloan Kettering Cancer Center." There are also problems with the "other (uncategorized)" group – some institutions and locations have similar or overlapping names (for instance, Mayo Clinics in three different locations, or 33 different Springfields in the United States). At the moment, because of these issues, analysis of affiliations is limited and has a high degree of "background noise." The ideal solution would be for meetings such as USCAP to create drop-down menus from which authors can select their affiliations, eliminating duplications and uncategorized affiliations.

Additionally, we determined the weightings of each author position arbitrarily for the purpose of this analysis. A formal study to determine accurate weightings would objectify the analysis. Better still would be a system by which contributions are recorded for each abstract or authors are placed in pre-determined categories with existing weightings.

The geographical factor affects the representation of pathology researchers at the USCAP annual meeting, which is always held in either the US or Canada.

Finally, our analysis is limited to the abstracts as published

in Modern Pathology. This does not take into account the two different forms of abstracts presented at the USCAP Annual Meeting – posters and platform presentations (known as "proferred papers"). The latter are generally considered to be more significant contributions; however, our system did not distinguish between the two and thus did not weight those authorships more heavily.

Free for all to see

Although it's clear that the analysis of free text in this way has limitations, there are clearly useful insights we can gain – both about research trends and about the output of individuals and institutions. Because the barriers to these types of analyses are moderate, they will likely become common in the future. It seems certain that data will play an increasing role in the allocation of resources and the measurement of academic productivity. As a result, we as a field need to determine how best to record the appropriate author data – and how to create a next-generation system that rewards innovation and progress and minimizes the degree to which the system is inevitably "gamed." How the data is collected determines how easy it is to analyze. In this regard, categorical data – rather than free text – is key. If the data were available in a format that could be more easily processed by a machine, it would facilitate further work.

We now hope others will be motivated to conduct their own analyses. The use of USCAP abstracts as a metric for research productivity would not only enhance the standing of USCAP's Annual Meeting as a venue to present research, but also allow healthcare leaders to better identify both budding star researchers and those who show great promise in the absence of conditions required to reach their full potential.

Discover the extended dataset including all authors (with the abstract ID numbers) and longer top contributor list: thepathologist.com/fileadmin/pdf/USCAPAnalysisData.ods

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Contributions

Michael Bonert conceived the study, wrote the computer code that completed the analysis, and drafted a manuscript.
Gaurav Vasisth audited the output of several hundred abstracts, provided feedback to improve the computer code, and revised the manuscript.
Christopher Naugler critically reviewed the analysis, suggested further analysis work that was included, and revised the manuscript.
Asghar Naqvi molded the study's concept with comments and observations and critically reviewed the manuscript.

References

1. *KJ Meador, "Decline of clinical research in academic medical centers", Neurology, 85, 1171 (2015). PMID: 26156509.*
2. *Trade Show News Network, "USCAP celebrates more than a century as largest annual pathology meeting" (2018). Available at: https://bit.ly/2RhKim7.*
3. *J Song et al., "The outcome of abstracts presented at the United States and Canadian Academy of Pathology annual meetings", Mod Pathol, 23, 682 (2010). PMID: 20173734.*
4. *Modern Pathology, "Abstract" (2019). Available at: https://go.nature.com/382uCt2.*
5. *Poppler, "Poppler" (2019). Available at: https://bit.ly/2LgN2wo.*
6. *MO Baerlocher, "The meaning of author order in medical research", J Investig Med, 55, 174 (2007). PMID: 17651671.*

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In Practice

Technologies and techniques
Quality and compliance
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Trust Is Earned

Tips and tricks for an effective clinical pathology consultation

By Gene R. Shaw

Many pathology practices have a call schedule for clinical pathology that largely revolves around approving or denying esoteric test requests during off-hours. In academic settings, trainees are typically given a beeper (or, nowadays, a cell phone) and put on call to field these requests. Unfortunately, this tends to pit the laboratory against the requesting physician – clearly not an ideal situation for interdisciplinary cooperation. So how can this gatekeeper role be handled without either side risking its relationship with the other? And, in a broader sense, how can clinical pathologists and clinical PhDs effectively collaborate with colleagues who interact directly with patients to improve overall care?

The on-call gatekeeper

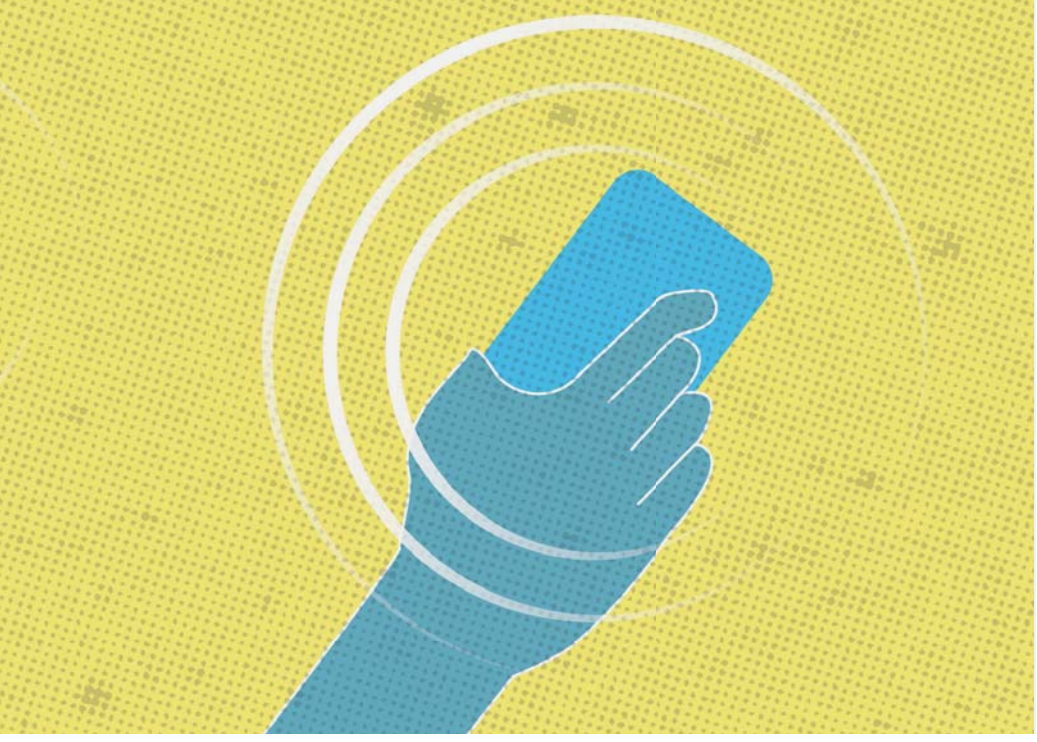
Many tests cannot be offered routinely 24/7 because of limited staffing or instrumentation that is not up and running. Pathologists and clinical PhDs are tasked with balancing clinical necessity against the financial costs of such off-hours testing – staffing, instrumentation, reagents, and more. And, when it comes to disruption of lab personnel, don't expect to get much sympathy from the on-call physician who is managing the patient in the middle of the night.

Here is some practical advice:

- During the initial phone call, gather information, but don't make any promises. Do not ask the seemingly logical question, "Will this test result change the management of the patient?" Any halfway savvy clinician will always answer, "Yes!" And then you've backed yourself into a corner where approval is expected.
- A better approach is to start the conversation with the following statement: "I will have to check on staff and instrumentation availability to see if the test can be performed." You want the tone to be one of collaboration; you are both on the same team and you will explore what can be done. Then proceed to gather clinical information. Inpatient or outpatient? Has the sample already been collected? Will someone be available to receive and respond to the lab result during off-hours? Conclude by getting a contact number with whom to follow up, once a decision on whether to proceed with off-hours testing is made.
- Now go into the medical record and gather additional patient-specific information. If this is an area with which you have limited familiarity, contact a lab colleague. This could be another pathologist/PhD who directs that section of the lab, or it might be an experienced technologist in that lab section. Sometimes, the request is obviously inappropriate and you may hear, "Not another one of these!" Other times, it may be clearly indicated. Not infrequently, it is a "gray zone" issue – and, in those cases, offering the test first thing during regular hours (for instance, on Monday morning) will often suffice.
- Beyond this, there is no cookbook approach; each situation needs to be assessed individually. As a laboratorian, you need to do your homework. Convincing a clinical colleague to cancel or change a test request usually requires that you know the test(s) better than they do regarding specimen requirements, stability, turnaround time, diagnostic sensitivity/specificity, alternative testing options, and so on. Don't be deterred. Do the right thing for patient care and for appropriate utilization of lab resources. Remember, you have worked hard to have the letters MD, DO, or PhD behind your name, too.

A question of test utilization

A large percentage of ordered lab tests are not indicated for a variety of reasons. Often, it's because they're redundant; busy physician A may not know that busy physician B ordered that test only



"As a laboratorian, you'll have to prove your worth [...] Look for opportunities to proactively interact with your clinical colleagues."

a few hours ago. Sometimes, physicians order tests out of habit, rather than based on current evidence-based guidelines. Other times they "know enough to be dangerous" – they have read a recent article about a new test, but don't fully understand its costs and limitations.

Nevertheless, many (perhaps even most) physicians don't feel that they need assistance in ordering or interpreting lab tests. After all, it's what they do every day. So, as a laboratorian, you'll have to prove your worth. If you only function in the off-hours gatekeeper role, you may be viewed as an obstacle rather than an ally. Look for opportunities to proactively interact with your clinical colleagues. Call or email them with a "heads-up" on an unusual result. Send them an insightful article on an area of interest. Work closely with technical staff to stay updated on unusual results, interferences, and instrumentation or reagent issues. Encourage questions from clinical colleagues.

In a broad sense, test utilization encompasses the lab test menu and how the test is offered. Tests of very limited clinical utility should be "buried" far down in the ordering options. Newsletters, presentations to key clinical departments, and grand rounds can all be used to raise awareness and increase understanding – but with a caveat: increasingly busy and distracted clinicians often don't read or attend. And, if they do, they have often forgotten the salient information a few weeks later when they actually need to order the test. Thus, succinctly communicating information at the time of test ordering is the most effective means of impacting behavior.

Fortunately, there are now many information technology tools that can help. Several months ago our lab implemented a pop-up window in our test ordering software. It informs clinicians that dilute Russel viper venom time (DRVVT) and partial thromboplastin time-lupus anticoagulant (PTT-LA) should not be ordered for patients taking the new direct oral anticoagulants (apixaban, rivaroxaban, or dabigatran) because of the likelihood of false-positive results. This fits nicely with the Choosing Wisely campaign's September 2019 recommendation: "Do not perform a hypercoagulable workup in patients taking direct factor Xa or direct thrombin inhibitors."

Monitor tests that are frequently inappropriately ordered. Focusing on expensive tests may yield more "buck for your bang." As a hematopathologist, I use our cytogenetics staff to police not only conventional cytogenetics, but also molecular tests for hematologic neoplasms (for example, JAK2/CALR/MPL, BCR-ABL, plasma cell proliferative disorder FISH, next-generation sequencing panels). We assess previous testing, specimen adequacy, indications, and liberally communicate with our physicians. We typically cancel or change two to four tests every business day, with a cost savings exceeding US$1,000 per day. We also continually modify current tests, introduce new tests, and discontinue (or outsource) obsolete tests – a practice I recommend to all laboratories. Two notable recent examples from our lab have been the change to age-adjusted D-dimer testing and the introduction of high-sensitivity cardiac troponin I testing with a zero- and two-hour rule-out algorithm. Use these changes as teaching opportunities with your clinical staff.

Being based in the laboratory gives you a unique perspective on lab testing. You see far more abnormal results on a regular basis than your clinical colleagues. By using that information and communicating effectively with those colleagues, you will earn their trust as a valued member of the health care team.

Gene R. Shaw is a Hematopathologist at the Marshfield Clinic, Marshfield, Wisconsin, USA.

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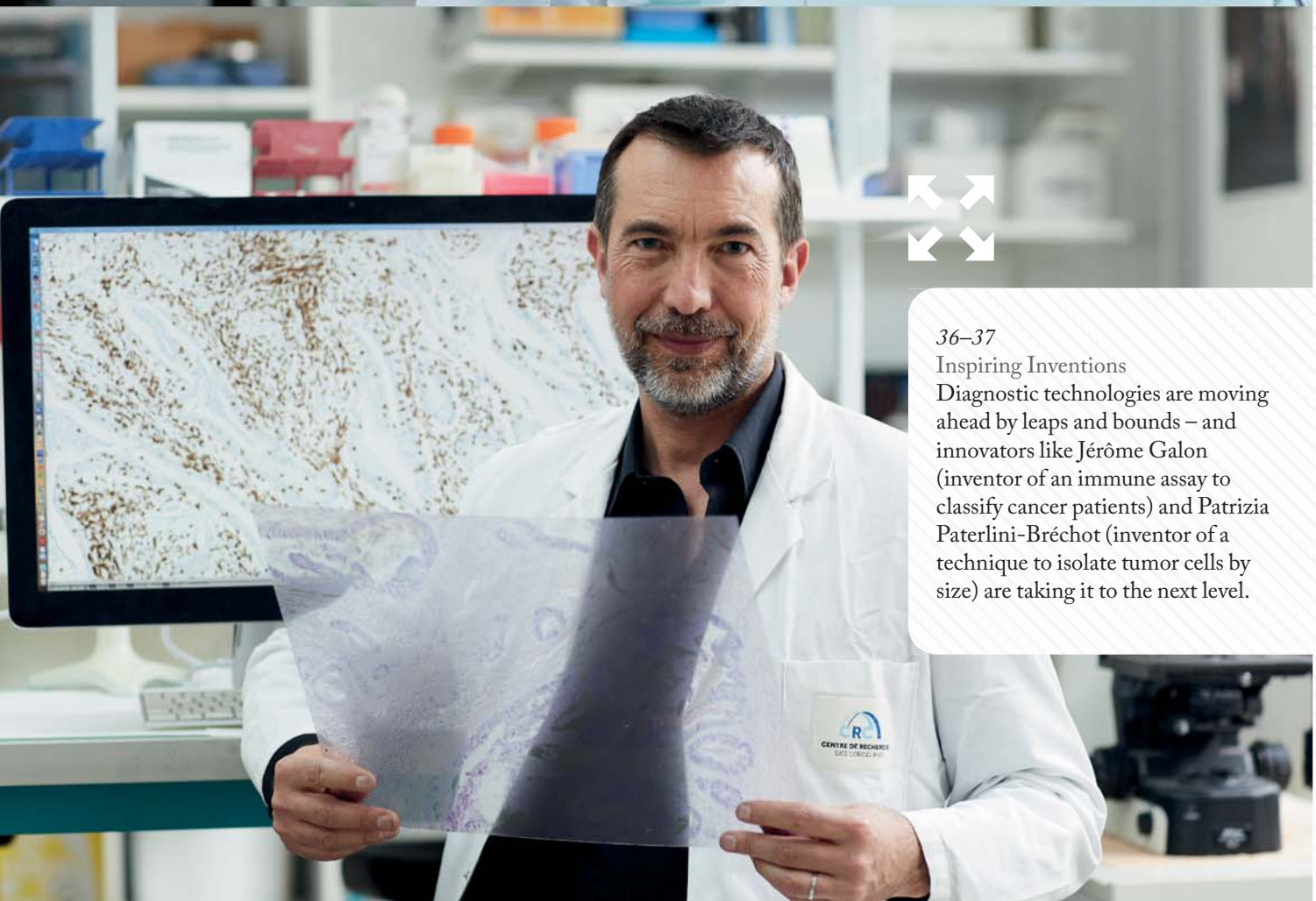

Inspiring Inventions

Two high-profile innovators describe new diagnostic technologies and the promise they offer for cancer detection and treatment

Jérôme Galon, Inventor of Immunoscore

Galon's new assay, winner of the European Inventor Award for Research, seeks to classify cancer patients in routine clinical settings

What inspired the invention of Immunoscore?

I wanted to demonstrate the importance of pre-existing immunity in cancer. At the time, the accepted hallmarks of cancer didn't even include the possible role of the immune system. We began a massive analysis of immune cells in large cohorts of patients to decipher the immune microenvironment using quantitative assessment of immune subpopulations within tumors – that is, quantifying immune cells using digital pathology and image analysis. We showed the significant contribution of memory T cells to the prevention of early-metastatic dissemination (1), and that numbers of adaptive immune cells were better predictors of the clinical outcomes for colorectal cancer than all traditional histopathological parameters (2). We validated our findings in several further studies (3,4).

The gold standard classification (AJCC/UICC-TNM) provides useful, but still incomplete, prognostic information. New ways to classify cancer focus on tumor cells, including molecular pathways, mutation status, and tumor gene expression-based stratification – but have shown only moderate prediction accuracy and limited clinical usefulness so far. Seeing the importance of pre-existing immunity, we knew we needed an immune assay to classify cancer patients in routine clinical settings.

And that's why we developed Immunoscore, an immunohistochemistry-based immune assay whose prognostic power has been defined, harmonized, and validated in colon cancer patients by an international consortium (5). It provides doctors with a comprehensive picture of patients' immune responses, enabling them to classify cancers more precisely to provide the most effective therapies. The assay has given us a completely different view of cancer – now, we know that these pre-existing adaptive immunity markers are not only prognostic, but can also predict response to treatment (6).

What surprises did you encounter along the way?

In 2005, we predicted one of two things: either that the immune system played no major role in preventing early-metastasis invasion and prolonging survival, or that the pro-tumoral innate immune system would have a negative effect. In fact, we found that quite the opposite was true! Patients with high densities of pre-existing T cells showed better long-term survival (2).

"Don't be afraid to push the boundaries and introduce novel paradigms."

As a result, we proposed the now widely embraced concept of tumor immune contexture – the immune parameters associated with survival. It was particularly unexpected that all traditional histopathological parameters (T-stage, N-stage, grade of differentiation, venous emboli, lymphatic invasion, perineural invasion, microsatellite instability) depend upon pre-existing immunity (6–9).

What advice do you have for aspiring inventors?

Don't be afraid to push the boundaries and introduce novel paradigms.

Patrizia Paterlini-Bréchot, Inventor of ISET

Paterlini-Bréchot's technique, nominated for the European Inventor Award for Research, enables lossless isolation of circulating tumor cells

What inspired the invention of ISET?

The invention of the Isolation by SizE of Tumor cells (ISET) technique was inspired by the need to extract extremely rare circulating tumor cells (CTCs) from blood without any loss – and while keeping them intact for further analyses of their morphology and molecular content. At the time of the invention, our team had tested myriad other possible approaches to isolate CTCs, but all had failed. In fact, circulating tumor cells are very rare – only a few mixed in with billions of blood cells – and extremely fragile; they can be destroyed by the manipulation needed to extract them. Furthermore, they do not have specific protein markers on their surfaces to allow us to "fish" them efficiently out of blood. Therefore, we had to come up with a different way to reach our goal. We decided to leverage a physical characteristic common to all tumor cells – the fact that they are significantly larger than blood cells.

What surprises did you encounter along the way?

The most surprising aspect was the combination of two challenges: the extreme heterogeneity of blood samples and the fragility of the CTCs themselves. These obstacles forced us to test hundreds of conditions to find the combination that allowed us to achieve our goal: extracting even a single tumor cell from blood without any damage.

What advice do you have for aspiring inventors?

My advice for those who want to find new routes to solving problems is to read all of the literature, consult experts on the subject, keep an open mind, and then carry out tests tirelessly, learning from mistakes until you hit your goal. Don't be afraid of despair; it often generates new ideas. And don't listen to those who say, "That's impossible." Just follow your deep belief, test, learn, and keep moving forward.

References

1. *F Pagès et al., "Effector memory T cells, early metastasis, and survival in colorectal cancer", N Engl J Med, 353, 2654 (2005). PMID: 16371631.*
2. *J Galon et al., "Type, density, and location of immune cells within human colorectal tumors predict clinical outcome", Science, 313, 1960 (2006). PMID: 17008531.*
3. *F Pagès et al., "In situ cytotoxic and memory T cells predict outcome in patients with early-stage colorectal cancer", J Clin Oncol, 27, 5944 (2009). PMID: 19858404.*
4. *B Mlecnik et al., "Histopathologic-based prognostic factors of colorectal cancers are associated with the state of the local immune reaction", J Clin Oncol, 29, 610 (2011). PMID: 21245428.*
5. *F Pagès et al., "International validation of the consensus Immunoscore for the classification of colon cancer: a prognostic and accuracy study", Lancet, 391, 2128 (2018). PMID: 29754777.*
6. *J Galon et al., "The continuum of cancer immunosurveillance: prognostic, predictive, and mechanistic signatures", Immunity, 39, 11 (2013). PMID: 23890060.*
7. *J Galon et al., "Towards the introduction of the 'Immunoscore' in the classification of malignant tumors", J Pathol, 232, 199 (2014). PMID: 24122236.*
8. *J Galon, D Bruni, "Approaches to treat immune hot, altered and cold tumours with combination immunotherapies", Nat Rev Drug Discov, 18, 197 (2019). PMID: 30610226.*
9. *EK Broussard, ML Disis, "TNM staging in colorectal cancer: T is for T cell and M is for memory", J Clin Oncol, 29, 601 (2011). PMID: 21245434.*

Profession

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Come on Pathology, Light My Fire

How an unlikely collaboration between pathologist and rockstar is raising money and awareness for diagnostic medicine

By Luke Turner, with Michael Misialek

In 1967, legendary US rock band The Doors released their most famous – and possibly popular – single. The spark for the song came when Robby Krieger, the band's guitarist, asked lead singer Jim Morrison what he should write about, to which Morrison replied, "Something universal that won't disappear two years from now." Krieger decided to focus on one of the elements of nature. The resulting song – "Light My Fire" – spent three weeks at the top of the US Billboard Hot 100. Over 50 years later, it's safe to say the hit single has stood the test of time; just last year, the Recording Industry Association of America certified it as platinum with over 2,000,000 copies sold.

What does the story of a timeless rock song have to do with pathology? Recently, Michael Misialek, Associate Chair of Pathology at Newton-Wellesley Hospital in Massachusetts, discovered that Krieger is an active philanthropist – and that gave him a brilliant idea. "As a band I enjoy listening to, I was interested to learn what the surviving members of The Doors – Robby Krieger and John Densmore – were up to today," says Misialek. "A simple online search told me that Krieger still performs around the country and that he regularly participates in fundraising events, especially for public health projects."

The unknown philanthropist

Because Misialek is passionate about the work of the CAP Foundation – a charitable division of the College of American Pathologists (CAP) – he was inspired to reach out to Krieger in the hope of forming an unusual collaboration. "I noticed that Krieger enjoys painting; many of his works are influenced by, or named after, songs by The Doors," explains Misialek. "I made an inquiry through his website, suggesting to him that I could buy one of his limited-edition prints and put it up for auction to see how much money we could raise for the CAP Foundation." Not only did Krieger respond, but he was also extremely enthusiastic about the idea and invited Misialek to his Los Angeles studio so that they could sit down together, discuss the collaboration, and film a short interview.

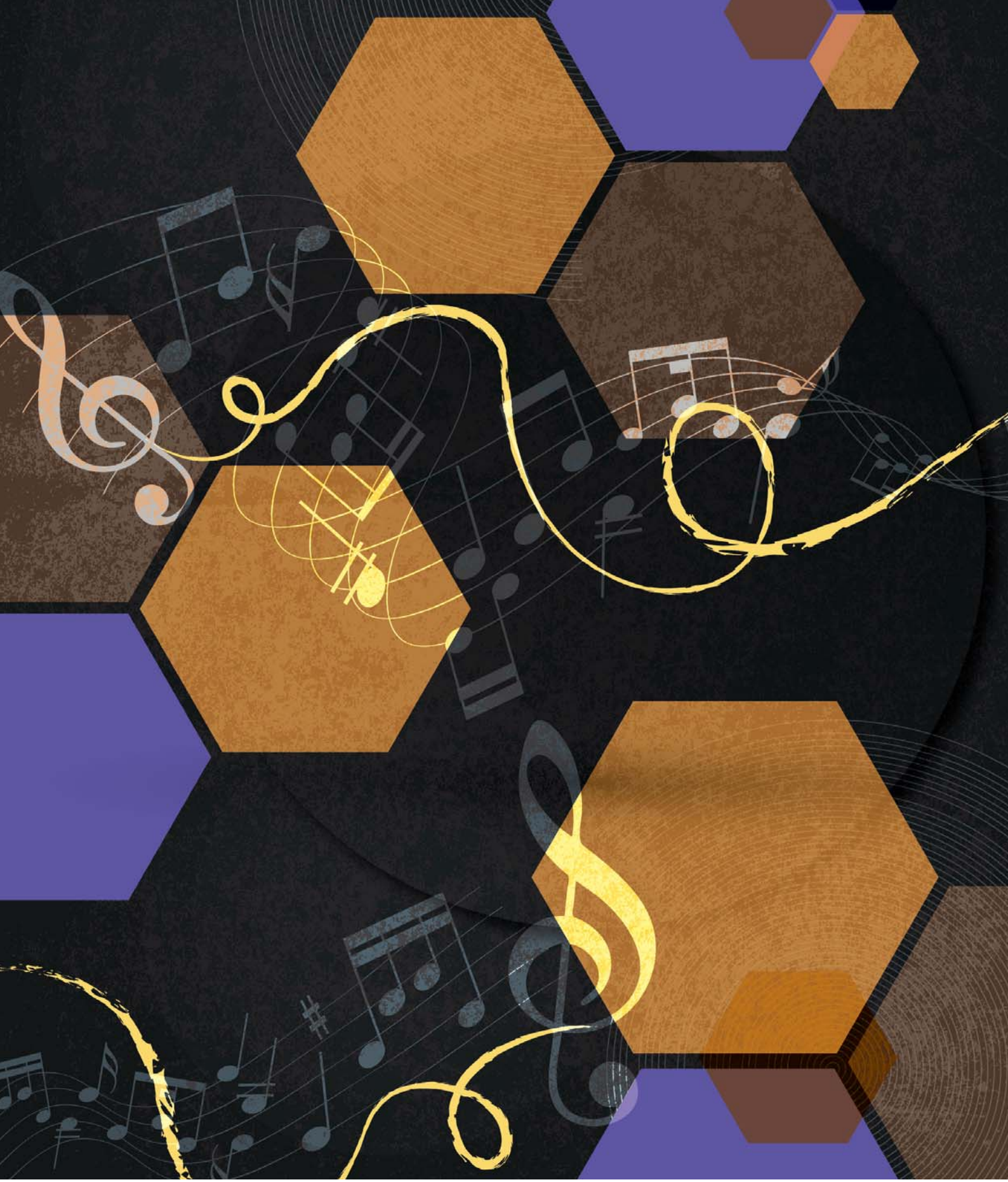
When they met at the studio in LA earlier this year, the pair talked about art, The Doors, and the visibility of pathology to the public (see the full interview at tp.txp.to/RobbyKriegerInterview). Misialek received a tour of the studio and was even treated to a few chords on the guitar. "He's a really down-to-earth guy whom you'd never realize is a talented rock superstar!" While they were together, Misialek purchased a signed print of Light My Fire, a painting Krieger produced to depict The Doors' hit single.

Ordinarily, anyone can purchase Krieger's artwork – and the proceeds are split between his own music charity, which funds local schools to encourage young people to play instruments and join bands, and a charity of the purchaser's choice. But Misialek told Krieger to take the entire fee for his own charity, then auctioned the piece online. It sold for just over US$2,000 – all of which went to the CAP Foundation to support cervical cancer screening in underserved women across the US. "I decided to donate the money to the See, Test, and Treat program run by the CAP Foundation,"

"Based on estimated test costs, the money raised by the artwork paid for 60 women to receive a Pap smear."

Misialek explains. "They run free health fair-style events around the country, at which women receive a Pap smear test and a mammogram to screen for breast cancer, before a pathologist reviews the cervical cells – all in the same day." Thanks to the pathologists, radiologists, and gynecologists who donate their time and the vendors who donate supplies, the sessions bring together diagnostic professionals to ensure that every woman receives these vital health checks. Based on estimated test costs, the money raised by the artwork paid for 60 women to receive a Pap smear at one of these events.

Misialek's ultimate ambition is to build momentum around the campaign and inspire others to follow suit. "This kind of project isn't unique to the CAP Foundation; I chose them because I used to be part of the charity and it's something that I'm passionate about. I wanted to see what kind of response I could get and use it as a platform to encourage others to pursue their own unique collaborations or form new relationships with charitable organizations." Neither is Misialek's idea exclusive to the US. The Doors have international appeal, especially across Europe and Asia, and a plethora of societies and colleges could benefit from funds generated by artwork.




Dodgers


WHISKY
a GOGO

Pathologists aren't strange

As well as raising valuable funds for a worthy cause, Misialek hopes his actions help to highlight pathologists, educating the public about their presence and the crucial work they do. "The general movement of the field at the moment is to bring pathologists into the limelight as visible members of the healthcare team," he says. "This is a great vehicle to do just that, because The Doors still have an incredibly large following, many of whom probably don't know what pathology is."

It came as a surprise to Misialek when, during their time together in LA, Krieger opened up about his own health and revealed an already comprehensive understanding of pathology. After finding a lung lesion, Krieger's pathologist diagnosed it as metastatic melanoma despite the absence of a skin lesion and no history of the disease. "He understood all about the pathologist's role, how we arrive at a diagnosis, and why immunotherapy can be so effective," Misialek explains. Thanks to successful treatment, Krieger went into remission and is now back to touring the US, collaborating with other artists, and working on soundtracks for movies.

Misialek believes that this personal connection – and others like it – can be harnessed to underline the importance of the field. "We have a lot of work to do in terms of spreading awareness about pathology and increasing its exposure to the wider public. Headway has definitely been made, though – and the number of pathologists who are engaged and outspoken has increased over the past few years." This, he says, has resulted in a surge in social media use and an increase in the number of pathologists who are actively involved in the healthcare team. "Although there is still work to be done, the younger generation generally feels more comfortable promoting themselves and their field to the public, legislators, and the press."

But what impact does Misialek think his own creative and charitable idea can have on others? "I hope that more pathologists will be inspired to seek opportunities that give them a visible platform, not just within their institution, but also to the public," he says. "This includes speaking at health fairs or to community groups, going into schools to educate children about diagnostic medicine, and inviting people for hospital tours so that they can appreciate the interesting challenges we face every day." Ultimately, Misialek hopes to cement pathology on the healthcare map to ensure that administrators and colleagues recognize pathologists and involve them in important decision-making.

"The sky is the limit and it's fantastic to think that you can just reach out to influential people, pitch an idea, and see where it takes you!"

Breaking on through

As for the future of the current collaboration, will it be a case of "Love Me Two Times" or "The End?" Misialek remains passionate about the potential to champion pathology alongside Krieger through his considerable following with The Doors. "I'd really like to continue to promote this project to bring the field into the public eye – and even show people that pathologists can be cool and talk to rock stars!" He recognizes the potential branding that could result from such partnerships, suggesting "Pathologists Rock" and "Light My Fire" as titles for his current endeavor.

"One of my biggest hopes is that somebody will read my story and dream up their own novel idea of how to raise awareness," explains Misialek. "The sky is the limit and it's fantastic to think that you can just reach out to influential people, pitch an idea, and see where it takes you! I reached out to Robby Krieger on a whim, but it turned out he had experienced his own health battles and knew all about the work of pathologists. There was a story there waiting to be told... and there are plenty of other untold stories out there ready to be unearthed and leveraged for everyone's advantage."

Since buying and auctioning Light My Fire to raise money for the CAP Foundation, Misialek has made the trip back to LA to go backstage at one of Krieger's concerts. Held at Whiskey A Go Go on Sunset Strip in West Hollywood, this was a particular honor for Misialek – not least because it was the venue where The Doors got their first break in 1966. "I had always enjoyed their music growing up and it was an amazing experience to hear some of it live!" At the concert, the duo agreed to take their collaboration to the next level. "Our second endeavor will be to partner with Gibson, who will provide a guitar that Krieger will sign and play before we auction it off. We hope this generates high demand – and the proceeds will be entirely donated to a pathology-related charity of the winner's choice!" says Misialek.

With the opportunity to secure a one-of-a-kind prize and provide valuable funds for a worthy cause, the guitar is likely to prove extremely popular. But it's not the only good idea out there – so if you have a novel idea to raise funds or awareness, don't hesitate. You may just land on a winner!

Michael Misialek is Associate Chair of Pathology and Medical Director of the Vernon Cancer Center at Newton-Wellesley Hospital in Newton, USA.

Midas Touch or Fool's Gold?

A regulatory science perspective on whether digital pathology can capture the US$223 billion digital health market

By Richard Huang and Veronica Klepeis

The world of healthcare has seen a technological explosion over the past few years – especially with respect to digital medical devices. But despite an estimated global digital health market of $223 billion by 2023 (1), digital pathology's penetration into the space has been limited. Only a few of the artificial intelligence/machine learning (AI/ML)-based medical devices approved by the US Food and Drug Administration (FDA) over the past several years have been in the digital pathology sphere (2). Now, the FDA has proposed new regulatory frameworks to account for the expected growth and iterative nature of AI/ML-based medical devices (3) – and it's vital that companies stay on top of the new regulatory paradigms so they can gain the necessary regulatory approvals to bring their products to market. After all, until a medical technology reaches the market, it cannot help real patients in real-world clinical settings.

Will digital pathology take advantage of this change and turn all that it touches into gold… or will it lose out on the quarter trillion-dollar digital future?

Probing precertification

We examined and summarized the FDA's proposed precertification and software as a medical device (SaMD) regulatory frameworks (4). To do this, we selected three digital pathology companies with publicized AI/ML-based products that would be categorized as SaMD under the FDA's frameworks. To perform our mock Excellence Appraisal and review determinations, we examined publicly available company and product descriptions, as well as news releases about the companies and their products obtained from the organizations' websites (5, 6, 7). Where appropriate, we also gave recommendations as to how these companies might demonstrate the "Excellence Principles" required of them.

"It's vital that companies stay on top of the new regulatory paradigms [...] to bring their products to market."

The FDA outlines two new approaches: one for organizational precertification that involves five "Excellence Principles" and one for review pathway determination for SaMD product approval that involves four risk categories (see Tables 1 and 2). In brief, the process begins with an Excellence Appraisal; here, the company must demonstrate a culture of quality and organizational excellence (CQOE), before receiving a precertification level based on its previous experience with SaMD. Next, the SaMD product's review pathway is

1. Excellence Appraisal	a) Company shows "culture of quality and organizational excellence" (CQOE)
	There are five Excellence Principles: **Product Quality:** Demonstration of excellence in the development, testing, and maintenance necessary to deliver SaMD products at their highest level of quality. **Patient Safety:** Demonstration of excellence in providing a safe patient experience and emphasizing patient safety as a critical factor in all decision-making processes. **Clinical Responsibility:** Demonstration of excellence in responsibly conducting clinical evaluation and ensuring that patient-centric issues, including labeling and human factors, are appropriately addressed. **Cybersecurity Responsibility:** Demonstration of excellence in protecting cybersecurity and proactively addressing cybersecurity issues through active engagement with stakeholders and peers. **Proactive Culture:** Demonstration of excellence in a proactive approach to surveillance, assessment of user needs, and continuous learning.
	b) Company receives precertification
	Level 1 Pre-Cert: Designed for companies with CQOE that have limited or no experience developing, delivering, and maintaining SaMD products. **Level 2 Pre-Cert:** Designed for companies with CQOE that have extensive experience developing, delivering, and maintaining SaMD products. *Level of Pre-Cert partly determines the premarket review pathway (see below).*

Table 1. Excellence Appraisal for the FDA SaMD Pre-Cert process.

2. Review Pathway Determination

a) SaMD evaluated for…

Clinical Decision Significance	
To treat or diagnose (high)	To provide therapy to a human body. To diagnose/screen/detect a disease or a condition.
To drive clinical management (moderate)	To aid in treatment by providing enhanced support to a safe and effective use of medicinal products or a medical device. To aid in making a definitive diagnosis. To triage or identify early signs of a disease or condition.
To inform clinical management (low)	To inform options. To provide clinical information by aggregating relevant information.

Clinical Severity State	
Critical (high)	Life-threatening states, requiring major intervention, and may not leave enough time for user to detect SaMD errors.
Serious (moderate)	Moderate progression, often curable states, may not require major intervention, and may leave enough time for user to detect SaMD errors.
Non-serious (low)	Slow or predictable progression, may not be curable but may be effectively managed, requiring minor intervention, and leaves enough time for user to detect SaMD errors.

b) SaMD receives risk categorization

	Treat or diagnose (Tx/Dx)	**Drive clinical management**	**Inform clinical management**
Critical	IV	III	II
Serious	III	II	I
Non-serious	II	I	I

c) Premarket review pathway

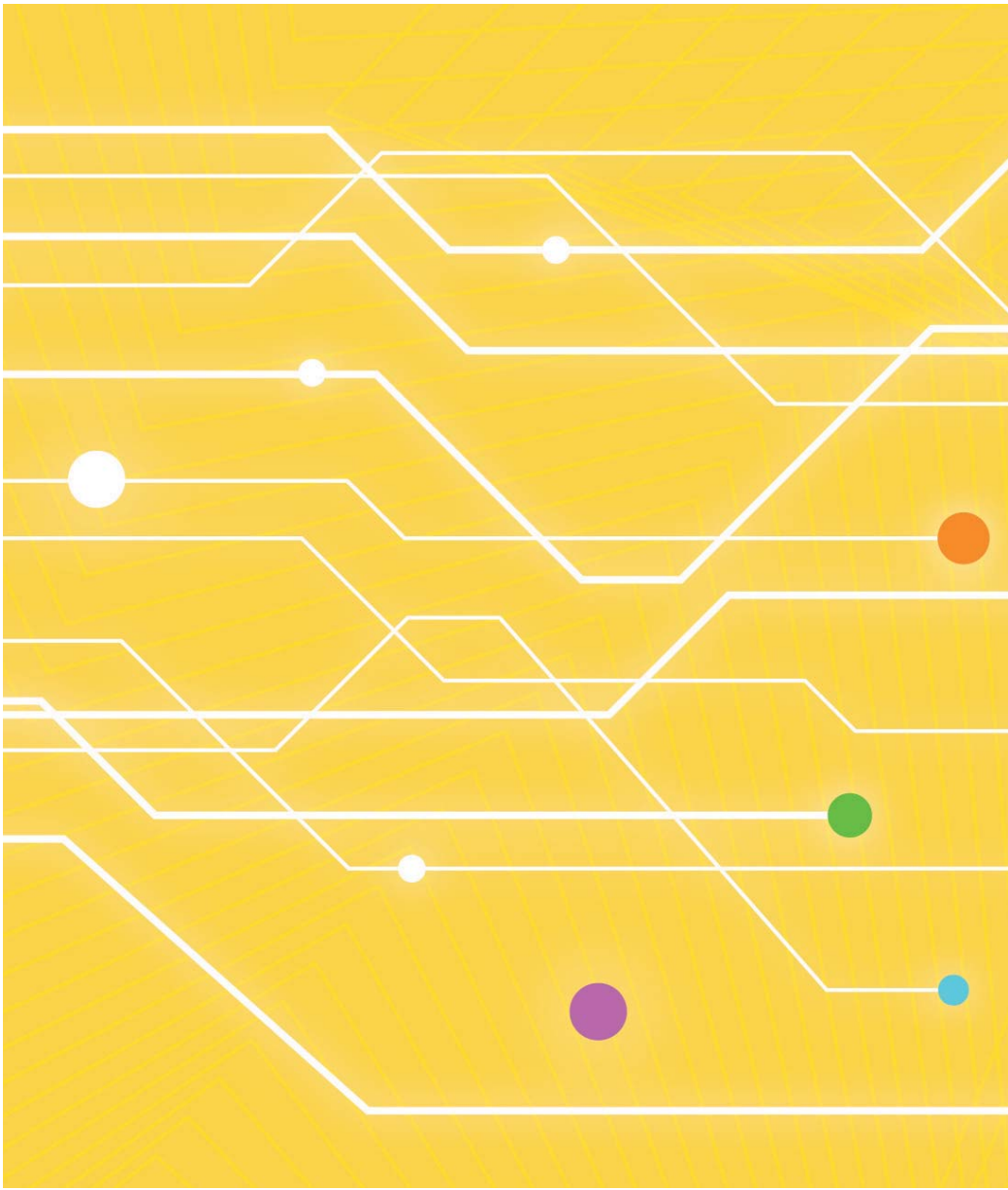
Risk category	**Severity and significance**	**Initial product**	**Major changes**	**Minor changes**
IV	Critical and Tx/Dx	Streamlined review (SR)	Streamlined review (SR)	No review (NR)
III	Critical and Drive		Level 1: SR Level 2: NR	
III	Serious and Tx/Dx			
II	Serious and Drive	Level 1: SR Level 2: NR		
II	Non-serious and Tx/Dx		No review (NR)	
II	Critical and Inform			
I	Non-serious and Drive	No review (NR)		
I	Serious and Inform			
I	Non-serious and Inform			

Table 2. Review Pathway Determination for the FDA SaMD Pre-Cert process.

From the FDA

"The FDA is encouraged by the interest expressed in our Digital Health Innovation Action Plan, including the Software Pre-Cert Pilot, as we seek to harness the power of real-world data to provide new insights into device performance and accelerate the development of AI/ML-based medical devices and services. Working together, this effort will support device makers in developing and maintaining cultures of quality and organizational excellence, which are fundamental to ensuring that patients have access to safe and effective medical devices, diagnostics, and cutting-edge digital health tools. Digital pathology is uniquely poised to leverage advances in imaging, computing, and information technology to expedite diagnosis and improve quality of care. We welcome feedback and engagement from all stakeholders as we work to build, test, and refine critical new regulatory approaches to address emerging technologies and improve the lives of patients."

Sara A. Brenner, Associate Director for Medical Affairs and Chief Medical Officer for In Vitro Diagnostics, U.S. Food and Drug Administration

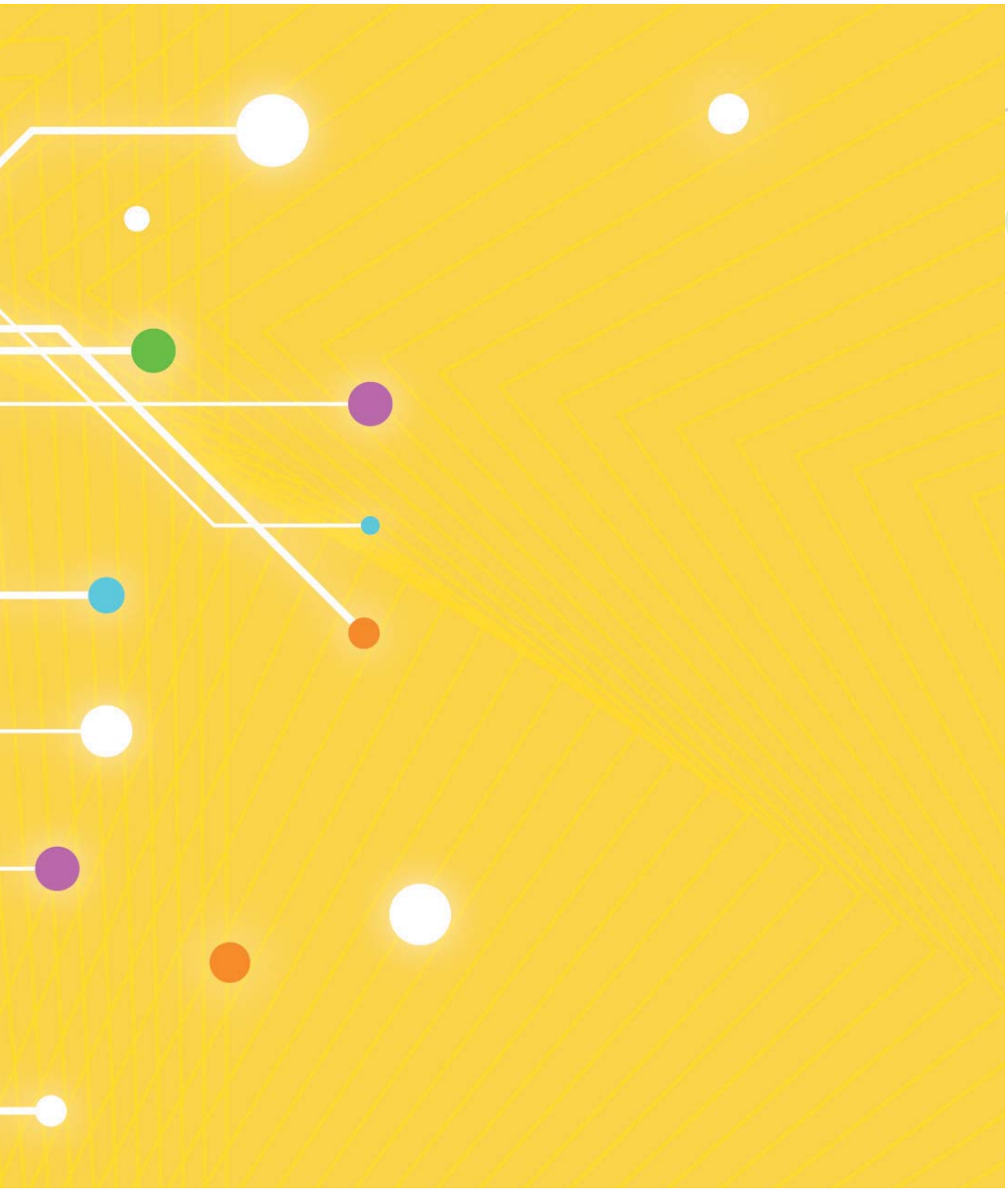


determined – a three-step process that involves evaluating its clinical decision significance and clinical severity state, giving it a risk categorization, and combining those factors to select the appropriate premarket review pathway.

The three companies we chose to examine for our mock Excellence Appraisal and review pathway determination were Paige (Modules), Huron Digital Pathology (Index & Search), and Proscia (DermAI). Ultimately, we categorized Modules as Type IV (highest risk) and Index & Search and DermAI as Type III. Under the traditional regulatory model, these products would all require burdensome premarket approval – but if these companies were precertified, even the highest-risk product would be eligible for streamlined premarket review.

Opinions and opportunities

Despite the clear advantages, however, none of the organizations we examined were compliant with precertification requirements (see tables online at

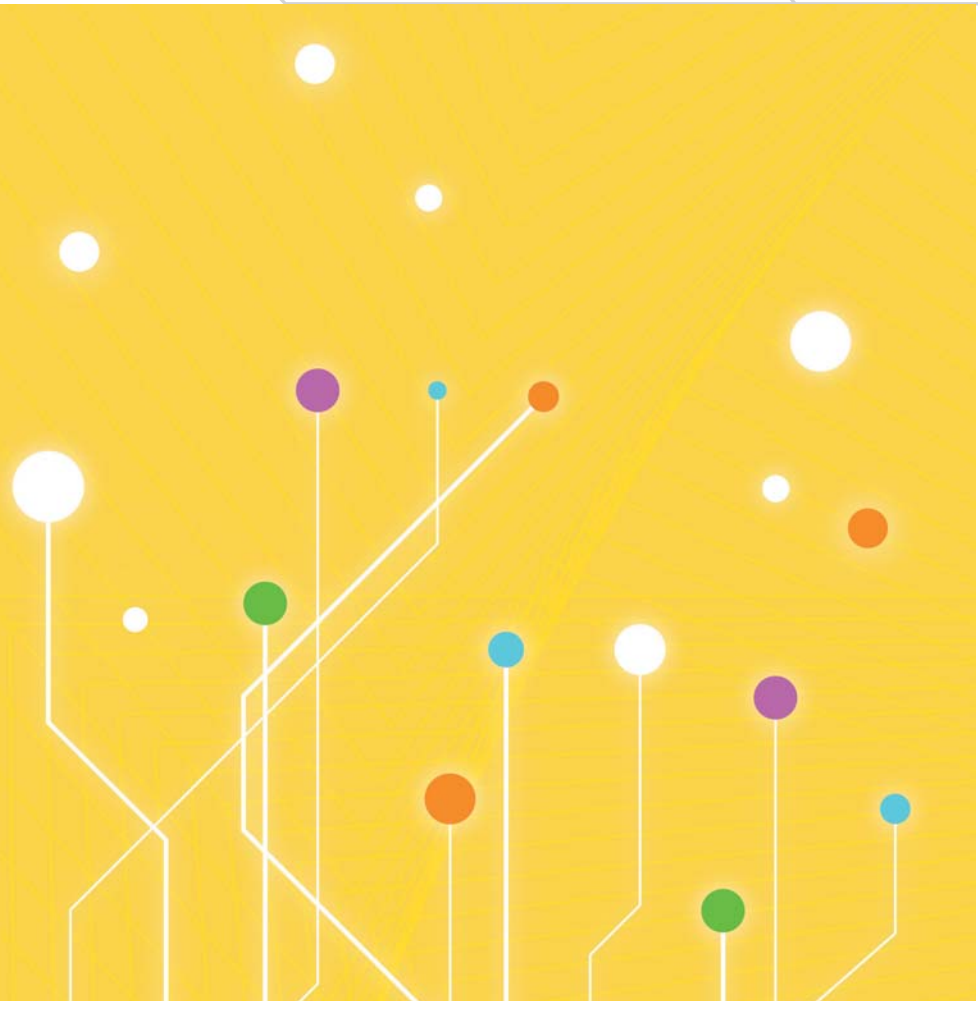


"The FDA is actively seeking participation from companies to join its Test Plan, with the goal of finding out more about the obstacles to real-world implementation."

tp.txp.to/midas/touch). Why? Most companies are not aware of the Pre-Cert program; they are instead familiar with the traditional established regulatory pathways, such as the 510(k), De Novo, or Premarket Approval (PMA). Companies have not kept up-to-date with future pathways that are being considered, developed, or even piloted. The Pre-Cert program is still a working model, and the FDA is still actively developing and updating the program. Therefore, there is no clear, finalized guidance on how to become compliant. However, the FDA is actively seeking participation from companies to join its Test Plan, with the goal of finding out more about the obstacles to real-world implementation. If companies are interested in the Pre-Cert program, we recommend joining the Test Plan; by collaborating with the FDA, they can establish the necessary knowledge and experience needed to become precertified once the program is finalized.

We are entering an era of "high-performance medicine" (8) in which advanced technologies, including AI, could dramatically amplify our natural human abilities to diagnose, treat, and manage patients. The FDA has taken the forward-thinking step of proposing new regulatory pathways to embrace the world of digital health. These pathways should allow companies to gain regulatory approval faster, enter the market faster, and ultimately increase and improve the digital diagnostic and therapeutic options available to patients.

But this is not a one-sided advance; digital pathology companies must also be proactive. The FDA sought



public comments on the two proposed regulatory frameworks (9, 10) – and yet, although these regulatory frameworks have a direct future impact on digital pathology, it is a field that is severely underrepresented in the public comments. When the Pre-Cert program first launched in 2017, the FDA's pilot program involved nine companies (11) – almost none of whom were in the pathology sphere. Now, the FDA is actively soliciting new companies to join their Pre-Cert Test Plan (12) – and we strongly encourage digital pathology companies to take advantage of this opportunity by volunteering test cases. If digital pathology is to thrive in the booming digital health market, companies need to be at the forefront of adapting to new regulatory changes.

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References

1. *MarketWatch, "Global digital health market is expected to attain a size of $223.7 billion by 2023" (2018). Available at: https://on.mktw.net/34jdbSk. Accessed October 31, 2019.*
2. *The Medical Futurist, "FDA Approvals For Smart Algorithms In Medicine In One Giant Infographic" (2019). Available at: https://bit.ly/2NsrOvJ. Accessed October 31, 2019.*
3. *S Gottlieb, "FDA Announces New Steps to Empower Consumers and Advance Digital Healthcare" (2017). Available at: https://bit.ly/2JBw9vB. Accessed October 31, 2019.*
4. *US FDA, "Developing a Software Precertification Program: A Working Model" (2019). Available at: https://bit.ly/2JDZFAL. Accessed October 31, 2019.*
5. *Huron Digital Pathology, "Huron Digital Pathology" 2019. Available at: https://bit.ly/2N5l6Nf. Accessed October 31, 2019.*
6. *Paige, "Paige" (2019). Available at: https://bit.ly/2qc5vCI. Accessed October 31, 2019.*
7. *Proscia, "Proscia" (2019). Available at: https://bit.ly/2Py4aRa. Accessed October 31, 2019.*
8. *EJ Topol, "High-performance medicine: the convergence of human and artificial intelligence", Nat Med, 25, 44 (2019). PMID: 30617339.*
9. *Regulations.gov, "Fostering Medical Innovation: A Plan for Digital Health Devices; Software Precertification Pilot Program" (2019). Available at: https://bit.ly/32zxqKi. Accessed November 11, 2019.*
10. *Regulations.gov, "Proposed Regulatory Framework for Modifications to Artificial intelligence/Machine Learning (AI/ML)-Based Software as a Medical Device (SaMD) – Discussion Paper and Request for Feedback" (2019). Available at: https://bit.ly/2qG6yel. Accessed November 11, 2019.*
11. *FDA, "FDA selects participants for new digital health software precertification pilot program" (2017). Available at: https://bit.ly/2oyk96C. Accessed October 31, 2019.*
12. *FDA, "Digital Health Software Precertification (Pre-Cert) Program: Participate in 2019 Test Plan" (2019). Available at: https://bit.ly/2N6IEkZ. Accessed October 31, 2019.*

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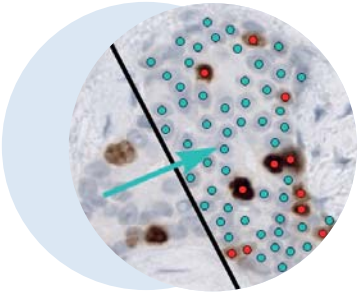

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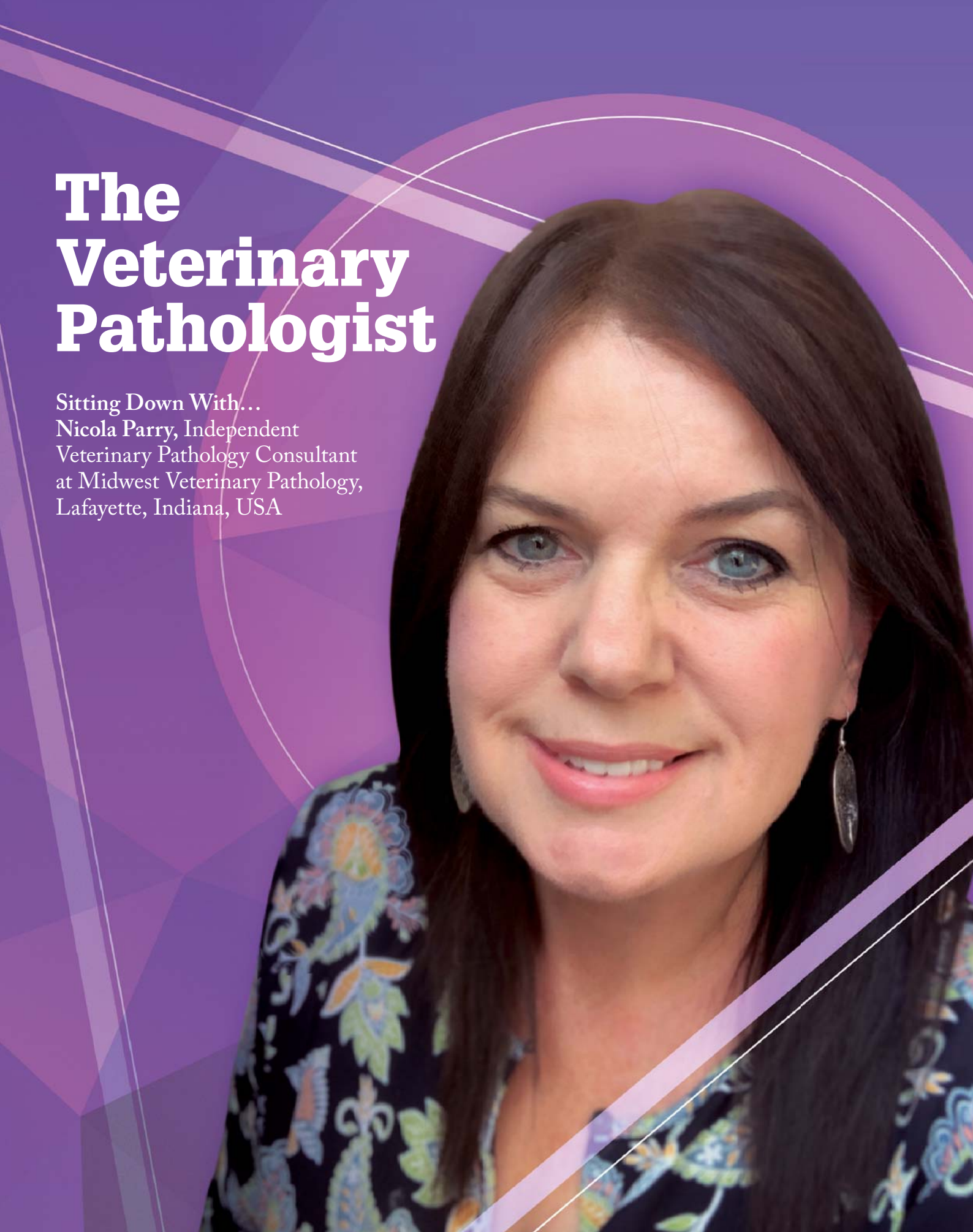
The Veterinary Pathologist

Sitting Down With…
Nicola Parry, Independent Veterinary Pathology Consultant at Midwest Veterinary Pathology, Lafayette, Indiana, USA



What led you to a career in animal health?

Even as a little kid, I always wanted to be a vet. Apparently, I was never the stereotypical little girl who played with dolls – I only wanted animal-related toys! My desire to be a vet stemmed from more than just liking animals, though. I grew up with a granddad who loved animals and gardening, which often led him to find injured animals outside. I'll never forget watching him warm a hypothermic fledgling. He rigged up his own double boiler system by stacking two pans, added warm water to the lower pan, and placed the bird in a container suspended in the upper one so it would benefit from the warmth below without overheating. His resourcefulness and practicality inspired my interest in becoming a vet.

Why specialize in pathology?

Before starting vet school, I had intended to work with small animals (predominantly dogs and cats) as a general practitioner – but my training opened my eyes to the broad range of specialty areas in which vets can work. I really enjoyed the training and found many areas of interest, including pathology. I had worked in the pathology department before starting vet school and continued to do so in school holiday breaks.

I enjoyed discovering the wide reach that pathology has both within and outside the veterinary profession; it's a specialty that cements many areas of patient care in daily practice. In addition to its key role in diagnostics, pathology protects and advances both animal and human health – especially through the critical involvement of veterinary pathologists in evaluating the safety of drugs and medical devices, and through their work in public health and One Health initiatives. Pathology also serves as an important link between the basic and clinical sciences.

For me, the best part of my job is knowing how integral it is to patient care and how my daily work interfaces with that of fellow vets and professionals in other disciplines. Veterinary medicine is truly a team sport and, in diagnostic pathology practice, I get to communicate with a range of professionals. On occasions, I might communicate directly with an animal's owner. And, because I also work in research pathology, I frequently communicate with researchers about their projects.

How has veterinary pathology changed over the course of your career – and how might it continue to evolve?

When I look back over the past 20 years, I think the biggest changes relate to the advances we've experienced in science and medicine. Improvements in areas such as genetics, genomics, and proteomics have improved our understanding and diagnosis of many cancers and other diseases. Advances in technology outside the medical field have also affected the practice of pathology. Importantly, digital pathology, or virtual microscopy, has flourished, especially since the commercial introduction of whole-slide imaging (WSI). At the same time, improvements in computational technology and storage have allowed us to efficiently process large WSI datasets.

But we still need to learn a lot about things like the genetics and genomics of animal cancers or the role of epigenetics in animal diseases. I think growing efforts in these areas will allow researchers to develop tools to improve our understanding, and I think this will have significant implications for advancing the use of precision medicine in our animal patients. For example, we have only one targeted cancer therapy available for dogs right now – but no doubt that will change.

Specialized imaging technologies would also benefit our profession. Methods like imaging flow cytometry and histology-directed imaging mass spectrophotometry are currently too expensive for routine use, but they are used in research and may eventually enter the veterinary diagnostic space. Innovations in artificial intelligence will also eventually help to support the work that we do by improving our decision-making in certain areas and helping us work more efficiently.

What has been the proudest moment of your career?

This year, I was awarded Fellowship of the Royal College of Veterinary Surgeons (RCVS), which is given in recognition of outstanding contributions to the veterinary profession. It's an amazing honor, and I feel grateful and humbled to have received it.

What has been your most unexpected case?

In the first year of my residency at the University of Pennsylvania School of Veterinary Medicine, a giraffe at Philadelphia Zoo died unexpectedly. The zoo's pathologist was out of town, so they called our department and I went with a couple of other residents to help with the postmortem. As you can imagine, performing a postmortem on a giraffe is a little more complicated than performing one on a horse. Although the principles of the examination are the same, the sheer size of the animal requires a supersized, all-hands-on-deck approach. I think we had at least eight people working as a team on that giraffe. And, although we pathologists are very accustomed to using power tools to complete postmortem examinations, an animal the size of a giraffe certainly raises the stakes on that front. Let's just say this was the first time I'd ever used a chainsaw during an examination!

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