APRIL 2020 # 64

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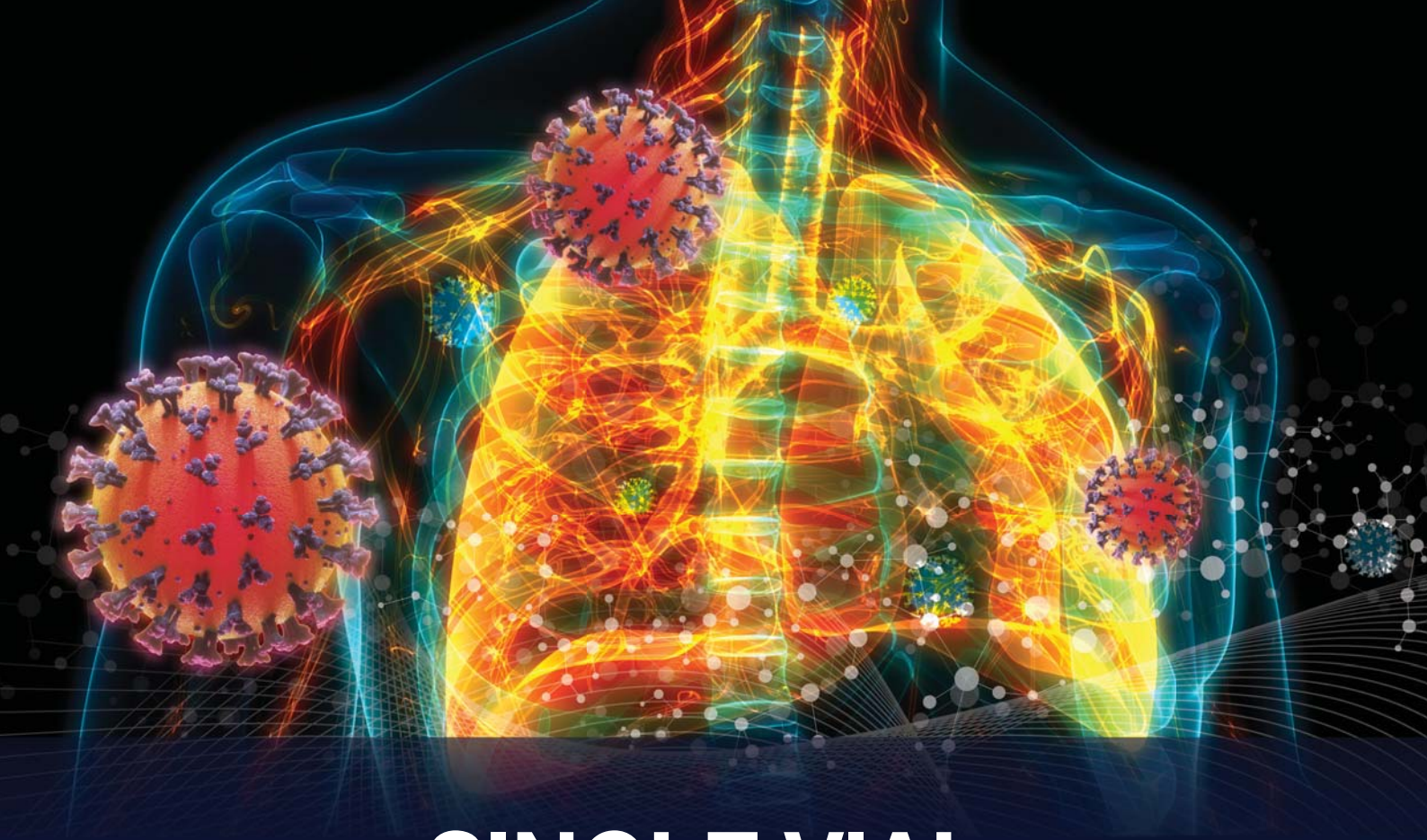

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A Letter From Lockdown

With a pandemic at hand, laboratory medicine professionals must no longer be hidden heroes

As a child in the Canadian wilderness, I went survival camping every year in the Rockies – in one of the highest-density bear populations in North America. The park rangers taught us how to tell the difference between black bears and grizzlies (far more dangerous): climb a tree. If the bear climbs up after you, it's a black bear. If it stays at the bottom and shakes you down, it's a grizzly.

But there's no such risk stratifier for unprecedented events like the COVID-19 pandemic that's currently gripping most nations of the world. How could we be certain of the risk posed by a virus like SARS-CoV-2 without adequate tools for testing and tracking? How could we count the number who had been infected and survived if we didn't have retroactive antibody tests? And – now that these tools are beginning to gain approval and reach end users – how can we be sure of what we think we know about COVID-19 if we're not able to test everyone with symptoms of the disease?

The headlines are full of conversations about capacity. How many ventilators do we have? How many hospital beds are available? At what point must we begin to decide which patients warrant hospitalization, medication, ventilation? Less commonly discussed is the laboratory's capacity to take on testing for up to 60 percent of the population (1) – and that's on top of its regular workload. Laboratory staffing shortages have been reported for years and burnout levels were high long before COVID-19 was on the horizon. Now, pathologists and laboratory medicine professionals are being asked to deliver long hours in risky circumstances for a patient population that may never be aware of the lab's role in their care – and in helping to stem the tide of a pandemic that has claimed tens of thousands of lives.

The cynics among you may ask, "How is that different to any other time?" But now, more than ever, the lab is proving its importance not just to current patients, but to all seven and a half billion people on Earth. And now, more than ever, it's our job to listen to the lab's results and recommendations, and to take them seriously. That's why I'm writing this editorial from lockdown – where I'll be staying until the laboratory medicine and public health professionals I trust tell me it's safe to leave.

Michael Schubert
Editor

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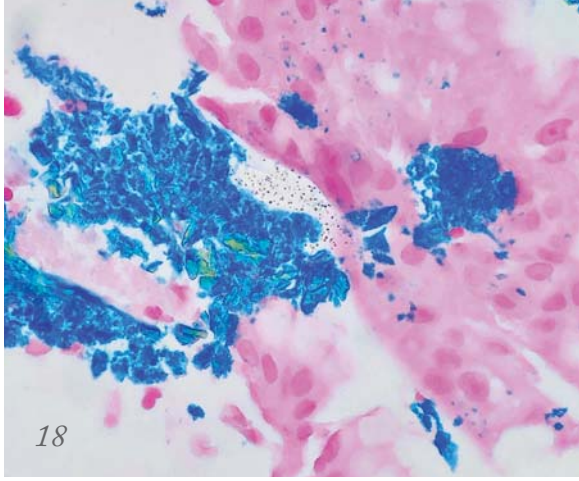

On The Cover

"Happy Faces." See page 17 for more information.

Upfront

In My View

From The ASCP

Feature

In Practice

NextGen

Profession

Sitting Down With

the Pathologist

ISSUE 64 - APRIL 2020

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Upfront

Research
Innovation
Trends

In Focus: Diffuse Large B-Cell Lymphoma

Key features of diffuse large-B cell lymphoma in the leukemic phase

In non-Hodgkin's lymphoma, the most common type of general lymphoma, tumors develop from the lymphocytes. Diffuse large B-cell lymphoma (DLBCL) accounts for 30–40 percent of newly diagnosed adult non-Hodgkin's lymphoma, making it the most prevalent of these cancers. But DLBCL exhibits a key difference to other lymphomas: it rarely presents in the leukemic phase (1).

Lymphoma differs from leukemia by its primary site of disease, which is typically peripheral lymphoid tissue rather than blood or bone marrow. The presence of neoplastic lymphoid cells in lymphoma indicates that the peripheral blood and bone marrow have been infiltrated, ultimately giving rise to the leukemic phase. Although DLBCL patients rarely present with leukemic transformation, those who do frequently exhibit a high tumor burden, involvement of extranodal sites, and high lactate dehydrogenase levels.

DLBCL is microscopically characterized by the presence of large, atypical lymphoid cells; round, irregular vesicular nuclei with prominent nucleoli; and a moderate-to-abundant amount of pale blue cytoplasm. Immunophenotypically, DLBCL is positive for B-lineage markers, such as CD20, and variable immunoglobulins. Germinal center markers, such as CD10 and BCL6, are positive in 40–60 percent of cases; post-germinal center markers, such as CD38 and MUM1, are also expressed.

The basic pathogenesis of leukemic transformation in lymphoma, and the degree to which it occurs among different lymphomas, is still unclear. One possible mechanism for the migration of atypical lymphoid cells to the bloodstream is the expression of adhesion molecules, although this still requires validation.

Patients with DLBCL presenting in the leukemic phase are prone to extranodal and bone marrow involvement. One study of 29 patients uncovered the involvement of spleen in 62 percent, lung in 41 percent, liver in 21 percent, bone in 17 percent, cerebrospinal fluid in 14 percent, and bowel in 7 percent of cases (2). Such patients have a higher chance of early complications and death. Fortunately, treatment with anthracycline- and rituximab-based regimens is effective and associated with a four-year survival of approximately 50 percent.

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INFOGRAPHIC

Hematology: Challenges and Opportunities

Data from a recent hematology laboratory workforce survey

The UK's Royal College of Pathologists recently conducted a survey of the hematology laboratory workforce to identify challenges and shortfalls (1).

THE RESULTS?

Hematology faces difficulties in the near future, with significant increases in workload, limited time in the laboratory, and a lack of new trainees to fill current and predicted vacancies.

Increases in hematology testing

- Full blood counts:25% increase
- Hematinics: 20-30% increase
- Bone marrow aspirates and trephine biopsies: 20% increase
- Immuniphenotyping: 100% increase

* based on data from one representative department.

BUSINESS IN BRIEF

We take a look at this month's laboratory medicine business news

Up to (Genomic) Speed

Advances in sequencing technology have produced an unprecedented amount of genomic data, now doubling every seven months. Genomic analysis is typically a computational bottleneck in the pipeline – but Parabricks has recently developed a GPU-based solution to analyze whole genomes in under a minute (1).

T In the Cloud

The FDA has awarded a five-year, US$20 million contract to DNAnexus to power the precision FDA Collaborative Omics Environment in the Cloud. Launched in December 2015, precisionFDA has led to advances in regulatory science for NGS-based drugs and devices. It unites government, academia, and industry to provide a community platform for NGS assay evaluation (2).

Standard of Care

Laboratories have a key role to play in diagnosing cases of SARS-CoV-2 – and well-defined standards are crucial for test validation. Bio-Rad Laboratories have now launched a SARS-CoV-2 Standard that contains synthetic COVID-19 RNA transcripts and human genomic DNA. This allows labs to test molecular assays, including extraction, amplification, and detection of the virus (3).

A New Horizon

The Human Protein Atlas (HPA) will use Horizon Discovery's CRISPR-edited knockout cell models in its Cell Atlas program, which aims to improve our understanding of genetic factors in disease. The new partnership will expand open-access resources and boost global genetic research (4).

A Molecular Touch

A method for rapidly detecting somatic mutations from tissue sections has proven successful in colorectal cancer. The Biocartis Idylla system runs cartridge-based assays that facilitate a "molecular-touch" preparation method in which filter paper is pressed against fresh tissue in the grossing room; it can return somatic mutation results even before the tissue has been processed (5).

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Behind the COVID-19 Curve

A slow diagnostic response to the coronavirus outbreak put the USA on the back foot

Efforts to ramp up diagnostic testing for SARS-CoV-2 in the USA have been hampered after a slow response to the outbreak. The original test kit distributed by the Centers for Disease Control and Prevention (CDC) contained a faulty reagent that, in many cases, reacted to the negative control, rendering results invalid (1). Hospitals and academic labs across the country were restricted from developing their own test kits until February 29.

Since then, testing has moved away from the CDC and state labs toward hospitals and commercial companies – and, as of March 14, labs using the CDC assay are no longer required to submit samples for confirmation. But where does that leave the USA? As of March 18, 37,824 tests had been conducted (2), leaving the country lagging behind others. Health officials hope that new drive-through test centers and quicker processing will help them hit testing targets.

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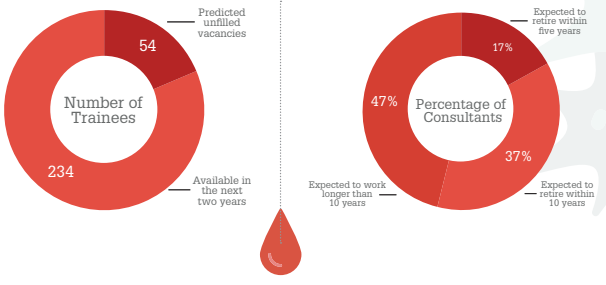
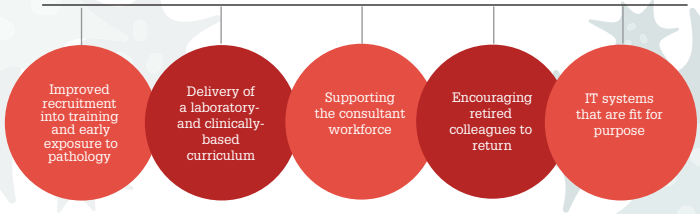
Predicted hematology workforce changes



What is needed?



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SPECIAL SERIES
Infectious Disease

What's Up With Bats?

Viruses that originate in bats – such as the 2019 novel coronavirus – exhibit unusual virulence… but why?

Like its predecessors – SARS, MERS, and Ebola – the 2019 novel coronavirus has been making headlines for its high transmissibility and climbing fatality. Although COVID-19 doesn't yet spark the same degree of alarm as those viruses, it does have one thing in common with them: its potential chiropteran origins.

In an effort to understand why zoonotic viruses that originate in bats are so dangerous when transmitted to humans, researchers from the University of California, Berkeley, studied virus infectivity in bat cell lines (1). Their findings? Bats have highly robust antiviral defenses – a phenomenon that prevents pathogens from damaging cells. In response, bat viruses often develop rapid replication and transmission so that they can mount an attack before the bat's defenses can be raised. "The bottom line is that bats are potentially special when it comes to hosting viruses," said study author Mike Boots in a recent press release (2). "It is not random that a lot of these viruses are coming from bats. Bats are not even that closely related to us, so we would not expect them to host many human viruses. But this work demonstrates how bat immune systems could drive the virulence that overcomes this." Additionally, thanks to the need to protect their tissues from high metabolisms and extreme levels of physical activity, bats exhibit an anti-inflammatory response that can protect them from their own defense mechanisms.

When powerful bat viruses enter another organism – for example, a human – that lacks these unique protective mechanisms, the result can be catastrophic. Worse yet, the more a bat's habitat is disturbed, the more likely it is to shed viral particles that can be transmitted to other organisms. The lesson? Understanding the transmission of viruses from bats to humans can help us predict and prevent outbreaks – and protecting bats' environments means protecting ourselves.

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Yes, We Gly-Can!

Glycan recognition assays could improve COVID-19 diagnosis

A new test seeks to identify viruses, including influenza and SARS-CoV-2, by glycan recognition. Many viruses invade humans via the respiratory tract, whose cells are coated in glycans that the viruses recognize as part of their infectious process. By reversing this process using an artificial glycan receptor, diagnostic devices can capture the virus, yielding a yes/no answer in under 20 minutes. But speed is not the only advantage over PCR-based diagnostic methods; the device is also hand-held, meaning it can be used at the point of care, and glycan-based testing is unaffected by changes to the virus' genetic code.

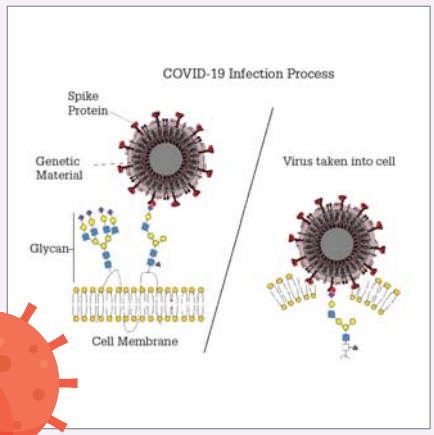

IMAGE OF THE MONTH

The Kids' Club

X-WOW's Kids' Club introduces Nigerian children to the world of microscopy, touring schools in Abuja and allowing them to explore the wonders of microbiology

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

QUOTE of the month

"With more than two million new cases identified each year and as many as one in eight women diagnosed with breast cancer, it is a disease that impacts many lives. But with more people leaving the professions that help identify cancer than joining, it is vital that we empower those left with the tools to do their jobs as effectively as possible, and AI technology can do just that.."

Joseph Mossel, CEO and co-founder of Ibex Medical Analytics

This Time for Africa

How the African Centre for Translational Genomics aims to boost genetic research and inspire the next generation of scientists

A lack of genetic diversity in genomic research poses a significant threat to the future equitability of precision medicine (1). Genetic studies predominantly focus on groups of European ancestry – but a new African initiative is set to encourage translational genomics research in an area frequently overlooked. By providing grants, fellowships, internships, and training for researchers and trainees, the African Centre for Translational Genomics (ACTG) aims to empower the next generation of African scientists.

Its first project, the Non-Communicable Diseases – Genetic Heritage Study (NCD-GHS), will recruit over 100,000 Nigerians to better understand the genetic basis of highly prevalent NCDs, such as diabetes and chronic kidney disease, within the nation. "The NCD-GHS has the potential to rewrite the playbook of genomics research, where African scientists will be at the forefront of new discoveries for conditions that affect Nigerians and people worldwide," said Abasi Ene-Obong, CEO of 54gene, the company behind the ACTG (2).

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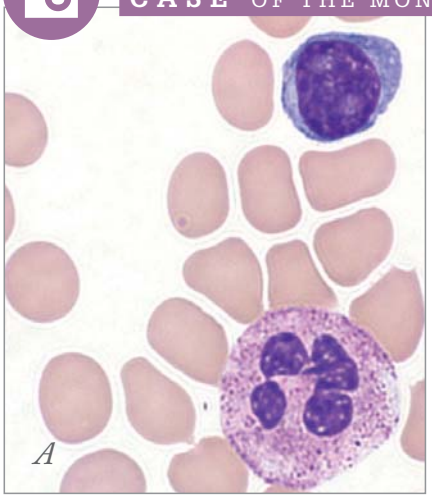
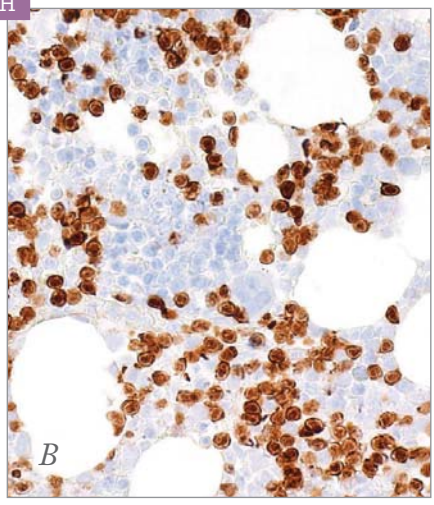
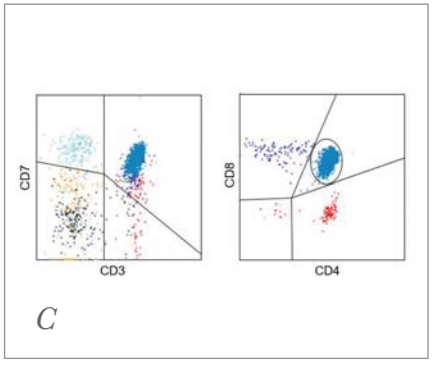
CASE OF THE MONTH







A 59-year-old man presented with left upper quadrant discomfort and was found to have hepatosplenomegaly. Complete blood count (CBC) showed WBC of 19.0 K/μL. Red blood cell indices and platelets were within normal limits. The peripheral blood differential showed 72 percent lymphocytes, 23 percent neutrophils, and 4 percent monocytes (A). A bone marrow biopsy demonstrated diffuse interstitial involvement by small lymphoid cells, comprising approximately 30 percent of bone marrow cellularity. TCL-1 immunohistochemical stain was performed on the bone marrow core (B). Flow cytometric analysis (C) and FISH study for TRA/D locus (D) are shown.

What is the most likely diagnosis?

a) T-cell large granular lymphocytic leukemia
b) Adult T-cell leukemia/lymphoma
c) Mycobacterial infection
d) Sezary syndrome
e) T-cell prolymphocytic leukemia
f) Peripheral T-cell lymphoma, NOS

Answer to last issue's Case of the Month…

c) Mycobacterial infection

Sections demonstrate hypercellular bone marrow; sheets of large histiocytes (Image A) appear to have a "crinkled tissue paper" quality to their cytoplasm (Image B). A Ziehl-Neelsen stain highlighted numerous intracellular acid-fast bacilli (Image C). Bone marrow aspirate cultures were positive for *Mycobacterium avium*.

Submitted by Anna B. Owczarczyk, University of Michigan, Ann Arbor, Michigan, USA.

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To register your guess, please go to http://tp.txp.to/0420/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.

The African Imperative

The importance of diversity in biobanking and genomic data

By Aminu Yakubu, Vice President of Research Planning and Ethics at 54gene, Lagos, Nigeria

Humans are incredibly diverse. It stands to reason that this diversity would be reflected in our susceptibility and response to disease. Some illnesses are more prevalent in certain populations than in others. Not all populations respond similarly when treated in the same way for the same disease. Some populations even have higher survival rates than others.

Our genes have specific sequence variants that could explain these differences. By exploring these variants, we could learn how to better manage diseases in different populations, improve patient treatment selection and outcomes, and identify gene targets for the development of new drugs. However, one of the most widely used reference genomes applied to achieve these aims is largely comprised of genes from a single human being (1). Although more representative reference genome datasets are being developed, many are limited in diversity and representation – and others are developed ab initio to serve only a particular population group.

This limited diversity is even more concerning for those of African descent. Although these populations have the highest genetic diversity of all, they only provide about three percent of all genetic data used for research and drug discovery (2). This scenario does a great disservice to humanity. First, it has the potential to further exacerbate the disparity in disease morbidity, because those developing drugs from new target genes may lack the information needed to make such drugs effective for African populations. Second, the world is being denied access to novel genetic variants from the huge diversity inherent in African populations, as seen with the 300 million DNA letters from African populations reported missing from the human reference genome in 2018 (4). Equally, some 9.5 million variations identified in African populations have not been previously reported at all (5).

Some of these genetic variations could have informed the identification of valuable new drugs. For example, a mutation discovered in one African individual inactivates a gene that has been implicated in high cholesterol levels – and its identification has led to a drug used to better manage this condition (6). Another recently identified variant, said to have the potential to affect glycated hemoglobin levels, may inform research into better ways of managing diabetes (5) – a condition affecting many underrepresented populations. The findings of new variants among non-European populations, in particular those that can inform drug discovery, are a clear indication of the importance of diversity in genomics research. This diversity is achieved in two ways – by including more genomics data from underrepresented populations in research and drug discovery efforts and by further enriching the human reference genome to inform better imputation of genetic variants from other non-European populations and identification of novel variants.

New biobanking facilities and other efforts by academics to increase access to genomics data from African populations will go a long way towards addressing this gap. But there are important considerations in taking biobanking and genomics research to scale in underrepresented populations. African researchers and communities, for example, remain skeptical of the intent of research studies for which samples are collected and shipped to other countries. There are concerns about the use of the samples beyond the stated intent and researchers feel a sense of disempowerment once the samples leave the shores of their countries.

Such concerns about social value and benefit remain at the core of expectations from biobanking and genomics research – and yet, the research does not promise immediate benefit to participants. To address this, research efforts must include some degree of individual and institutional capacity building to sustain and drive future research by African scientists.

Overall, one thing is clear: if the world is to optimize the potential of the human genome in improving health, underrepresented populations, especially those from Africa, must be included. And not only in terms of their genomic data;

researchers from underrepresented areas must be involved in these efforts. And, last but not least, African governments must provide an enabling environment, appropriate regulations, and support for biobanking and genomics research. This is vital for not only addressing the limited reach of current international funding, but also creating a sustainable industry in the long run.

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A Model Career

Role models can have a powerful influence on career choice – so we must strive to be good ones

By William E. Schreiber, Clinical Director of Chemistry at LifeLabs, Professor of Pathology and Lab Medicine at The University of British Columbia, Canada, and Past President of the American Society for Clinical Pathology

Pathology is an unpopular career choice for graduating medical students in the United States; in last year's National Resident Matching Program, only 201 graduates were matched to an available 600 positions. But that's nothing new – the numbers were not much better in any match result from 2015 onward.

Accompanying this training dilemma is a 17 percent drop in the number of practicing pathologists in the USA between 2007 and 2017. Pathologists now represent 1.43 percent of all physicians in the USA, down from 2.03 percent just a decade earlier (1, 2).

This seems like an appropriate time to stop for a minute and ask ourselves i) how we decided on a career in pathology, and ii) what we can do to address the current situation.

Students make these choices with less than complete information. They are heavily influenced by what they see in the medical school and hospital settings, what they hear from fellow students, and even what they watch on television. Forget everything you learned from residency onwards; what influenced you to select this field?

"Pathologists play many roles in the medical system, and we can show off those talents to prospective recruits."

Based on several decades as an educator, including stints as a residency director and associate dean for undergraduate medical education, I have developed my own theory. During their journey through medical school, students are exposed to numerous faculty members. Some of these physicians leave a lasting impression of what it means to be an excellent doctor. Role modeling is a powerful way to teach medicine and influence behavior.

Think about the instructors and practitioners who impressed you with their knowledge, skills, compassion and wit. Were any of them pathologists?

If we want more applicants to pathology programs, let's give them something to admire. Pathologists play many roles in the medical system, and we can show off those talents to prospective recruits. Because the field is so broad, summer placements and elective rotations can be tailored to a variety of interests – everything from community pathology to academic research. It's not about content; it's about modeling confidence, passion, and professional success.

The message to department heads should be clear: get your best teachers and practitioners to take medical students for a month, a week, or even a day, so that they can see pathologists at the top of their game.

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The Future of Microscope Imaging

Fully integrated, digitized systems will yield more information than ever before

By Jürgen Reymann, Product Manager Digital Platform, Leica Microsystems, Germany

The science of microscopy is hundreds of years old. The first compound microscopes were made in Europe in the early 1600s – and, since then, the field has steadily evolved. Each advance has brought continuous improvement in quality, accuracy, and efficiency for life science research. In the past, the microscope was used purely for raw data acquisition – but, today, sophisticated algorithms support scientists in the interpretation of images, providing immediate insights. In the future, I anticipate that the microscope will likely be fully integrated and digitized, with intelligent solutions that allow scientists in a laboratory to more fully visualize what is happening throughout a biological sample. Although optics will always remain a key component in microscopy, the image itself is now only one part of the process. More important are the technological advances being made to provide scientists with visual information and interpretations to which they may otherwise have remained blind.

Key to the growth of modern microscopy is our evolving ability to clearly and accurately visualize samples in three dimensions – which comes mainly from advances in software and graphical processing that improve our ability to capture, store, and examine complex 3D data. Imaging beyond two dimensions remains difficult because of the need to properly prepare the sample and optimize the technology to acquire and transform the data – but imagers are being developed to address those challenges. Novel software removes unwanted signals from out-of-focus regions of the specimen to reveal the in-focus region of interest, automatically increasing the visibility of structures without any manual real-time modifications. Such processing minimizes modification of the raw sensor data from the region of interest, preserving the image structure and other parameters while minimizing user interaction. The resulting precision and reliability offer reproducible and statistically relevant results.

In a similar vein, manufacturers are developing solutions for extracting as much information as possible from samples. Confocal laser scanning microscopy is the standard for true 3D-resolved fluorescence imaging and, together with modern technologies, helps researchers extract as much information as possible from images. However, as with all imaging systems, physically caused diffraction can still lead to blur, reducing the effective resolution and causing misplaced imaging of the exact position of individual photons. Additionally, biological sample background noise means that faint details of the raw data close to the noise level might be hard to extract. These effects can be displayed by the triangle of microscopy, whose three components – resolution, speed, and sensitivity – are incompatibly located at each corner of the triangle. Increasing one of the accessible areas decreases the others accordingly, so a system that aims to obtain true images must infiltrate these limits in near real time and "push the corners of the triangle." Ideally, such a system would be automated for inexperienced users, but allow full control for those who wish to fine-tune each parameter individually.

"I anticipate that the microscope will likely be fully integrated and digitized, with intelligent solutions that allow scientists in a laboratory to more fully visualize what is happening throughout a biological sample."

In my view, the future of microscope imaging hinges on the development of systems that enable a user to precisely and confidently visualize samples in 3D. Future microscope systems will likely be fully integrated and digitized, with intelligent software solutions that give an unprecedented look into what is happening throughout a biological sample. The new information will be an asset when it comes to big data, because a larger sample base will allow researchers to combine results from different experiments and identify previously unknown rules. Such capabilities will not only spearhead a new age of scientific imaging and fundamentally change the way that researchers work when imaging model organisms, tissue sections, and 3D cell cultures like organoids; they will also optimize and further evolve what is already in place.

AI's Evolving Role

A veterinary pathologist's perspective on how AI can support pathology

By Gillian Beamer, Assistant Professor, Department of Infectious Disease and Global Health, Tufts University's Cummings School of Veterinary Medicine, North Grafton, Massachusetts, USA

I am excited that AI tools are becoming widely available to extract information from experimental histopathology samples. In research settings, AI has many advantages over visual scoring and manual annotation – in particular, eliminating some tedious and time-consuming tasks; reducing inter-pathologist variability; and offering greater capacity to analyze archived samples. I've started to train, validate, test, and use my own algorithms to rapidly identify and quantify regions of interest within *Mycobacterium tuberculosis*-infected lungs. AI can speed up data acquisition – and, unlike human pathologists, algorithms happily operate 24/7. This means that I can set data-extraction and low-level analytical tasks to run overnight. AI cannot replace a pathologist's interpretation and intellectual contribution regarding mechanisms of disease or hypothesis generation and testing. However, the two – human intelligence and artificial intelligence – can certainly complement each other.

After training and validation, algorithms can detect, quantify, and spatially locate tissue, cell, and subcellular features. In research settings, pathologists often score, grade, or quantify visual changes in tissues where the diagnosis is already known. Many research pathologists spend a substantial amount of time quantifying patterns, rather than establishing diagnoses. For example, in my own research laboratory we study host responses to *M. tuberculosis*. All samples come with a diagnosis: tuberculosis. Similar scenarios occur across many research fields each day. A major benefit of AI for research pathology is automatic recognition and quantification of visual information. Thus, AI algorithms can transform complex visual patterns into rich, quantified data sets that can be rigorously analyzed by statistical or machine learning methods. A second benefit is that AI doesn't need sleep or caffeine.

Like in human medicine, the emerging use of AI in veterinary medicine is a disruptive technology that needs early adopters to gather data and feedback in testing phases, critical evaluation of the pros and cons, and a rational path forward. All aspects of digital pathology, including AI, are now being examined by our professional organization, the American College of Veterinary Pathologists. We are engaging in discussions across many sectors: industry, academia, and diagnostic and research laboratories. We have challenges to be addressed and overcome. Some of those challenges are physical or resource-related: access to equipment (scanners, servers, image-sharing software); hiring additional staff to perform and quality-control scans; and more. Other barriers are within our minds: fear of the unknown; fear of losing jobs; fear of becoming obsolete. These are scary concepts that have no easy solutions.

In our profession, we have realized that faculty who are training veterinary pathology residents need reliable information on digital pathology and AI. They need equipment and time to train themselves to become comfortable using it. And they need to understand the limits of this new tool. What I find interesting and exciting is that current trainees and recently boarded pathologists have found and adopted AI on their own through other resources. Some have produced and tested algorithms of their own; others are skilled coders who know more than their teachers (which I think is a great thing). The future of digital and computational pathology is bright, and education is the key. We must educate both ourselves and the next generation.

"Like in human medicine, the emerging use of AI in veterinary medicine is a disruptive technology that needs early adopters to gather data and feedback in testing phases, critical evaluation of the pros and cons, and a rational path forward."

Laboratories in the Age of the Pandemic

We must work together to fight the outbreak of COVID-19

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

In modern times, we have never before seen a global crisis like the current coronavirus outbreak, and never has the laboratory been more central and critical to healthcare than it is today. As pathologists and medical laboratory scientists, we are at the epicenter of the pandemic as we strive to keep our patients – and ourselves – safe. As we try to slow the spread of COVID-19, we must take extraordinary measures around the world to do our part for patient care – and we must act as a cohesive unit. Although the pathology and medical laboratory professional community often feels fractured, now is the time for us to band together, share knowledge with one another, and be in constant communication with our clinical care colleagues. In doing so, we provide the critical information needed to stem the tide of the outbreak.

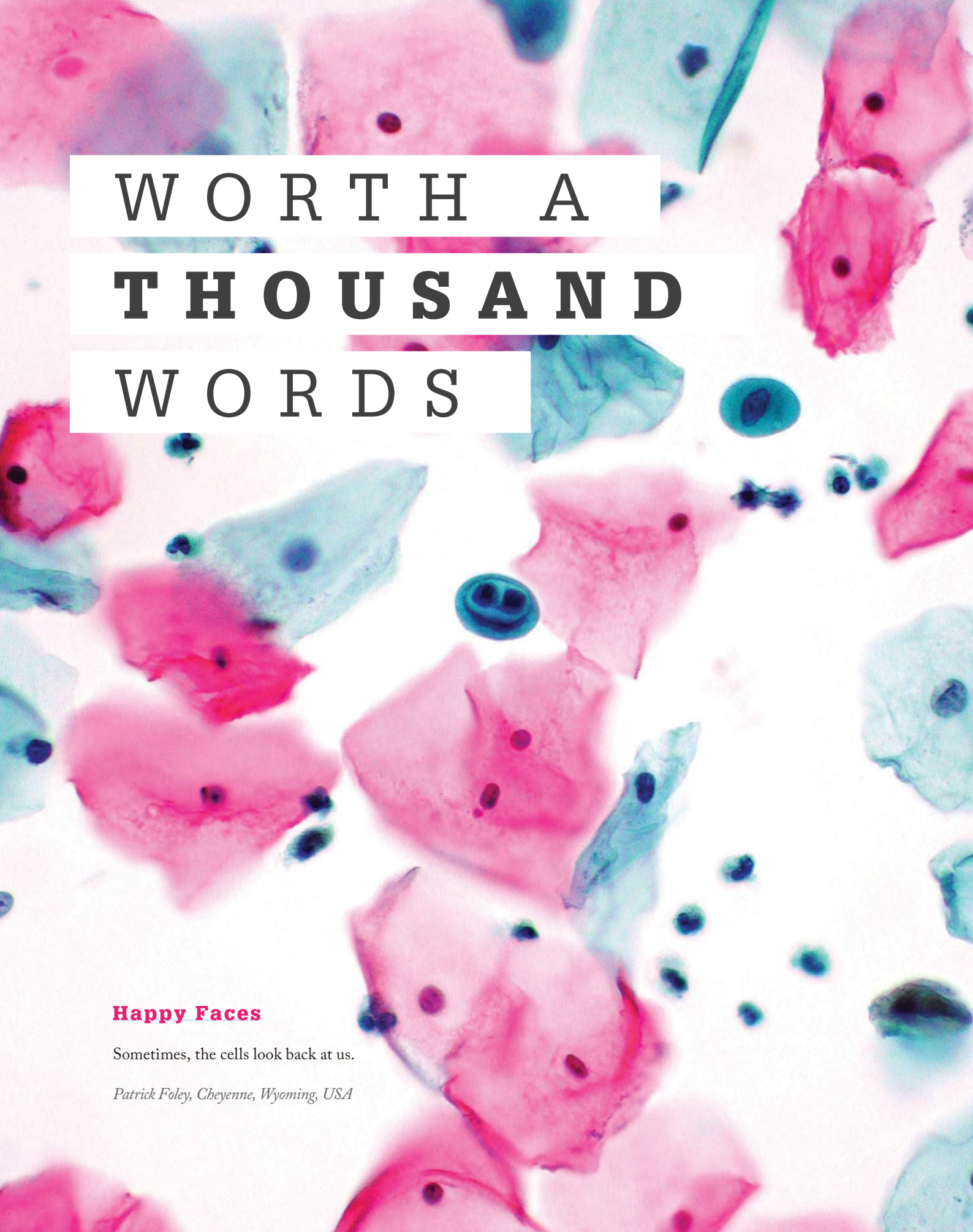
With so many unknowns about COVID-19, and without any real way of knowing when this pandemic will end, these are challenging and fearful times for many. But we also need to recognize that, in the face of crisis, the laboratory is a place where innovation thrives. This virus has shown us that our federal procedures and regulations aren't as nimble as they could be. We must take that lesson to heart as we work to bring laboratory-developed and commercial platform diagnostics online quickly. The saying, "Without the laboratory, you're just guessing," is on everyone's mind now, and we must endeavor to eliminate guesswork and provide accurate results and solid data. Not only are we bringing diagnostic capabilities for the actual virus online, we'll soon also need diagnostic tests for antibodies against the virus. In the short term, we'll need to know who has been infected and recovered; in the long term, it will be critical to monitor the efficacy of vaccines that will be developed.

Knowledge is power, and as we gain more through our research on SARS-CoV-2, we must share it liberally to ensure that everyone, from health officials to patients, is well-informed.

When the influenza pandemic of 1918 swept the world, the virus devastated the global population. At that time, our specialty was in its beginnings. Since then, we have gathered so much expertise about disease and diagnostics that the practice of pathology and laboratory medicine is almost unrecognizable to what it was more than a century ago. It is our responsibility to share that expertise with the world at large, to communicate our knowledge, and to provide the stable foundation upon which we, and our patients, can begin to recover.

"Knowledge is power, and as we gain more through our research on SARS-CoV-2, we must share it liberally."

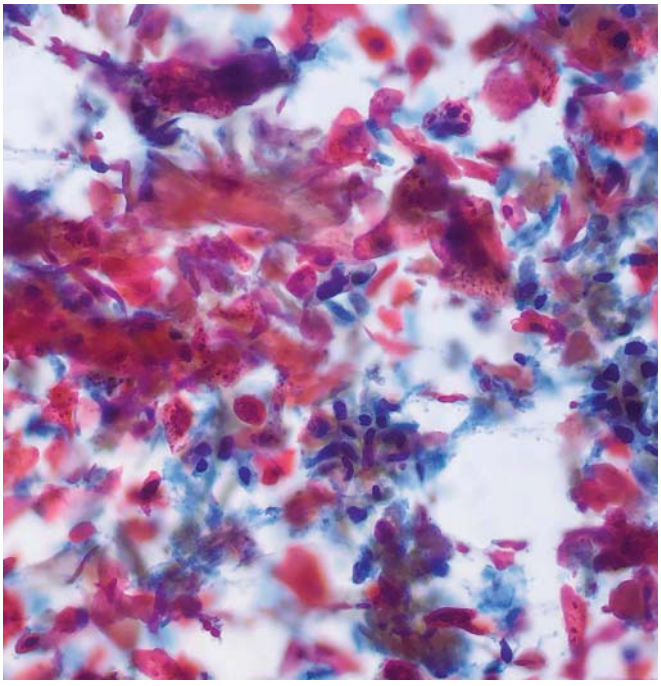
WORTH A THOUSAND WORDS

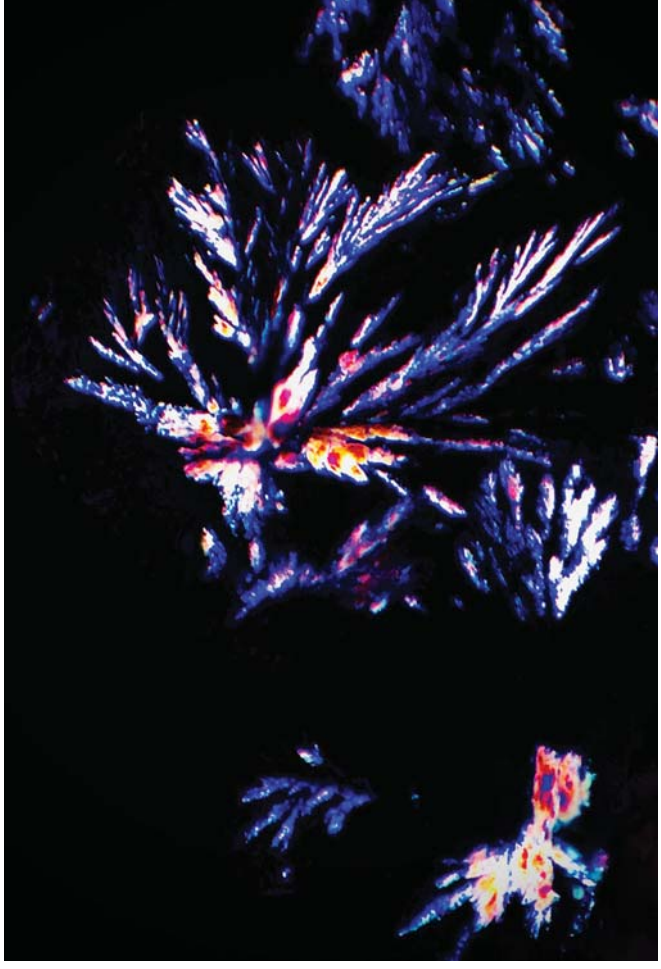


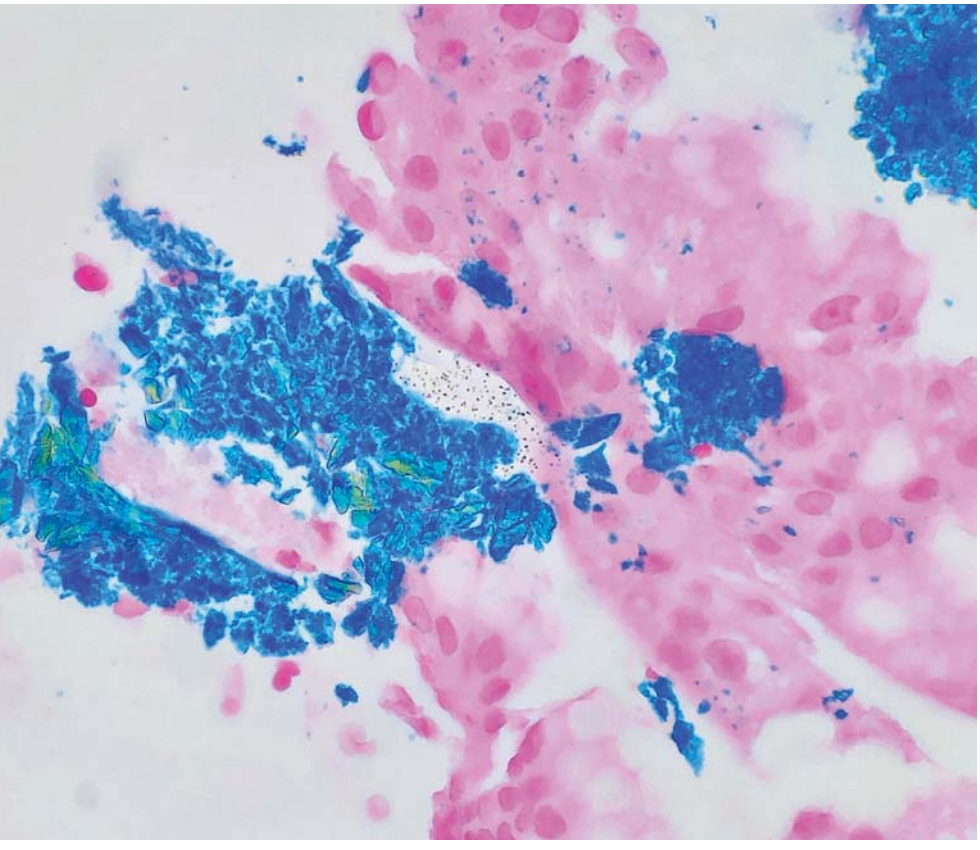
Happy Faces

Sometimes, the cells look back at us.

Patrick Foley, Cheyenne, Wyoming, USA







Don't Smoke

Top left: Keratinous debris from metastatic squamous cell carcinoma.

Fireworks at Night

Top right: Remnants of a painful knee.

Iron Gut

Bottom: Pink and blue in iron pill gastritis.

Adam L. Booth, AP/CP Resident, University of Texas Medical Branch, Galveston, Texas, and 2020–21 Gastrointestinal and Liver Pathology Fellow, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts, USA

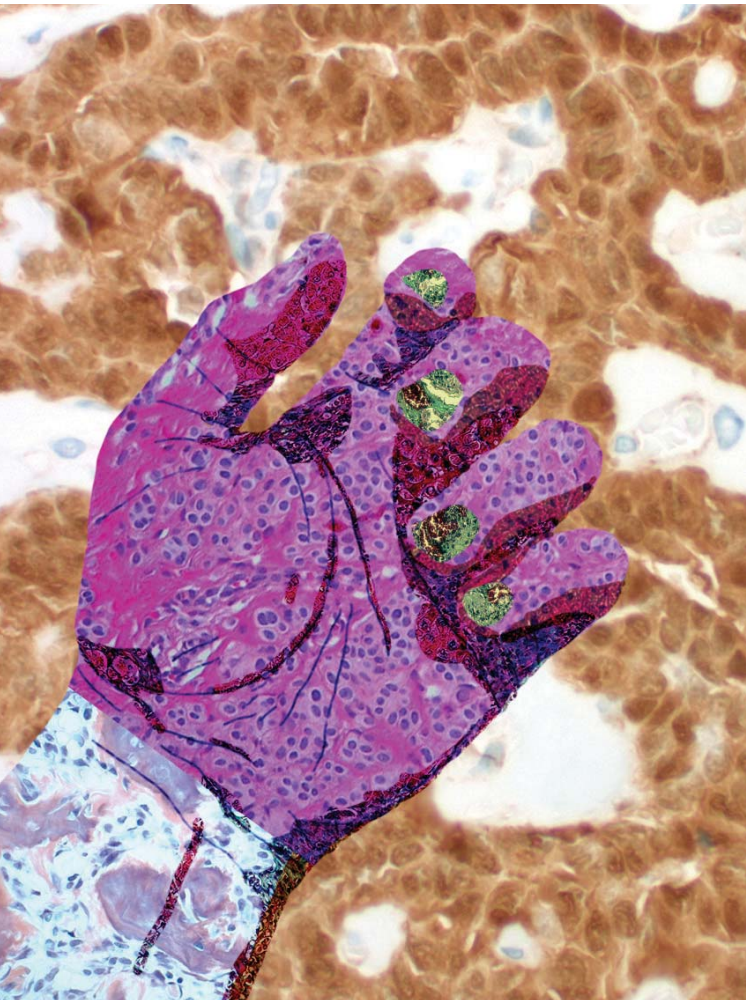
Blueberries for My Grandmothers

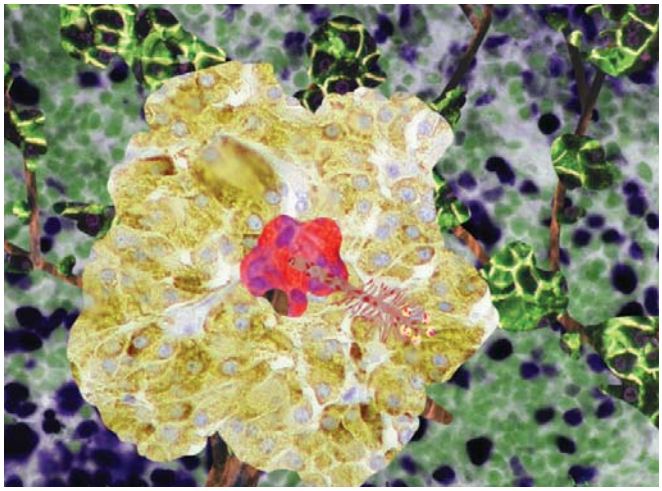
Top: Cerebrospinal fluid cytology positive for malignant cells (breast cancer), 40X digital photo and acrylic on canvas.

Nervous

Bottom: Gastric c biopsy, diff quick stain with H. pylori, 40X digital photo and acrylic on canvas.

Faye Smith-Chakmakova, Pathologist, Barton Memorial Hospital, South Lake Tahoe, California, USA





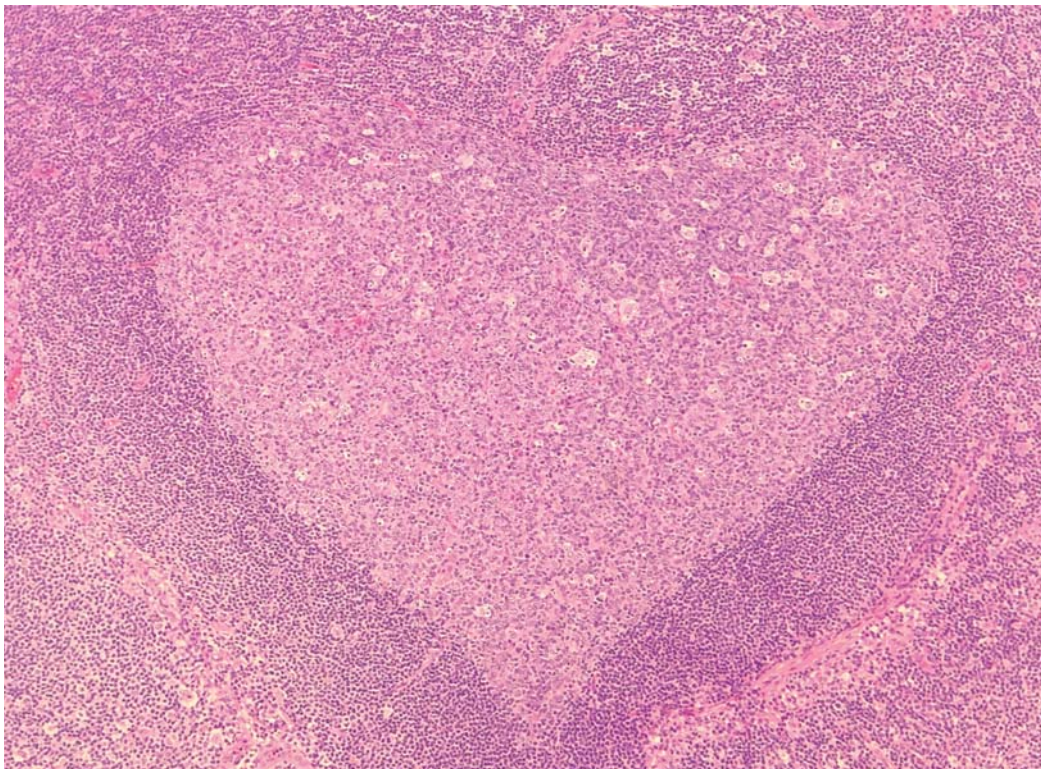
Hand

Left: Digital collage made from histology and histopathology images and edited in Adobe Photoshop.

Yellow Hibiscus

Top: Digital collage made from histology and histopathology images and edited in Adobe Photoshop.

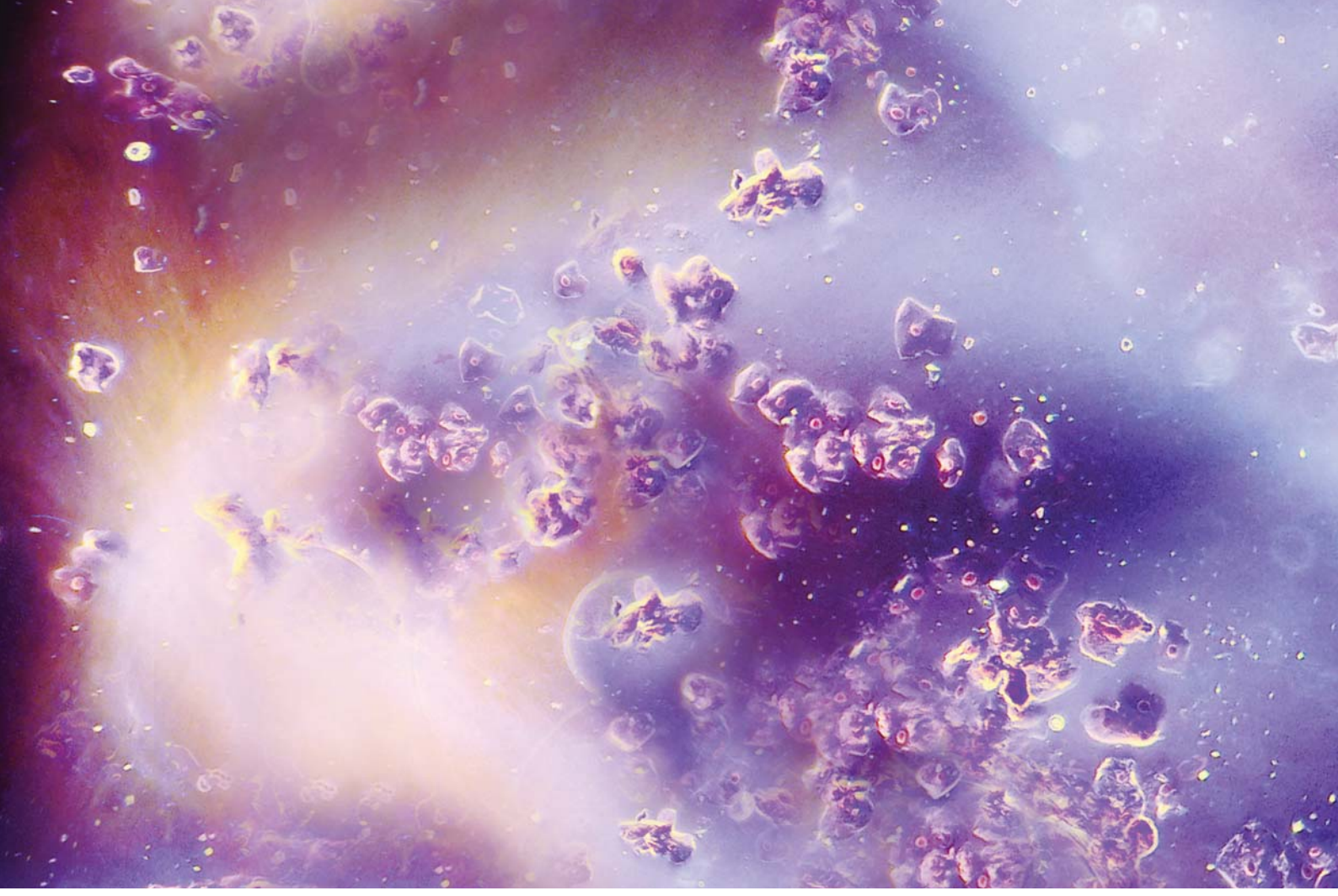
Cooper Schwartz, Alpert Medical School at Brown University, Providence, Rhode Island, USA.



Love Pathology

A heart captured on a histology slide.

Daoud Rahal, Head of the Surgical Histocytopathology Diagnostic Section and Pathology Anatomy Day Hospital, Humanitas Research Hospital, Rozzano, Milan, Italy.



Nebula

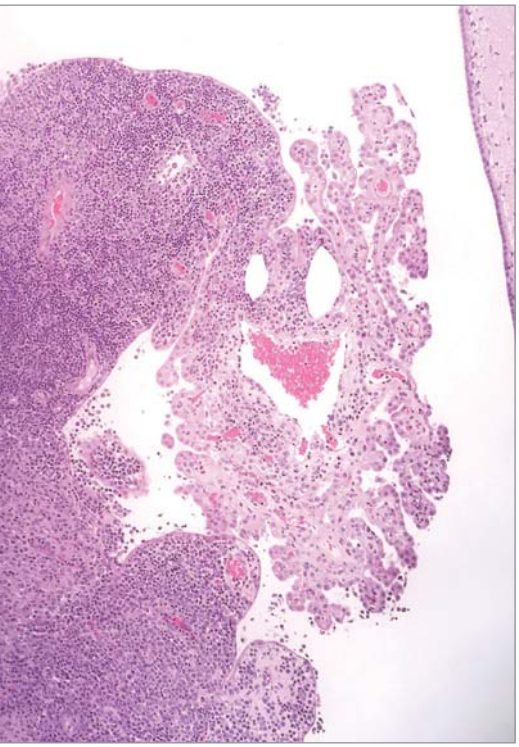
Top: This image is a slide of the creator's buccal epithelial cells, photographed during the first year of medical school and later edited to look like a nebula.

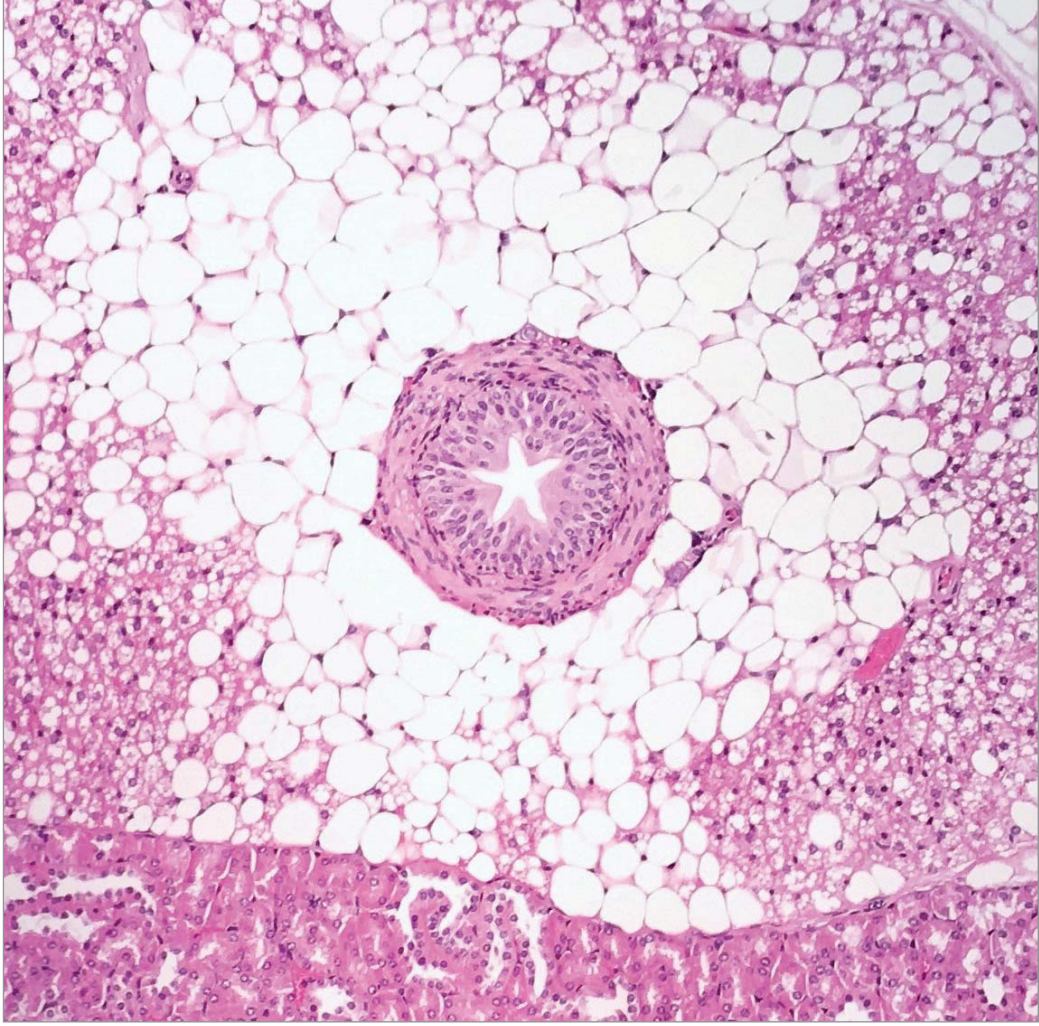
Amber Matkowski, Y4 Medical Student (intercalating), University of Manchester, UK.

Schistosoma cercariae

Left: Mobile microscopes help to diagnose schistosomes, which infect hundreds of millions of people with schistosomiasis every year. Because they are portable, high-resolution, and can share information, diagnosis can be made quickly even outside a laboratory setting.

Liverpool School of Tropical Medicine and ioLight Microscopes, Liverpool, UK.





We're Coming for You

Top left: A high-grade astrocytoma starts to invade a very happy, but unsuspecting, choroid plexus in the brain from an animal used in an animal model study.

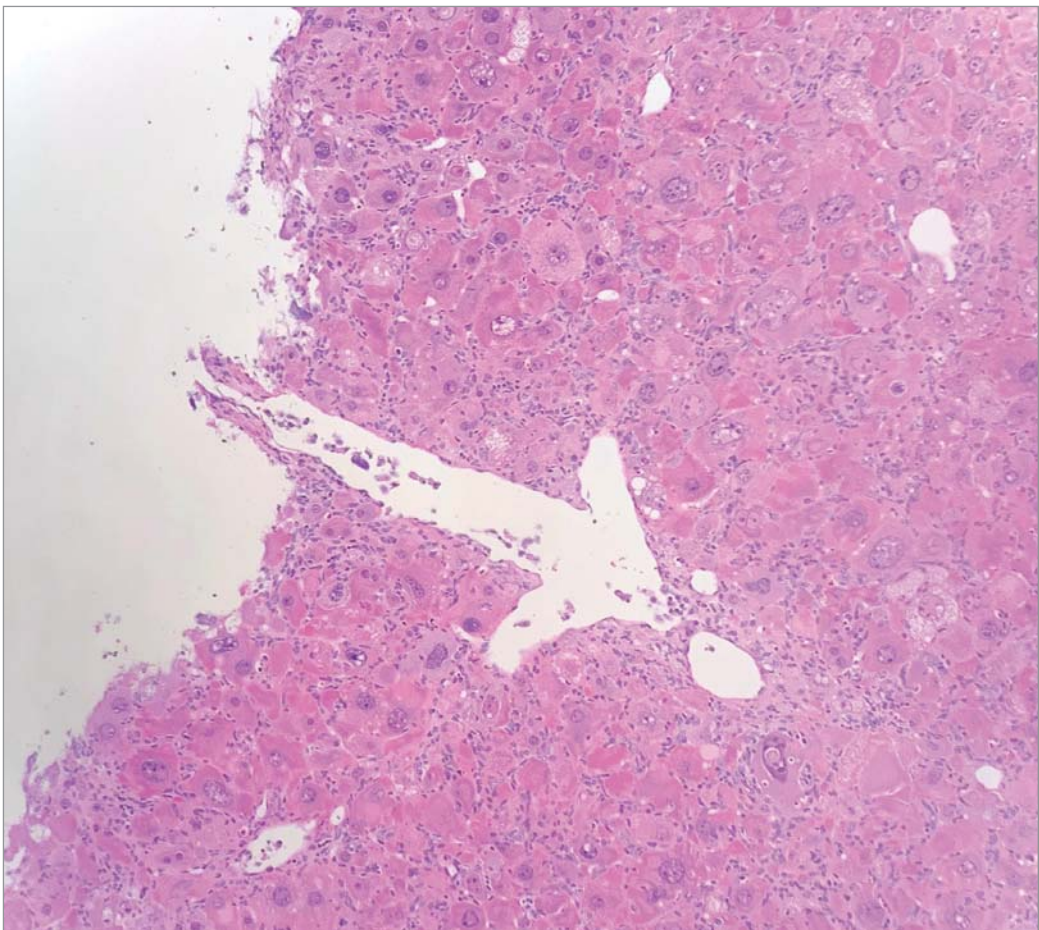
You're a Star

Top right: A small section of ureter is captured within the perirenal fat of an animal from a research study.

This Is How the Magic Works

Bottom: A helpful arrow-shaped artifactual space in the liver of a rat from a toxicology study.

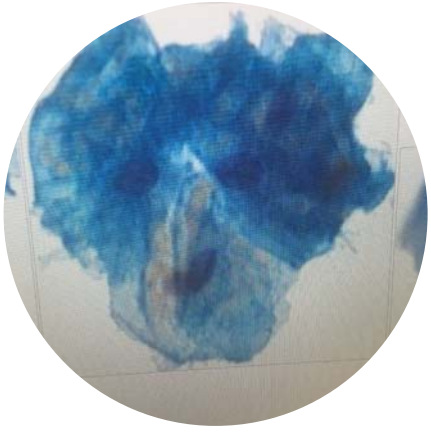
Nicola Parry, Independent Veterinary Pathology Consultant, Midwest Veterinary Pathology, Lafayette, Indiana, USA



The Tree of Life

A beautiful reminder of life just waiting to be discovered.

Christina A. Arnold, University of Colorado Anschutz Medical Campus, Aurora, Colorado, USA.



A Dog's Life

Seen on a Pap smear, squamous cells cluster together to look like a dog's face.

Laura Philbrook, Senior Cytotechnologist, CellSolutions, Greensboro, North Carolina, USA.

Monster

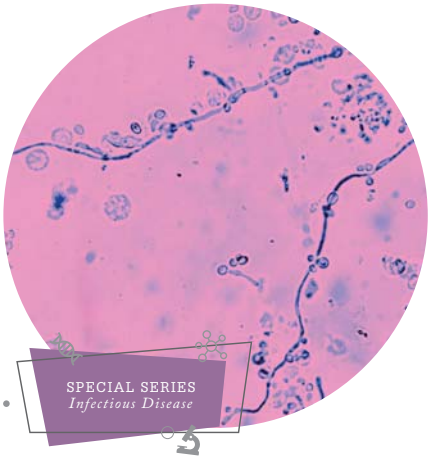
Spotted on an H&E slide, this monster just had to be captured!

San Yu Maung, Pathologist, Mandalay General Hospital, Mandalay, Myanmar.

The Kiss

This #PathArt shows the architectural resemblance of a famous painting by Gustav Klimt with keratin horn cysts of seborrheic keratosis.

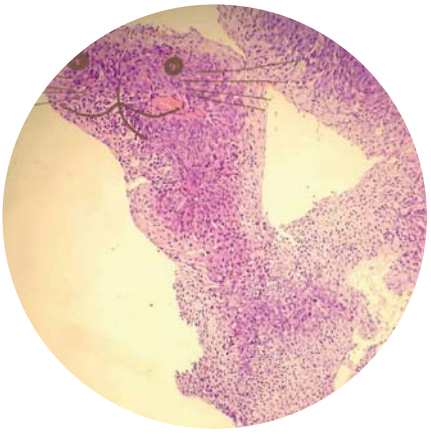
Muhammad Ahsan, Sahiwal Medical College, Sahiwal, Pakistan.



Cherry Blossoms

This urine microscopic contains branching budding yeast cells with pseudohyphae. The colors have been edited to reflect cherry blossom branches, which I have always found branching yeast reminiscent of.

Churcher, Medical Laboratory Technician at Crystal Run Healthcare, Middletown, New York, USA.



A Sea Lion is Lurking

A hematoxylin and eosin-stained bronchial biopsy from a 52-year-old male, which was diagnosed as severe dysplasia.

Felipe S. Templo, Jr., Philippine Heart Center, Quezon City, Philippines.

Artists' Impressions

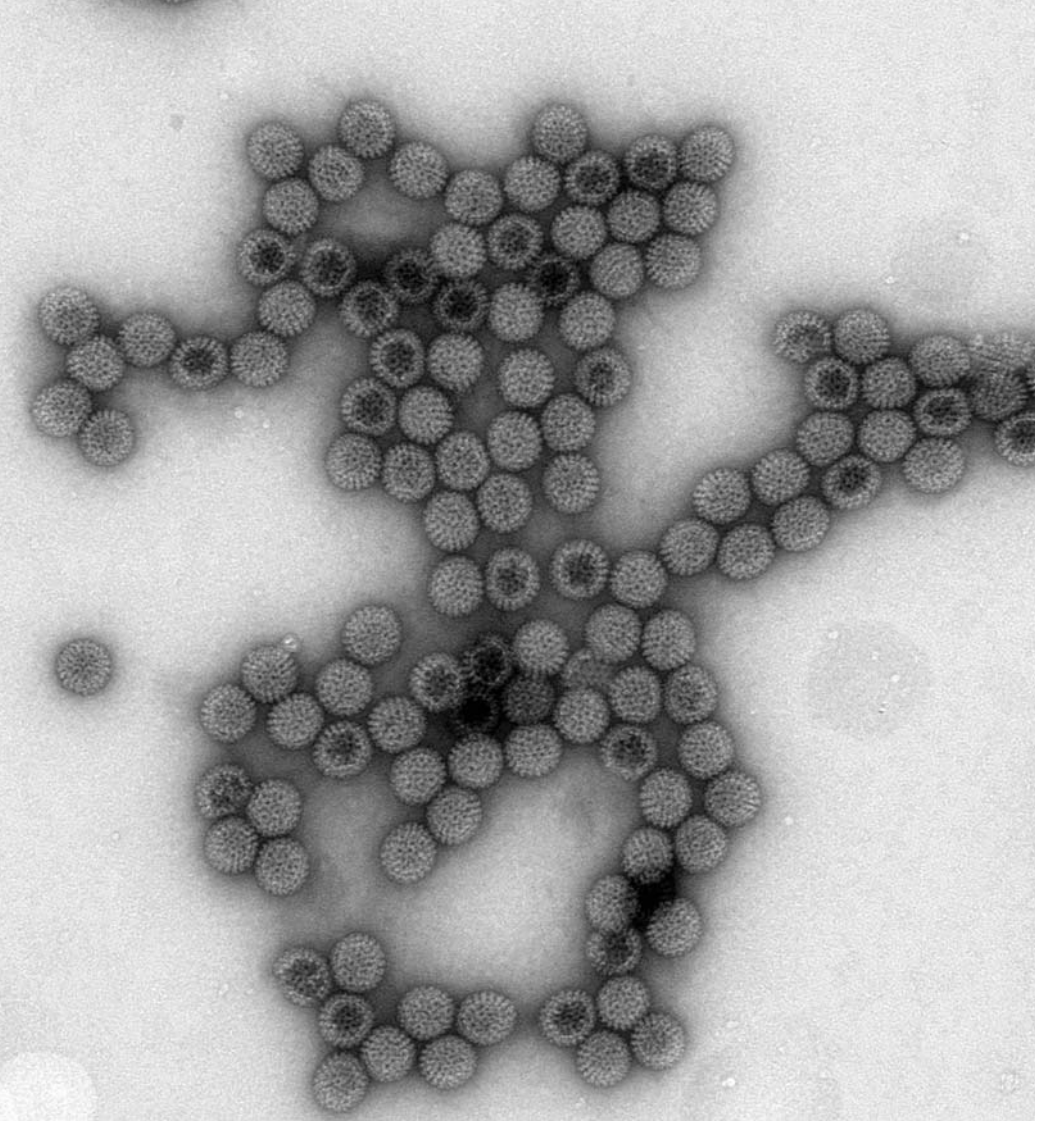
Two Danish painters were given slides of benign human tissue and asked to integrate the images into their artwork. Here are the results.

Top: Pancreas.

Nacis Gironell.

Bottom: Small intestine and the pathologist.

Troels Trier.



SPECIAL SERIES
Infectious Disease

Rotavirus

Negative stain image of Rotavirus showing complete and empty viral particles.

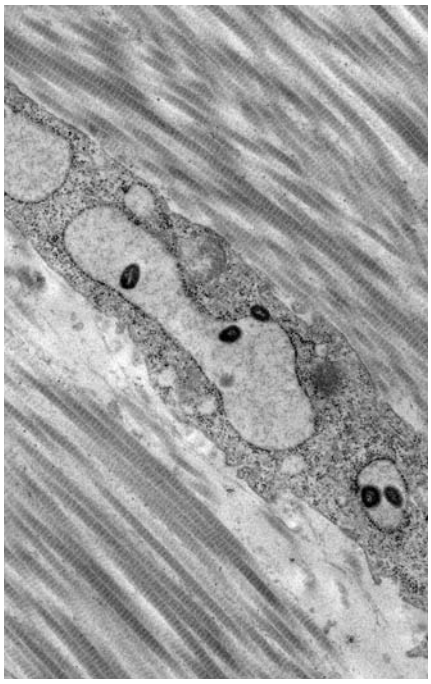
Lumpy Skin Disease Virus

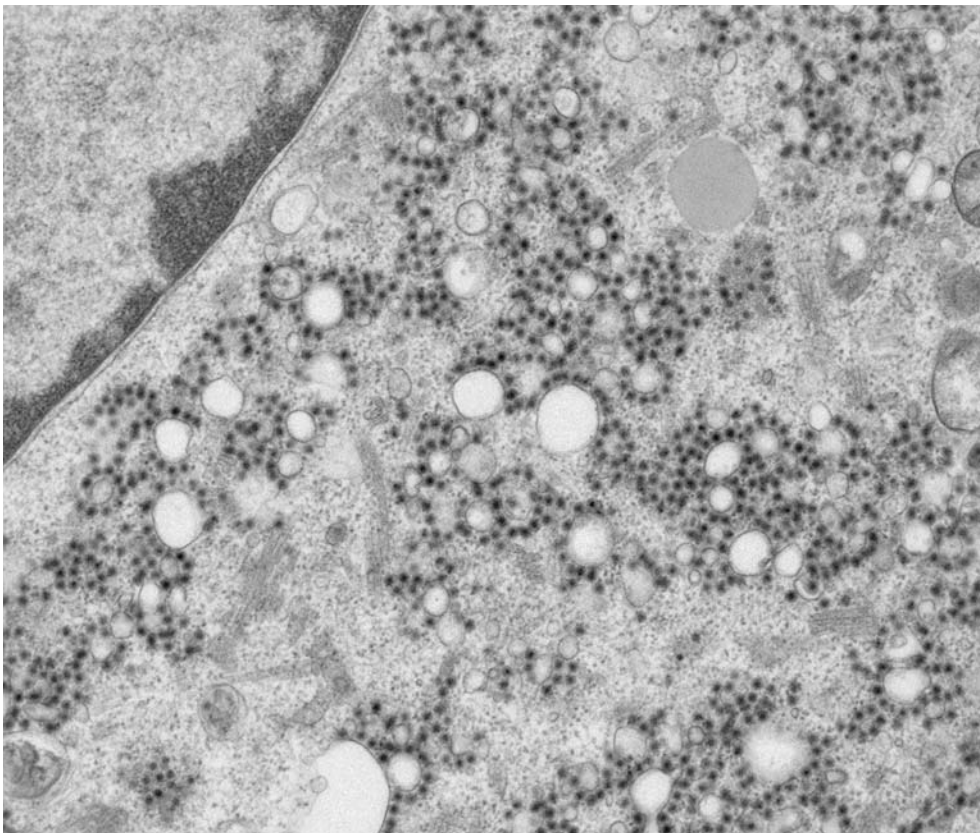
A poxvirus in the genus Capripoxvirus that causes systemic disease in cattle and buffalo. The image shows virions within an infected cell of the dermis.

Bluetongue Virus

The image shows a highly infected cell; each black dot is an individual viral particle.

Bioimaging, The Pirbright Institute, Pirbright, UK.





Animals + Movats = Art

Top left: Mouse

Sarah Ann Ducat, HTL, Tufts Cummings School of Veterinary Medicine, North Grafton, Massachusetts, USA.

Tiles

Top right: These ceramic tiles may look like plant cells due to their rigid geometric borders, but they were inspired by the appearance of human cells under the microscope.

David Grier, Associate Professor, Division of Pathology and Laboratory Medicine, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, USA.

Mother in Blue Dress

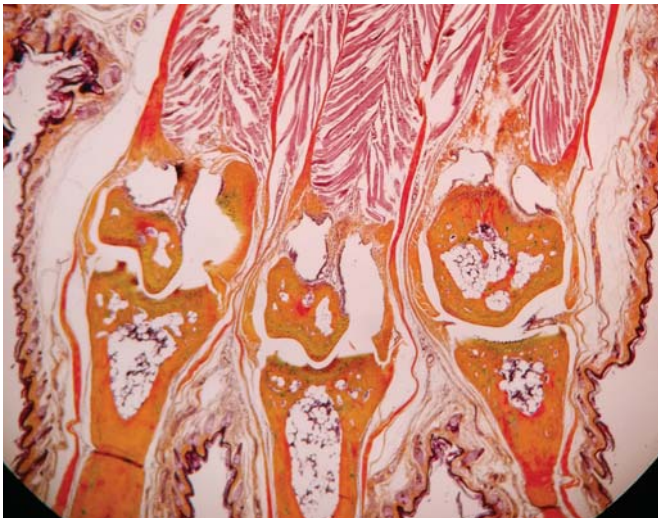
Bottom left: This slide image shows chorionic villi in the placenta, but I also saw a woman with a baby in her arms. The woman looked very fragile, so I wanted to paint her blue to give her strength.

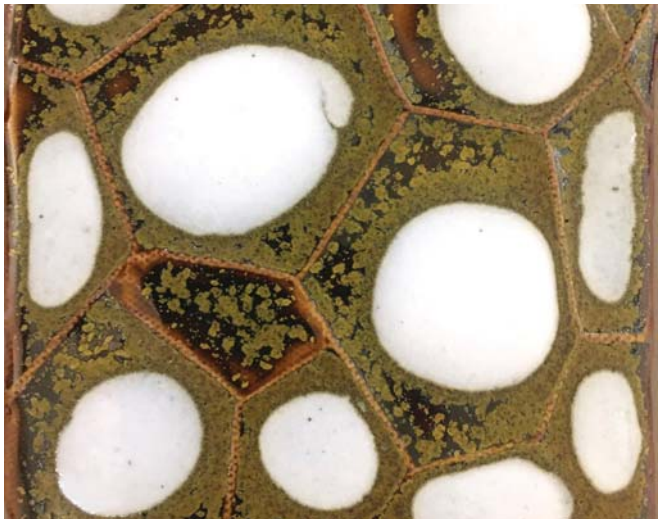
Latife Doğanany, Associate Professor Doctor at Kent Sağlık Grubu, Turkey.

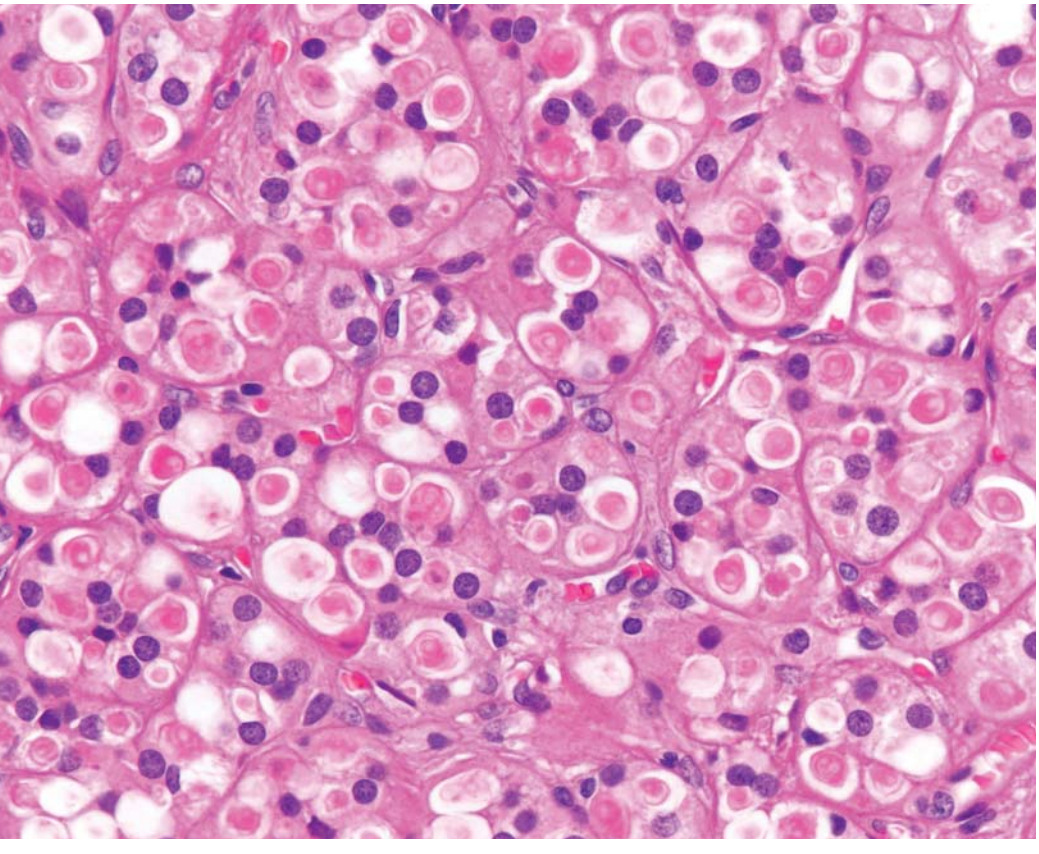
Hepatic Adenoma

Bottom right: Gross pathology of hepatic adenoma, post-fixation, close-up.

Sam Sadigh, Massachusetts General Hospital, Boston, Massachusetts, USA







Time: Portraits of Hope and Survival from Early Cancer Detection

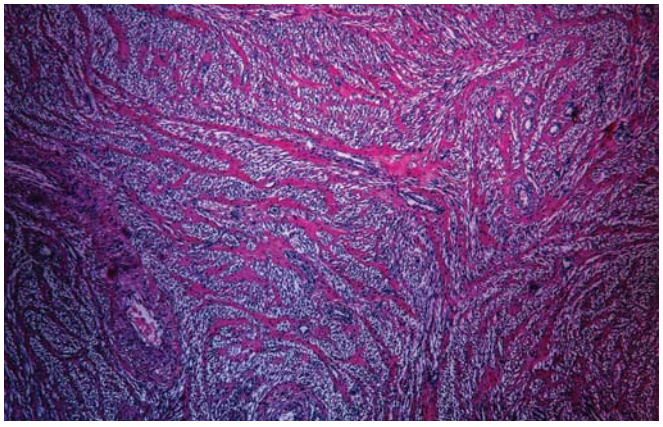
These are the portraits and stories of the people involved in the ECLS (Early detection of Cancer of the Lung Scotland) study, believed to be the largest randomized trial of a blood biomarker for early cancer detection. Read all five full stories online at *tp.txp.to/Thousand/Words/Gallery*.

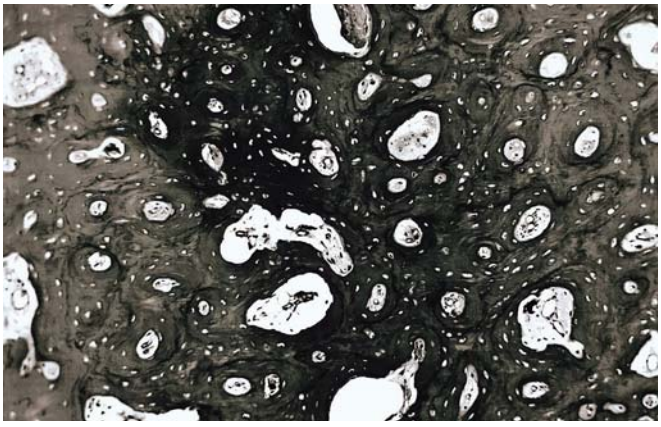
Photographs by Karena Perronet-Miller for Oncimmune, Nottingham, UK.

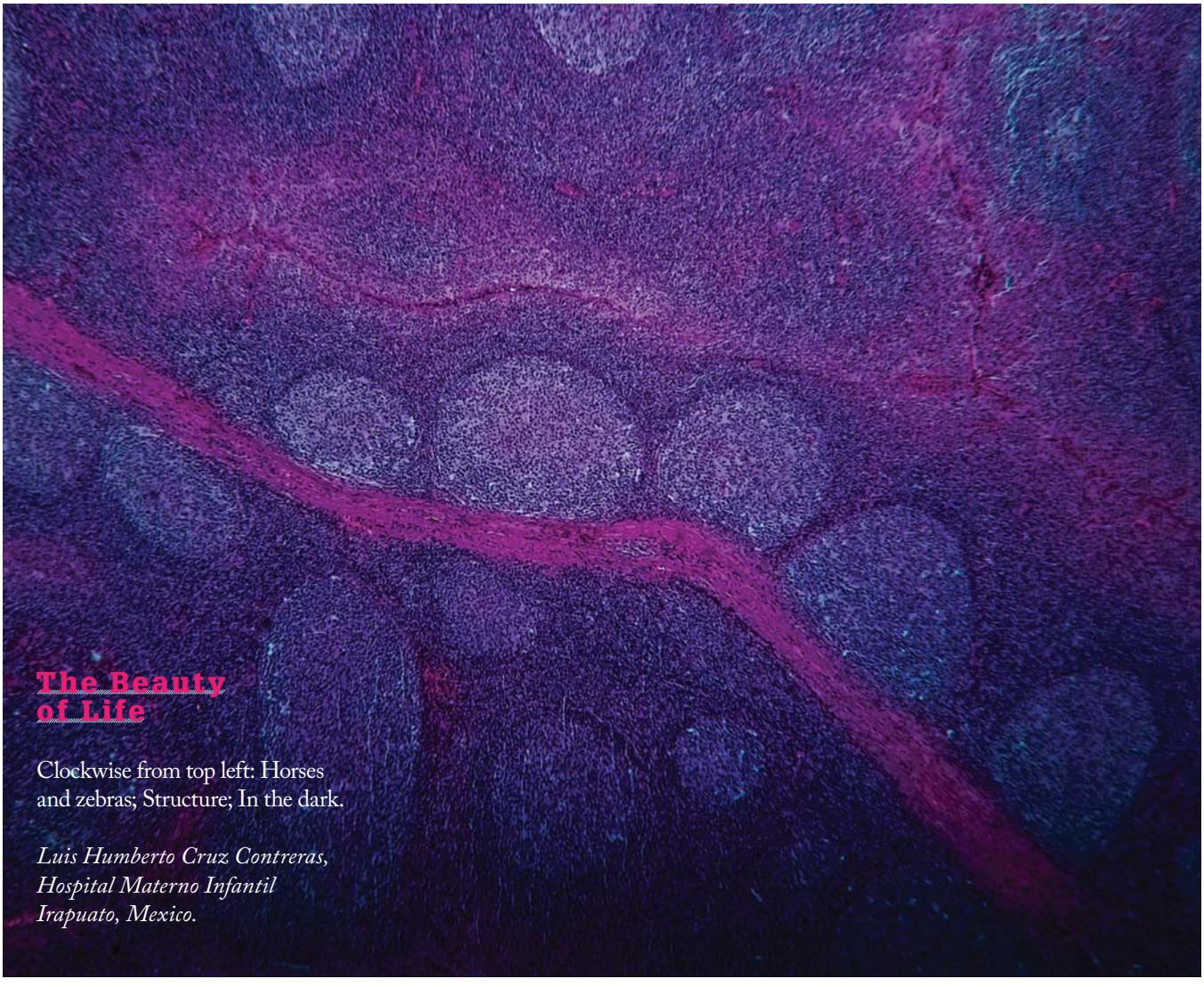
The Art of the Body

Adrenocortical adenoma with spironolactone bodies.

Evita Sadimin, Assistant Professor of Urological Pathology and Pathology Informatics, Rutgers Cancer Institute of New Jersey, New Brunswick, New Jersey, USA.



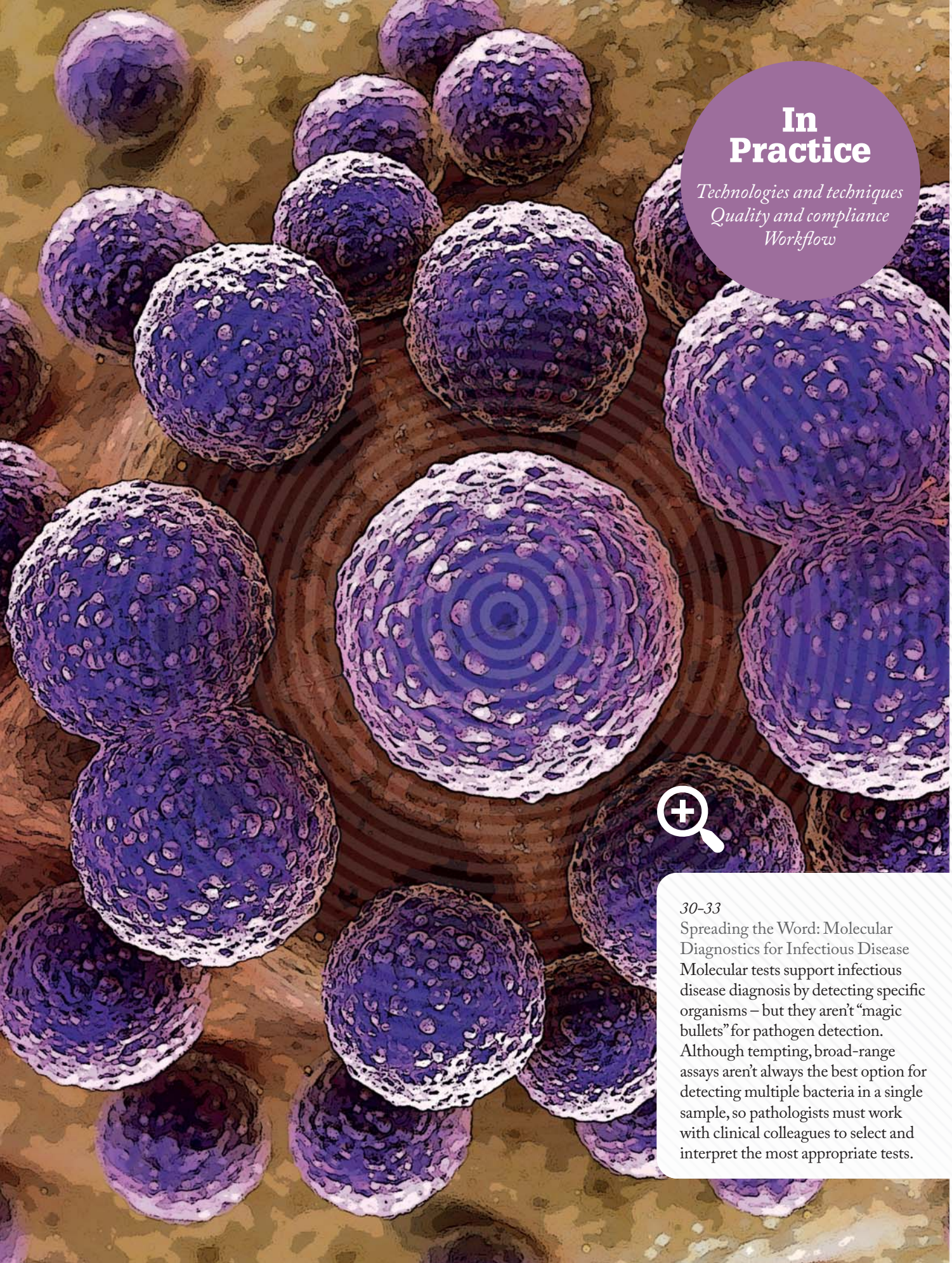




The Beauty of Life

Clockwise from top left: Horses and zebras; Structure; In the dark.

Luis Humberto Cruz Contreras, Hospital Materno Infantil Irapuato, Mexico.



In Practice

Technologies and techniques
Quality and compliance
Workflow

Spreading the Word: Molecular Diagnostics for Infectious Diseases

What role can cutting-edge assays play in the diagnosis of infectious diseases – and how do we maximize their potential?

By Bobbi Pritt

Molecular diagnostics have an increasingly important role to play across all areas of pathology, but their importance in infectious disease cannot be underestimated. Thanks to a simple, widely available technique – the polymerase chain reaction (PCR) – molecular techniques now serve a variety of applications in routine clinical laboratories, with real-time PCR allowing the rapid detection of various infectious microorganisms. But are these cutting-edge assays too easy? Often, pathologists perform them even when there is no prior evidence of infection. It's true that there are many circumstances where molecular diagnostics can be valuable, but we need to educate our surgical pathologists on what the tests can do – and when they might not be the best option.

As our clinical colleagues become more familiar with the molecular diagnostic tests that are now widely available, surgical pathologists can expect to receive more frequent requests for them. But we cannot blindly follow these requests; we are also diagnosticians and need to be prepared to turn down tests that aren't suitable or suggest more appropriate alternatives. Pathologists are physicians who are ultimately responsible for the tissue we work on, so we must play an active role in making these decisions. And to do so, we need to fully understand the applications and limitations of molecular diagnostic assays so that we can use them properly.

Target-specific or broad-range?

In the context of infectious disease, the strength of molecular diagnostic tools lies in identifying specific organisms. For example, a lymph node may be consistent with cat-scratch disease (CSD), but the pathologist wants to rule out any other potential causes. A PCR test for Bartonella henselae, the specific bacterium that causes CSD, would be entirely suitable – and a conclusive result would either rule in or rule out CSD.

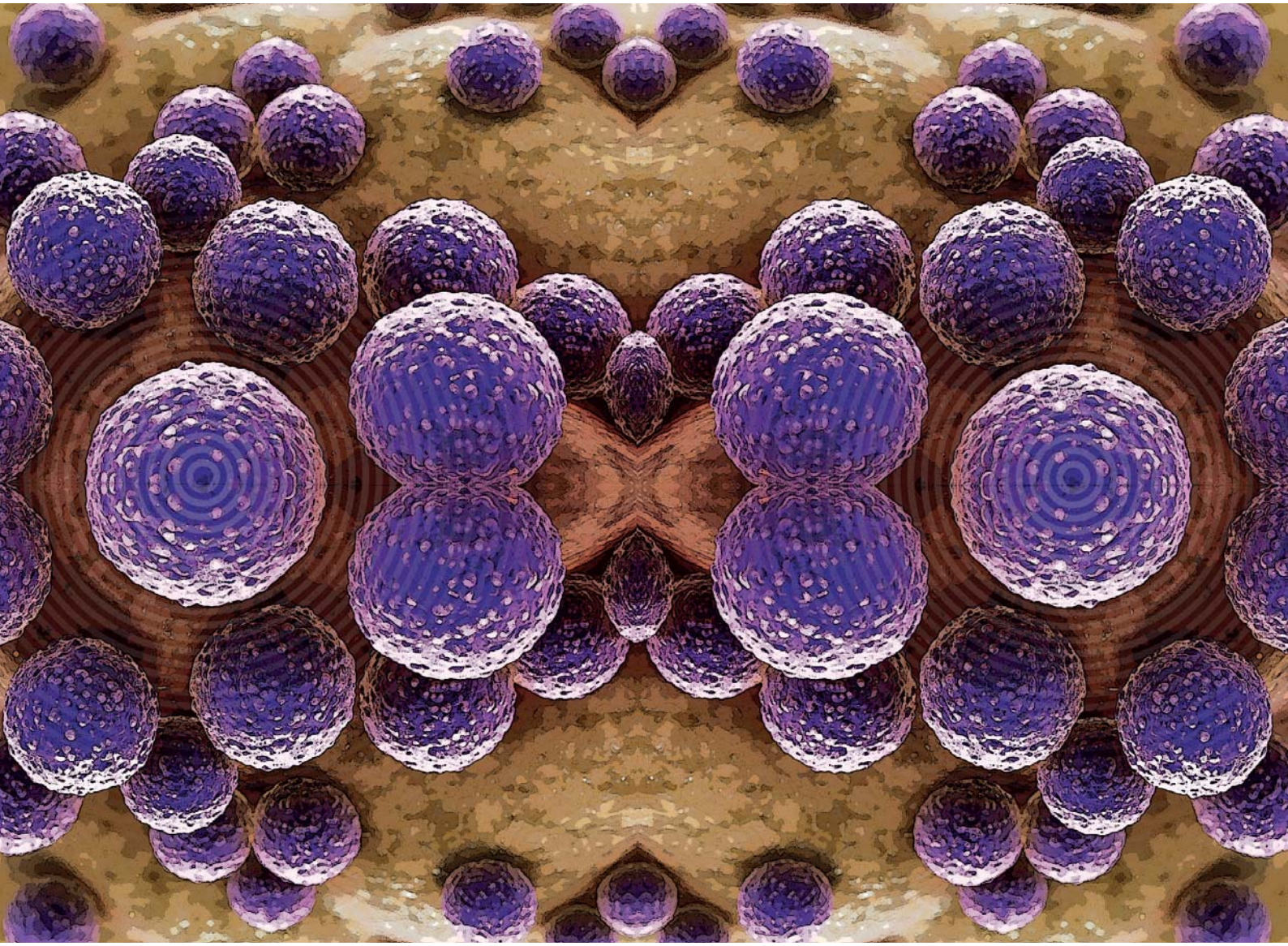
However, now that we can increasingly use broad-range assays that can detect multiple organisms simultaneously, things aren't so straightforward. The use of 16S ribosomal RNA gene sequences – present and highly conserved in nearly all bacteria – has opened new doors in terms of detecting multiple bacterial species in a single sample. The molecular amplification method can be applied to a number of different samples, including cerebrospinal fluid and both fresh and formalin-fixed surgical pathology specimens. Because it's essentially a PCR test, once you've amplified the 16S gene in a sample, you can sequence it to identify the specific bacteria that are present.

This broad-range test is ideal in a number of scenarios. For example, if a patient has received antibiotics, the bacteria may not grow in standard microbiology culture – which means that the surgical pathologist might be the only one who can provide insight by using the 16S test. This is particularly important for patients who have diseases such as infective endocarditis. These patients will almost always receive broad-spectrum antibiotics before surgery, so the 16S test can help determine which bacteria are present and therefore which specific antibiotics to use.

"The molecular amplification method can be applied to a number of different samples, including cerebrospinal fluid and both fresh and formalin-fixed surgical pathology specimens."

No magic bullet

But don't mistake the test for a magical, detect-all assay. The first thing to bear in mind is that a 16S test is only for bacteria; it won't detect parasites, viruses, or fungi. And when a sample doesn't show signs of any organisms, there's little reason to carry out the test, because the sensitivity plummets if you don't see anything that looks like inflammation or the presence of organisms. When a case that does require a 16S test arises, it's important to remember that the results will only be as good as the assay. Factors such as the extraction method, the gene region targeted, and the database used



for analysis can all impact their accuracy.

Another caveat to the test is that we don't live in a sterile world; bacteria are all around us. That's why it's important to familiarize ourselves with all of the ways that exogenous DNA can be introduced to tissue samples, so that we can account for any contamination. The journey that a sample takes from tissue biopsy to glass slide is long and convoluted. From the cutting block in the grossing room, to the reagents used during tissue processing, to the staining process when transferring a paraffin ribbon section onto a slide, exogenous DNA contamination is inevitable at some point.

The risk of contamination is simply a side effect of having a highly sensitive assay that can detect every single bacterium – and there's not much that can be done to prevent it. Ultimately, contamination means that the 16S test will detect bacteria with no clinical correlation to the patient. To combat this, it's important to know what you do – and don't – expect to find; for example, the presence of a species commonly found on skin has probably been introduced during the histologic process, rather than being an infective agent.

Consider the pathologist who notices bacteria in tissue and completes a Gram stain that indicates the presence of Gram

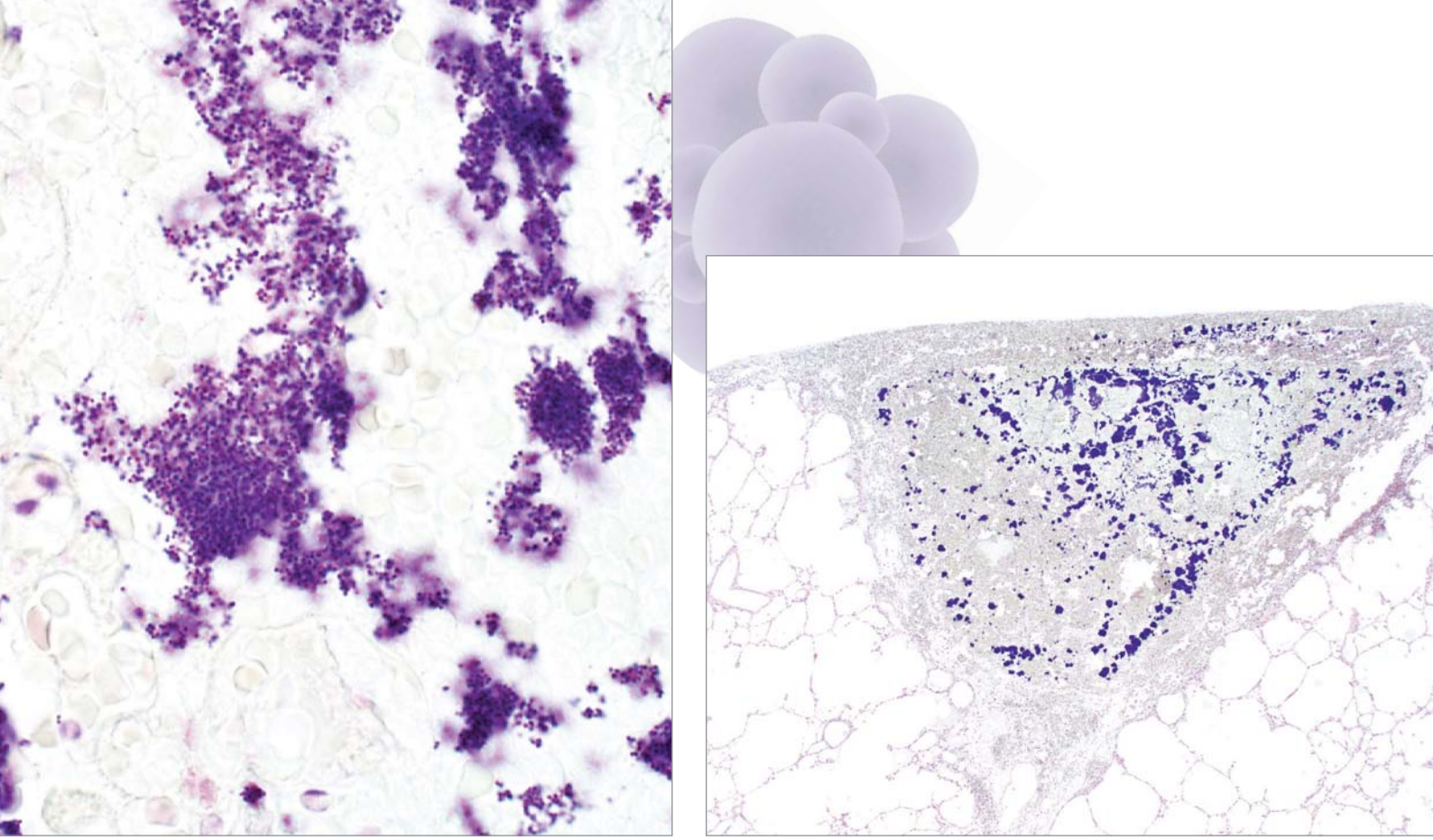


Figure 1. Numerous Gram positive cocci in a case where no tissue was obtained for culture (40X and 1000X magnification). This is an example where a broad range bacterial assay (16S rRNA gene PCR and sequencing) would be appropriate because there is an abundance of organisms and an identification cannot be made by morphology alone.

"Pathologists can also work with treating physicians to ensure that any tissue that might be used for molecular testing is sent without any type of media, as this could contain unwanted DNA."

positive cocci. A 16S sequencing assay that detects Gram negative bacilli is more likely to be showing contamination than the infection itself, because these are such different types of organism. We must ensure that there's a correlation between what the pathologist sees and what the test actually detects, and our clinical colleagues are on hand to help with the process of deciding whether a result makes sense for a particular patient.

Although we can't completely eliminate the possibility of contamination, we can control a few things to minimize the introduction of exogenous DNA (and false-positive results). For instance, if you know that you might want to carry out molecular testing on a specific sample, freeze a small piece of fresh tissue to serve as an ideal specimen, rather than using a formalin-fixed, paraffin-embedded block. This is sometimes easier said than done, but if a fairly large tissue sample comes into the frozen section lab, why not take a small piece and set it aside in case molecular testing is needed? This is much better than putting the tissue through a lengthy process that risks exposing it to numerous environmental organisms. Pathologists can also work with treating physicians to ensure that any tissue that might be used for molecular testing is sent without any type of media, as this could contain unwanted DNA.

Curbing temptation

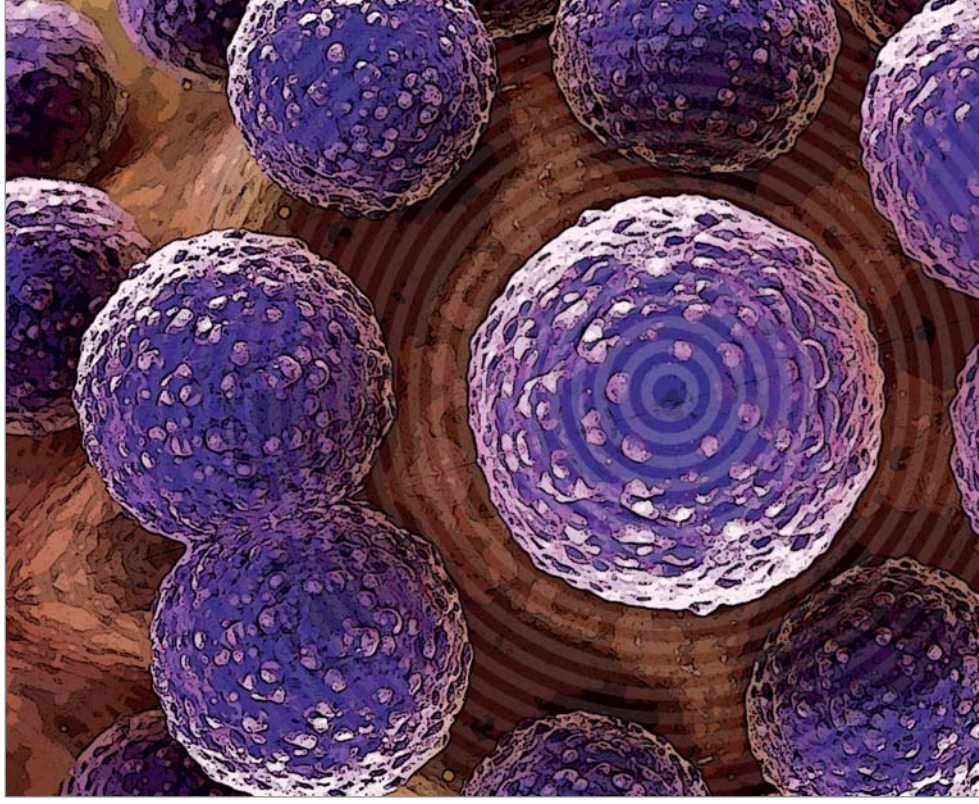
Pathologists are often faced with the difficult question of whether to select a broad-range or a target-specific PCR assay. If you're looking at a tissue and suspect that a certain bacterium is present, it's always better to order the target-specific PCR test, because it will be more sensitive and more specific than a 16S test. Despite this, there is often a temptation to opt for the broad-range test; it's easy to think, "Why would I

order a test that only gives me one answer, when I could order a different test that gives me every possible answer?" This is why it's crucial to understand that, although the 16S test can detect more organisms, it's more likely to produce false-positive and false-negative results – the former due to contamination and the latter because it's less sensitive than a target-specific assay.

One of the main limitations for molecular diagnostics in the US is that there are currently no FDA-approved tests. As a result, the test you'll find at the University of Washington may differ in sensitivity and specificity to the test you'll find at Mayo Clinic. The situation in Europe is similar – there are no CE-marked tests at the moment, and it's likely that it will be a few years before either region achieves standardization. Until that point, it's vital that pathologists have detailed conversations with the labs performing molecular diagnostic tests to ensure that everyone involved fully understands their capabilities.

As molecular tests are used more routinely for the diagnosis of infectious disease in clinical laboratories, a growing number of patients will have their pathology specimens tested this way. In general, this is extremely positive – after all, a new addition to the pathologist's toolbox can only be a good thing. But, as with any new tool, the key is to know its strengths and limitations so that we can use it correctly. By playing a more active role in the clinical team and taking responsibility for test selection, we can better help our clinical colleagues interpret results and fulfill the great potential of molecular diagnostics.

Bobbi Pritt is Director of the Clinical Parasitology Laboratory in Mayo Clinic's Department of Laboratory Medicine and Pathology, Rochester, Minnesota, USA.



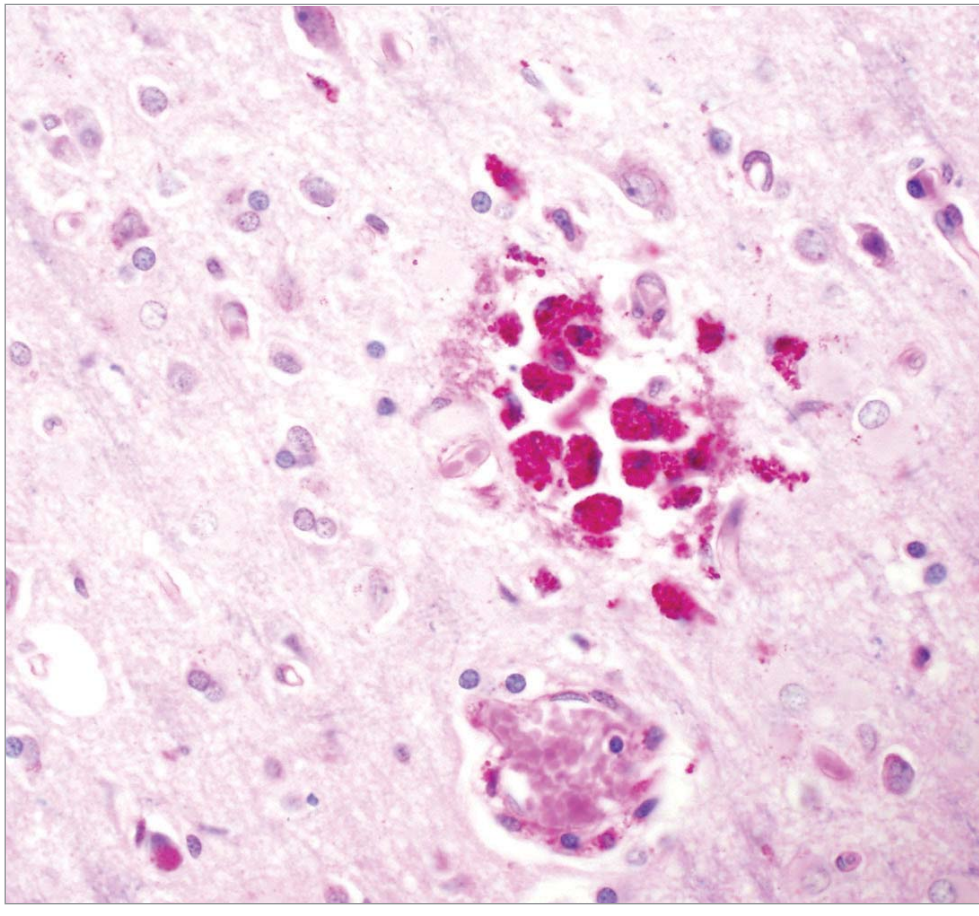


Figure 2. Whipple disease in the brain showing a cluster of macrophages with deeply positive cytoplasmic inclusions on PAS-D stain (400X magnification). If PCR confirmation is desired, the preferred test would be a *Tropheryma whipplei* PCR rather than a broad-range assay, because a specific organism is suspected.

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Test, Treat, Repeat

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

Patients are increasingly diagnosed with cancer during the earlier stages of the disease. Blood-based methods to screen for and monitor cancer have been a major contributor to this breakthrough; now, doctors can select and administer treatment before widespread progression occurs. But is this all we can do? No – and the next major breakthrough may be the development of cancer-wide biomarker panels to monitor treatment response and predict outcomes. Such panels could allow doctors to determine an ongoing treatment's effectiveness, alter dosage as needed, and even stop using therapies that are not working, avoiding unnecessary side effects.

Mutations in circulating tumor DNA (ctDNA) obtained through liquid biopsies can serve as biomarkers for such panels, enabling physicians to track disease progression and inform treatment strategy.

Genetic signatures in pediatric osteosarcoma

Pediatric osteosarcoma, which predominantly affects people between 10 and 30 years old, is the most common type of primary malignant bone tumor. Because there have been no significant advances in the treatment of this disease for 20 years, we have reached the limit of survival that current therapies can achieve for osteosarcoma patients – a five-year survival rate of 70 percent for all patients.

Standard therapy for pediatric osteosarcoma patients includes multi-agent neoadjuvant chemotherapy, followed 14 weeks later by tumor resection with the goal of complete tumor removal. Following primitive tumor surgery, a patient's treatment response is classified based on the amount of cell death within the tumor – also known as Rosen grading. A patient with large (>90 percent) levels of tumor necrosis after initial chemotherapy is said to be a good responder, whereas one with little to no tumor necrosis is a poor responder. Poor responders to chemotherapy and tumor resection have a worse prognosis and require more aggressive second lines of chemotherapy postoperatively. But because it is difficult to sample and measure necrotic tumors, it is difficult to accurately classify how a patient's tumor is responding to treatment. That's why, at the moment, we need highly sensitive molecular residual disease evaluation to detect a low burden of cells in the tumor and/or in the plasma.

However, if we could identify DNA biomarkers that correlate to treatment response, physicians could use this information to choose a treatment strategy for a patient ahead of time based on whether they are likely to be a good or a poor responder to a particular therapy.

To identify new biomarkers for pediatric osteosarcoma, Natacha Entz-Werle and a team of researchers from CHRU Strasbourg's Pediatric Oncology Department and the University of

Strasbourg's Laboratory of Bioimaging and Pathology retrospectively investigated the prognostic impact of three genes. Each of these genes – *MET*, *TWIST*, and *APC* – had been previously identified in the large tumor cohort of the French national protocol OS94 as biomarkers of bone dedifferentiation with a clear prognostic impact. Entz-Werle and her team carried out molecular assessments on the genes in an even larger cohort of patients in the OS2006 protocol, evaluating them by allelotyping and qPCR. They also used droplet digital PCR (ddPCR) to prospectively evaluate these metrics in a preliminary cohort of 20 patients with plasma available at diagnosis, before tumor surgery, and at the end of chemotherapy.

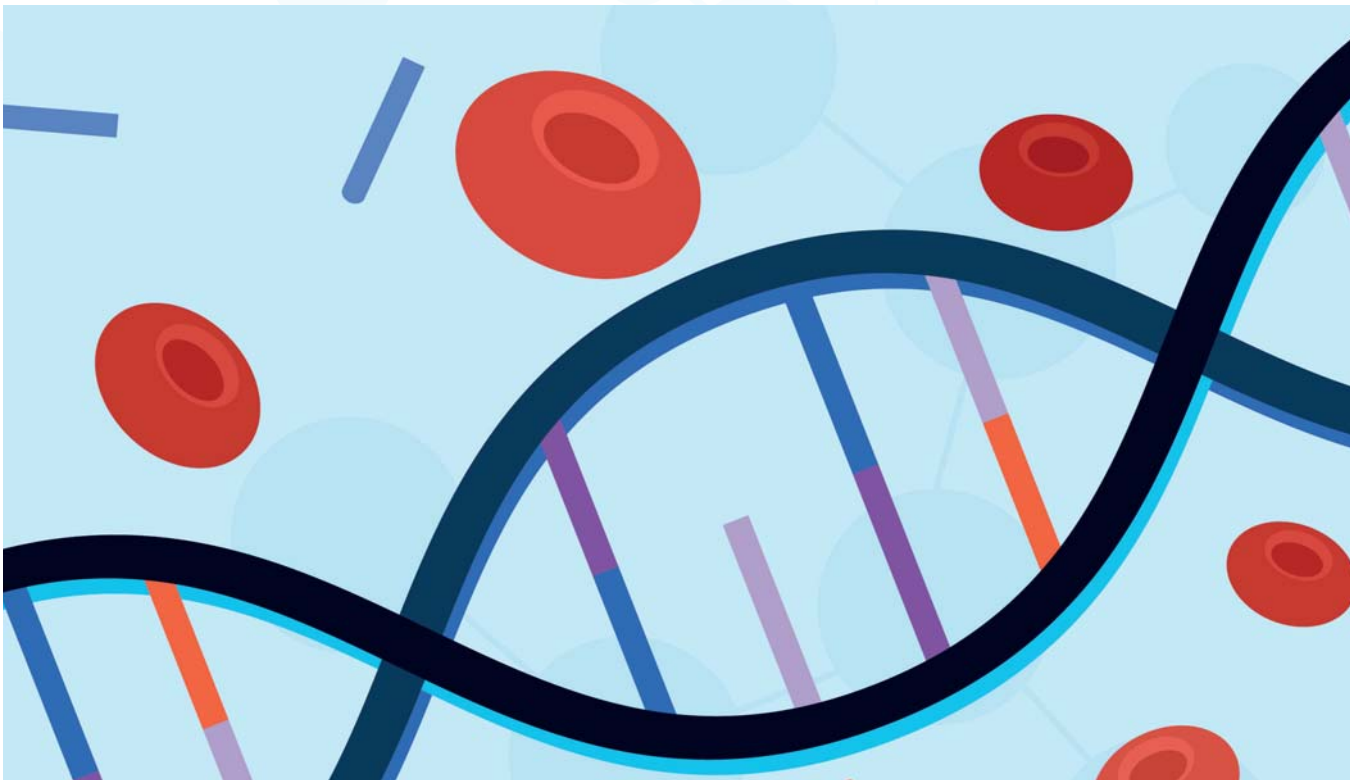
Because necrotic tumor cell DNA is difficult to analyze, the team used two separate methods for analysis. Complementary qPCR and allelotyping yielded accurate results in the diagnostic tumor, but not in plasma. These techniques were only sensitive enough to detect the three-gene signature in 65 percent of patients. The researchers therefore turned to ddPCR as an additional method to track DNA abnormalities at a level sensitive enough to reliably detect low DNA concentrations in the blood. Using ddPCR, they were able to track molecular abnormalities in both tumor tissue and cell-free DNA from liquid biopsy – making it a suitable method for monitoring treatment progression and checking for residual disease to quickly identify and treat relapse.

"Using ddPCR, they were able to track molecular abnormalities in both tumor tissue and cell-free DNA from liquid biopsy."

When correlating the results of these three methods to disease progression, the authors found that common rearrangements of ctDNA within the *MET*, *TWIST*, and *APC* genes could predict the therapeutic outcome of over 85 percent of their small patient cohort. They also found that persistence of this three-gene signature after neoadjuvant chemotherapy in the OS94 protocol indicated that the patient had not responded to initial chemotherapy treatment and was correlated with a higher likelihood of relapse after surgery. The researchers concluded that amplifying the three-gene signature with ddPCR could be used to track residual disease before and after tumor resection, giving physicians the ability to gauge the patient's response throughout the course of treatment.

A new metric for NSCLC

Pediatric osteosarcoma is not the only cancer in which biomarker discovery is driving better treatment strategy. Epidermal growth factor receptor (EGFR) mutant non-small cell lung cancer (NSCLC) is a subtype of lung cancer that occurs predominantly in people who have rarely or



never smoked. These lung adenocarcinomas carry mutations in the *EGFR* gene that render tumors susceptible to *EGFR* tyrosine kinase inhibitors (TKIs) for a limited amount of time – until the tumor develops resistance. Doctors will then analyze ctDNA to plan subsequent treatment options. If a tumor tests positive for the *EGFR* T790M mutation, it is resistant to first- and second-generation TKIs and must be treated with the third-generation TKI osimertinib.

Researchers led by Alexandra Pender at the British Columbia Cancer Agency performed a retrospective study of *EGFR* ctDNA testing in 142 patients with *EGFR*-mutant NSCLC who were progressing on treatment with first- or second-line TKIs. Of these patients, 62 percent were receiving a first-line TKI inhibitor, 25 percent had received two lines of TKI inhibitors, and 13 percent had exhausted three or more lines of systemic treatment at the time of ctDNA testing.

The researchers tested whether two separate circulating biomarkers – a patient's *EGFR* ctDNA mutational status and the concentration of circulating free DNA (cfDNA) in their bloodstream – could predict their overall survival. They first quantified the amount of cfDNA in each patient's bloodstream with a circulating nucleic acid kit, then quantified the amount of *EGFR* ctDNA using ddPCR. With a limit of detection of <0.1 percent variant allele fraction, ddPCR offered researchers a sensitive method to measure the low concentrations of each patient's mutant *EGFR* ctDNA and the means to multiplex the assay to examine more than one *EGFR* mutation simultaneously. Patients in the study were representative of an *EGFR*-mutant NSCLC population: a median age of 66 years, 64 percent female, 57 percent never having smoked, and 53 percent of Asian ethnicity.

Multivariate analysis showed a trend toward worse overall survival with a high cfDNA concentration, regardless of *EGFR* ctDNA result (p=0.086). The 12-month overall survival for patients with a cfDNA concentration above the median for the population was 50 percent, compared with 68 percent for those with a cfDNA concentration below the median. In addition, the researchers found that patients with detectable *EGFR* ctDNA had worse outcomes than those with undetectable *EGFR* ctDNA at the time of progression; the former population had a 12-month overall survival of 49 percent and the latter 68 percent (p=0.003). Patients with detectable *EGFR* ctDNA for the *EGFR*-activating mutation only (*EGFR* T790M negative, but *EGFR* L858R or exon 19 deletion positive) had a significantly worse 12-month overall survival of 11 percent, which remained

a significant predictor of mortality on multivariate analysis.

Optimizing outcomes

The future looks brighter for patients with pediatric osteosarcoma; one day, physicians tracking the three-gene signature may be able to use it to tailor treatments to individual patients during the early stages of disease. If physicians can use biomarkers to predict whether patients will be good or poor responders to treatment, then – instead of administering the same neoadjuvant therapy to all patients – they will be able to gauge the strength of therapy each patient needs prior to surgery to remove metastatic cells. After surgery, they will also be able to measure the patient's response and more decisively determine the degree of follow-up needed to optimize the outcome. For the first time in decades, we may be better equipped to improve survival rates for children suffering from this disease.

Similarly, tracking cfDNA in *EGFR*-mutant NSCLC patients could allow physicians to test patients for *EGFR* TKI resistance earlier and optimize treatment based on *EGFR* ctDNA testing results. Pender's results indicate that patients with lower levels of cfDNA on *EGFR* TKIs were likely to have a longer overall survival. In contrast, patients with detectable *EGFR* ctDNA – but who test negative for *EGFR* T790M – should be considered for a switch to chemotherapy instead of awaiting repeat *EGFR* T790M testing. These patients have a poorer prognosis, likely due to an *EGFR* T790M-independent mechanism of resistance, and delaying the switch to chemotherapy may mean missing the window for effective treatment.

Overall, the ability to track cancer biomarkers via liquid biopsy may allow physicians to understand the unique nature of each patient's disease. By using the strategies applied in the studies above in combination with other molecular diagnostics, we may eventually be able to generate a catalogue of biomarkers to improve outcomes for those with cancer.

Alexandra Pender is a medical oncologist specializing in lung cancer and melanoma. Her research interests include circulating tumor DNA in lung cancer and clinical trials.

Natacha Entz-Werle has been a pediatric oncologist since 2003 developing research studies with a focus on pediatric osteosarcomas and gliomas.

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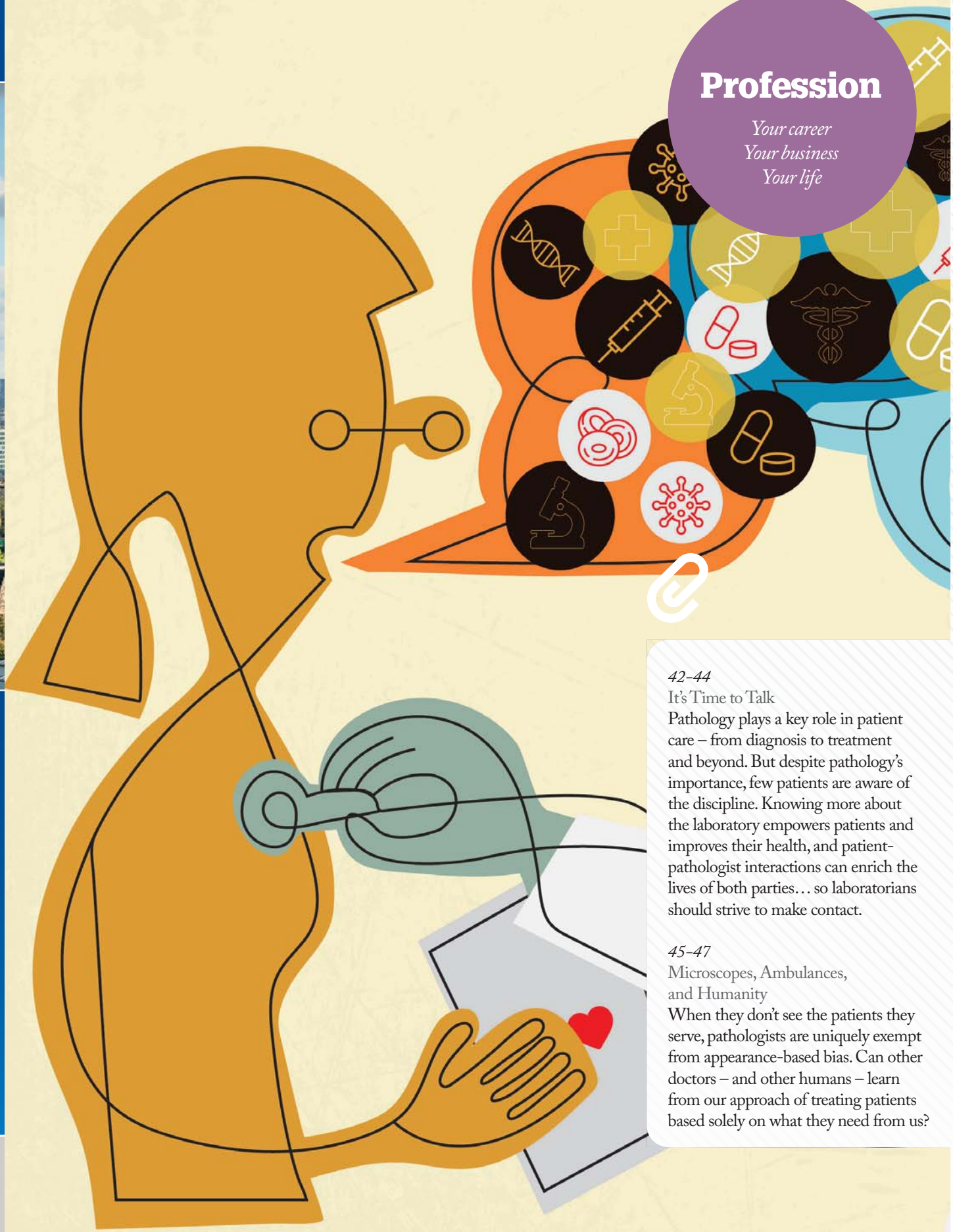
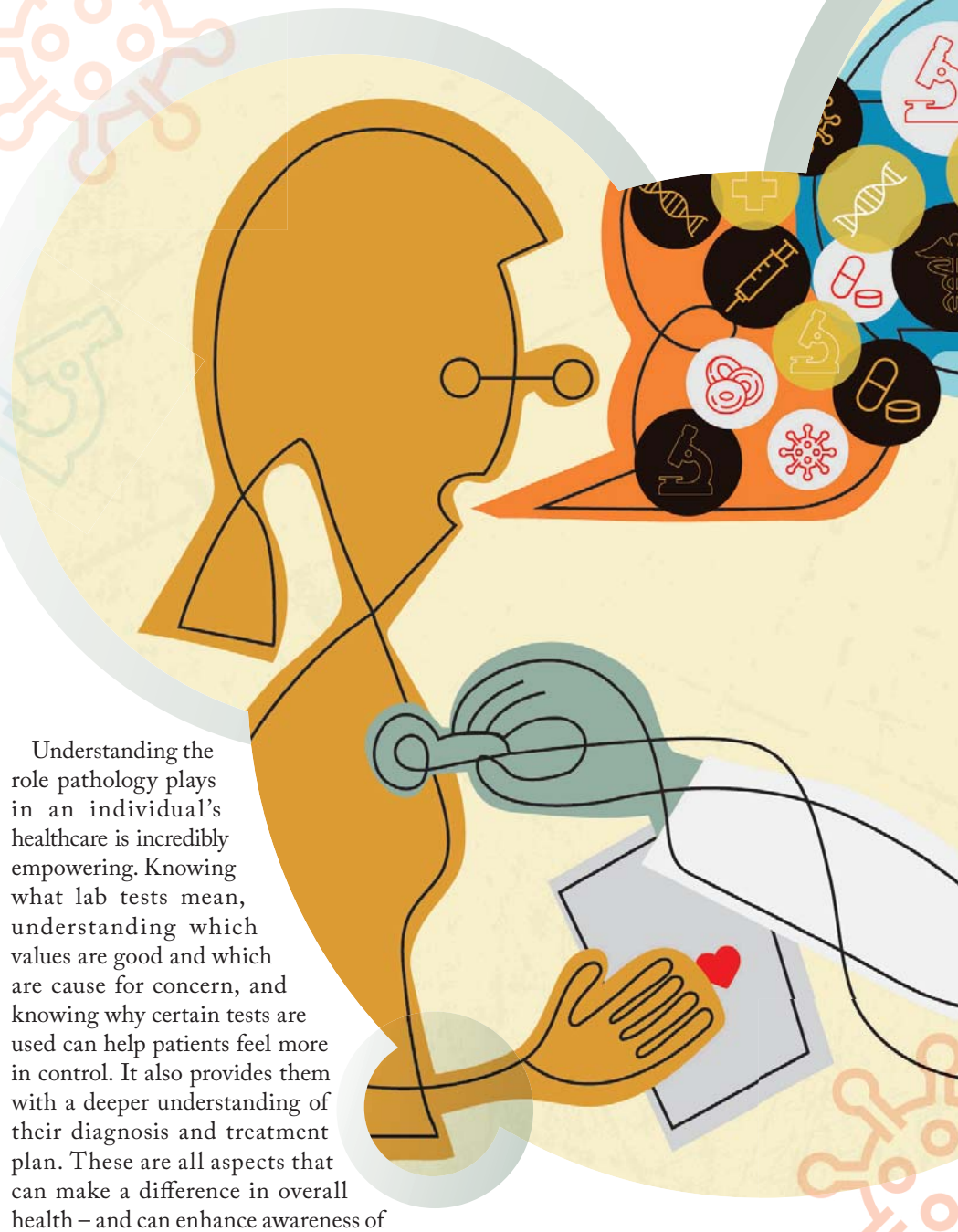


It's Time to Talk

The life-changing impact of patient-pathologist interactions

By Lotte Mulder, Jeffrey Myers, and Michele Mitchell



Patients' lives depend on pathology. It is through accurate and timely diagnostics that medical teams are able to treat, manage, and even cure patients' illnesses and maintain their health. Indeed, without accurate pathology and laboratory medicine systems, healthcare systems would fail, leading to enormous economic and personal losses (1–3). However, despite pathology's critical role in high-quality patient care, most patients are unaware of what pathologists do and why they are so important (4).

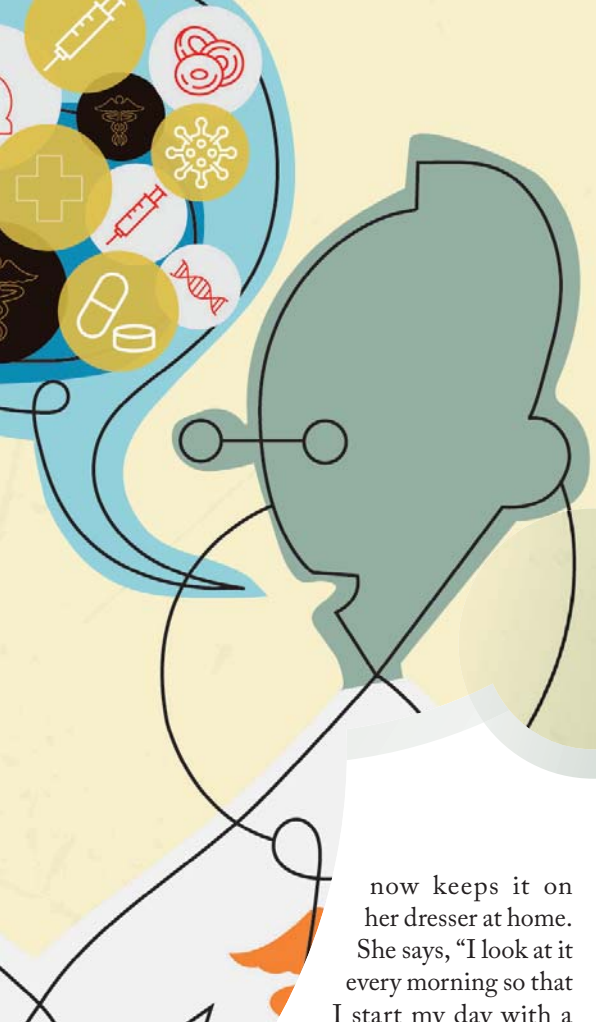
Why are patients so much in the dark about such a vital specialty? There are a variety of contributing factors. For one, laboratory reports rarely include the name of the pathologist (5). Additionally, when clinicians communicate directly with patients in reference to diagnostic medicine, they often refer to "the lab" rather than to the pathologists issuing the diagnosis. As a result, many patients view "the lab" as a sort of black box that takes in samples and churns out answers, rather than as a collection of highly qualified doctors and laboratory medicine professionals

"With the expansion of immuno-oncology treatments available to patients for a myriad of diseases, the role of the pathologist is evolving. Not only are pathologists involved in diagnosing patients, but they are also involved in treating patients – which many have referred to as 'therapeutic pathology,'" says Kim Sanford, ASCP President-Elect and Associate Professor of Pathology at Virginia Commonwealth University.

Understanding the role pathology plays in an individual's healthcare is incredibly empowering. Knowing what lab tests mean, understanding which values are good and which are cause for concern, and knowing why certain tests are used can help patients feel more in control. It also provides them with a deeper understanding of their diagnosis and treatment plan. These are all aspects that can make a difference in overall health – and can enhance awareness of pathologists and their work.

One of the authors of this article, Michele Mitchell, was diagnosed with breast cancer on the same day that her husband, Ray, suffered a stroke. Ray passed away a month later. Michele went through surgeries, chemotherapy, radiation, and adjunctive therapy, but it wasn't until midway through her treatment that she met co-author and pathologist Jeffrey Myers. And that's when she first understood that she could see her own pathology report and actually speak with a pathologist about her case. He showed her the tumor slides and pathology report, and it changed her view of her disease.

The meeting helped Michele better understand her diagnosis and treatment plan and embrace the necessary steps to beat her cancer. She framed the cancer slide and



now keeps it on her dresser at home. She says, "I look at it every morning so that I start my day with a re-commitment to living a healthy lifestyle."

Pathology touches the lives of nearly every patient who steps through a healthcare organization's doors, and although the specialty has traditionally lived behind a curtain (seemingly beyond the reach of patients), stories like these show that the paradigm is shifting.

Putting patients first

Patient-pathologist interactions can have a profound impact on both parties. Patients gain an increased understanding of their specific circumstances and treatment plan. If they have a life-threatening diagnosis, they can also form a clearer image of what exactly they are fighting. Pathologists, on the other hand, can understand how they impact patients' lives and increase their sense of purpose and accomplishments. As pathologist and ASCP Past President Jim Wisecarver states, "From a personal standpoint, having had the opportunity to work directly with patients during various types of apheresis procedures has reminded me that I, too, am a physician. Managing fluids and medications, consulting with their primary physician, and ultimately watching them improve clinically as a result of our efforts is very rewarding."

To better facilitate patient-pathologist interactions, some healthcare organizations today are adopting a patient- and family-centered care (PFCC) strategy. Not only do such strategies encompass clinicians working directly with patients and families in the context of an episode of care, but they also extend to how facilities are designed, how policies affecting care are developed, how quality can be achieved in our daily work, and how we respond to patient safety events. When pathology and laboratory professionals learn to interact directly with patients and families in all aspects of their work, it results in greater success. Moreover, the practice sets up an improved patient experience that impacts not only individual, but also the health of the community.

"Pathology touches the lives of nearly every patient who steps through a healthcare organization's doors, and although the specialty has traditionally lived behind a curtain (seemingly beyond the reach of patients), [...] the paradigm is shifting."

Implementing PFCC in your own practice begins with first learning what resources are available at an institutional level. This might include opportunities for active participation in an enterprise-level Patient and Families Advisory Council rather than creating your own. Either way, this is more easily done in partnership with others than as an isolated departmental tactic.

But many places are not there yet. A logical first step in the absence of a more global PFCC strategy is learning to talk directly with patients and families. Many will appreciate being given the tools to understand the information the laboratory provides and how it affects their care. It is not only an opportunity for patients, but also an opportunity for the laboratory; it's a chance to listen to patients' concerns

"When embraced by patients and organizations alike, pathology can transform itself into an enriching and essential service that offers far more than reports and data."

and address any gaps in care. It's also a chance to better collaborate with clinical colleagues and learn new ways to add value in an ever-changing healthcare environment. It allows pathology to become part of the patient care team. When embraced by patients and organizations alike, pathology can transform itself into an enriching and essential service that offers far more than reports and data.

There are a number of ways you can approach interactions with patients. First, make sure that you greet the patient personally and introduce yourself. If you state your specialty, explain exactly what you do, because the patient probably won't know. In fact, they might never have come into contact with a pathologist before – so try to use simple terms to increase their understanding of pathology. Next, assess their level of medical knowledge and use understandable analogies to explain their situation. Start with an open-ended question. For instance, "What is your understanding of your diagnosis"? Asking them the first question is a sign of respect; it develops a rapport and allows you to learn what they already know so that you can start from there. Make sure you pay close attention to the words you use in your explanations; they can have an impact on the patient's perception of their situation and their prognosis.

Always allow time for the patient to ask questions before you move from one topic to the next. Gauge the emotional landscape before you continue – after all, the information you are providing is familiar to you, but it's brand-new to the patient and it can be quite jarring to hear. Try to answer their questions in simple terms; if you don't know an answer, reassure the patient that you will look into it – and then make sure to follow up with them either in person or via a telephone call or message. Finally, tell the truth, and remember to show empathy for the patient. They are hearing life-changing information from you, often for the first time, so showing kindness and being prepared to handle emotional reactions gently will help you form the best possible relationship with your patients.

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

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Microscopes, Ambulances, and Humanity

How the pathologist's service to a patient is a rare example of an unbiased approach to healthcare – and life

By Kamran M. Mirza

I am a Muslim-American physician with brown skin and a trim beard. I have noticed that what I wear and how I carry myself in the hospital corridor can generate a highly variable response from the people around me – my patients, their families, our hospital support staff, even random strangers in my vicinity.

Here's a scenario: I am running late for a meeting and the elevator is closing as I rush toward it. I press the button in the nick of time. Instantly, an elevator full of people re-opens. I sheepishly get in, apologizing for making everyone stop. Let's say I am wearing jeans and have come in on a Saturday to catch up on work. Despite an obvious hospital ID bearing the title "MD," the elevator opens to an almost hostile attitude toward me. I am a big inconvenience. Stopping again was a huge problem. No one smiles or says anything. So awkward.

Now imagine that I am wearing a suit or have my doctor's coat on. The response from my own anecdotal cross-sectional analysis has been an outpouring of accommodation and smiles. "It's no problem, Doc!" "No worries!" This sentiment typically extends throughout the hospital halls and common spaces. Random hellos, warmth, and smiles when I overtly look like "Dr. Mirza."

How I look matters.

Moving beyond prejudice

My *actual* interaction with patients is indirect. As a pathologist, I see my patients through a microscope. Reviewing slides from patients' tissues is analogous to a meme I saw recently – several skeletons in a row, labeled with descriptors of their former owners: white, black, gay, straight, Muslim, Christian, Jew, Hindu, atheist. They are all identical (obviously) – the point being that we are all the same inside. When seeing patient samples through the "microscope curtain," the only thing I know about them is their names (from the requisition paperwork). I don't know what they look like, what religion they practice, how they dress, whether or not they smell bad, whether or not they are prejudiced against my religion or gender – and I don't care. All I care about is interpreting what their cells

"Inside, we are all the same. No one can testify to this more than a pathologist. Wouldn't it be amazing if all medicine were like this?."

are telling me. I know it sounds like a cliché but, inside, we are all the same. No one can testify to this more than a pathologist. Wouldn't it be amazing if all medicine were like this? If we all had the ability to look at our patients in this neutral manner, wouldn't the world be a more humane and loving place?

The same could be said for the reverse. What if our patients could all look at us the same way and not have prejudice against our race, religion, or gender? Susan and Jack would both be referred to simply as "Dr. Simpson." John wouldn't have to worry about decorating his office with a picture of himself with his husband and how some patients might react. Mohammad wouldn't have to care if a patient saw him walking out of the chapel after offering Friday prayers.

I think about my Muslim-American, head-scarf-wearing, ICU physician wife and wonder how her patients – very sick people with distressed families – look at her. She is an exceptional physician and a superlative human being. She has cried with patients, laughed with them, and bonded with their loved ones. But what if her patient's family is not an understanding one? What if she loses a patient who was bound to die no matter what the intervention and, just maybe, the way she looked influenced the family's response? What would she do then?

Lessons from the road

This business of what we look like and how it can influence others' reactions reminds me of a commuting story. Coming home from work a few years ago, navigating the usual heavy traffic had me on edge. My day, like any day in the life of a resident, had been jam-packed. It was the usual stress combined with years of traveling the same roads, with similar traffic, unending construction, and the same congested spots. At one point, two lanes abruptly became one. Lonely signs from miles away tried to warn oncoming traffic of this union, but seldom did anyone pay heed – and the result was the ultimate display of road rage and disgruntled behavior. Instead of yielding to one another to merge into a single lane, people tried to stay in both lanes for as long as possible. If their car fit into the second lane, they stayed.

In my tiredness, I had a range of reactions to this process. Most often, I angled my car so that it forced people to merge into one lane. "What will you do now, buster?!" I would say into my mirrors, my face clearly visible to the other drivers. Or – if I was feeling particularly nice – I would let them whiz by, riding the shoulder, and justify it by saying maybe they weren't local. Maybe they hadn't seen the signs. Maybe they didn't realize the lane closure would come so quickly. Maybe there was a family emergency. My physician training, I guess?

Witnessing this event every day allowed me to look at the faces, races, ages, and expressions of the drivers who participated in this undignified behavior. I found myself curious about who they were and what they might be possibly going through based solely on their driving. Less commonly, I found myself wondering if these people's upbringing, their socioeconomic status, race, religious background, or age played a role in their behavior. I wondered if some drivers felt more entitled to the road than others. In this crazy demonstration of commuter aggression, did how they look matter? Did how I look matter?

Once, while driving, I raised my hand to thank someone for letting me change lanes. (I do a little handwave as a gesture of gratitude.) This time, the car behind me sped up, cut across me, stopped dead in its tracks, and the driver stormed out and started banging on my car and window with his fists. He was irate! I hesitantly pulled down the window and realized that he thought I had shown him the middle finger. I was just thanking him! He was so angry that he even said "people like me" weren't welcome in his country. I guess how I looked mattered.

As a legal, law-abiding, tax-paying physician-immigrant with over a decade of being 'Murican and harboring a profound love for this country, these events stay fresh in my memory. I lost my first pathology residency spot due to a two-day visa delay. I had traveled, interviewed, matched, and done everything that was required of me. But the visa was late by one day and, just like that, my spot was rescinded. Did how I look matter? Since then, although I have successfully completed graduate and post-graduate education in the US, I have spent countless hours at O'Hare airport undergoing extreme scrutiny and "random" security checks. I guess how I look matters. In 2006, my wife and I – two resident physicians with paystubs and proof of employment – had to wait for two weeks before our Toyota dealer approved our secondhand car purchasing process because of the "Patriot" Act. What we believed mattered. When we bought our current home, old neighbors warned us that the area was not very "diverse." Nowadays, even when I am feeling lazy and don't want to rake leaves, I still go out and do it. Why? Because I don't want anyone to think "the Muslim family" doesn't rake the yard. Is this normal for all Americans – or is it because of how we look or what we believe?

Nevertheless, it isn't all doom and gloom. Despite having a ways to go as a country, these few instances are outnumbered by many wonderful moments. Although my wife, like all of us, has lost terminal patients, she has never had a negative, racially charged moment at work. Road rage is just that – silly road rage. Most people can mask their prejudices long enough to have a meaningful doctor-patient interaction (and, hopefully, educate themselves). My elevator experiences have been variable, but not malignant. Despite friendly warnings of "lack of diversity" by concerned friends, 90 percent of the people in our neighborhood are the best neighbors we could have asked for.

What of the ambulance?

But why do I mention the ambulance in the title of this article, you ask? Well, not everyone can understand the example of the microscope curtain – so let's discuss ambulances for a minute. If we were to take road rage, external bias, and general traffic happenings as a metaphor for bias in life then I want to bring your attention to the passing of an ambulance. Guess what? Everyone – white, black, brown, gay, straight, Muslim, Christian, Jew, Hindu, racist, xenophobe, tree-hugger, flat-earther, anti-vaccine dad, pro-vaccine mom, climate change activist, gun owner, anti-gun protestor, Democrat, Republican, independent – everyone slows down and moves to the side when an ambulance passes by. Does it matter what the patient looks like? Can they even see this patient? Do they know whether it's a boy or a girl – gay or straight – cisgender or transgender? Do they know about body shape, partnership status, presence or absence of body odor, or whether they wear headscarves, skullcaps, or have Nazi symbols tattooed on their bodies? No, they don't. And, just like pathologists making a diagnosis without one iota of bias, humanity comes to a standstill out of respect for a human they don't know passing by in an emergency vehicle.

As long as humans continue to slow down and move to the side for ambulances, I have hope that humanity will wake up and see how ridiculous they can be when basing their opinions on looks alone. May all physicians be like pathologists – making unbiased diagnoses from behind a "microscope curtain." And may all humans respond to others like those drivers who slow down and move aside for an ambulance.

Kamran M. Mirza is an Assistant Professor in the Department of Pathology and Laboratory Medicine, Loyola University Health System, Chicago, Illinois, USA.

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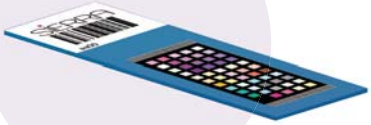

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FFEI's patented Sierra color management solution enables the standardization of digital images produced by WSI scanners. Sierra uses a biologically stained slide that mimics human tissue. To measure the spectral accuracy of a scanner, an ICC profile is then generated – meeting FDA colour reproducibility guidelines.
https://ffei.ai/

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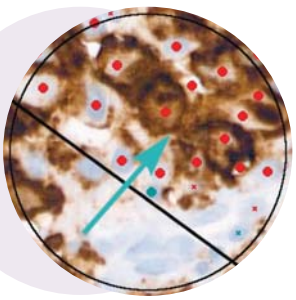
MacroPATH: The Game Changer in Gross Macro Digital Documentation

Milestone has specifically designed MacroPATH for use in the gross room to eliminate misinterpretation of descriptive reports, to reduce description time and provide greater accuracy. MacroPATH is a user-friendly, high-resolution image capture system that can fit any existing gross workstation or can be used as a shared, stand-alone resource.
https://www.milestonemedsrl.com/product/macropath



MindPeak Showcases Second Product for PD-L1 After Successful Launch of BreastIHC

After the successful product launch of MindPeak's BreastIHC, our second pilot product for PD-L1 stained cell quantification is coming. First tests on real-world clinical data show promising results concerning accuracy and robustness. Our goal is to relieve pathologists of the burden of PD-L1 scoring in clinical routine and research.
https://www.mindpeak.ai/

RedRick Technologies Ergonomic Workstations Alleviate the Risk of Repetitive Stress Injury

The shift to digital pathology will require pathology departments to create flexible and stable ergonomic workspaces that accommodate both a digital pathology viewer and a microscope. As other digital clinical departments have discovered, a well-designed workspace also facilitates collaboration and teaching and maximizes the use of space.
https://bit.ly/2GXBUBT

Thank You to Our Residents

Recently, several of our clinicians were infected with COVID-19 and medical services risked collapse. This group of pathology residents voluntarily joined the COVID-19 team attending patients in the hospital, taking on clinicians' shifts and helping with their tasks. We are proud of their generosity and professionalism. They truly demonstrated that pathologists also serve on the front lines in health emergencies – and we thank them.
Bellvitge University Hospital, Barcelona, Spain

The GIST of It

Sitting Down With… Markku Miettinen, Senior Clinician and Head of the General Surgical Pathology Section, Laboratory of Pathology, National Cancer Institute/National Institutes of Health, Bethesda, Maryland, USA

As Head of Surgical Pathology at the National Cancer Institute, what does your job entail?

I lead a group of three surgical pathologists and participate in clinical activities that include handling surgical pathology cases of all kinds, as well as internal and external cases of soft tissue and bone pathology. I also have a research group that studies the improvement of diagnostic methods, especially immunohistochemistry. Our research also includes the study of gastrointestinal stromal (GIST) and related tumors, including genomic studies. Today, we analyze not only stromal tumors and sarcomas, but also common tumors; lately, we have been focusing on fusion tumors. Last, but not least, I also participate in resident education.

Our pathology unit is called the Laboratory of Pathology. It supports both the National Cancer Institute and the diagnostic needs of all branches of the National Institutes of Health. Its clinical units support numerous clinical trials ongoing in our clinical center, which has a hospital solely devoted to such trials. The department also has investigators who perform basic research in pathology and cell biology and to whom I provide specialized pathology support.

How does your current work compare with your previous position?

Before coming to the National Institutes of Health, I was at the Armed Forces Institute of Pathology, which has now closed. The AFIP was a unique research institute devoted to studying the pathology of disease. It had a large collection of specimens, which gave me the opportunity to study rare tumors. Although it provided consultations for federal government entities and hospital pathologists, its staff did not work directly with clinicians.

In contrast, the NIH is a complex of institutes devoted to basic and clinical research. Our laboratory practices pathology in close contact with clinicians developing new treatments for cancer and other diseases. I am grateful for my time here, because I have learned so much from my colleagues on such a great variety of topics, including immunotherapy, immune deficiencies, genomic and epigenetic pathology, and even some clinical and therapeutic thinking.

After the closure of the AFIP, the Joint Pathology Center (JPC) of the Armed Forces took over AFIP's clinical activities. The NIH's Laboratory of Pathology remains, in many ways, connected with the JPC. For example, both institutions mutually support specialty pathology consultation and research collaboration on diagnostic pathology, especially with respect to advanced modalities, such as molecular diagnostics.

When I moved to the NIH, my study of cancer took priority – especially colon carcinoma, which is common, important, and easily available as a native specimen. Patients with less common rectal and gastroesophageal cancers usually receive neoadjuvant treatment so effective that no apparent tumor remains for study – so I opted for a disease that both needed and facilitated ongoing research.

What do you consider your most important contribution to surgical pathology?

Perhaps our studies on pathology and clinical correlation of GIST, including the generation of a prognostication system. It is well known that the availability of KIT/PDGFRA kinase inhibitor drugs made clinical study of GIST very popular – a fact reflected in the citation numbers of articles on GIST pathology. Some large surveys on the diagnostic utility of immunohistochemical markers may also fall into this category.

Books on soft tissue pathology are my main educational products; I have written several. And I have learned that writing a book teaches many lessons – not only to its readers, but also to its authors!

What do you see in pathology's future?

I think histopathology will remain valuable even as molecular tools become increasingly available. Although molecular diagnosis is essential in some cases (and important for finding treatment targets), most diagnoses can still be made using histology and immunohistochemistry. We know that many unrelated tumors have similar mutations and gene fusions, so a precise non-histologic diagnosis requires comprehensive expression profiling on top of genomic analysis. In comparison, classic histopathology is much faster and more cost-efficient.

The other big advance on the horizon is digital pathology. However, at least for now, I feel its time has not come – it remains more costly and time-consuming than traditional methods. However, digital diagnosis has major advantages in the creation of numeric precision, sharing histologic images, and allowing for telework, so I believe it will one day become a major, possibly dominant, diagnostic tool.

What advice would you give young doctors considering a career in pathology?

Pathology is an enormously satisfying specialty with unlimited intellectual challenges. To get the best of surgical pathology, one has to integrate new tools into the morphologic diagnosis: immunohistochemistry, molecular analysis, and epigenetics. Although pioneered by hematopathologists and neuropathologists, these are now becoming important in many subspecialties. It pays to become familiar with them, regardless of your field of focus. And, above all, entering pathology at this time of rapid change is an incredibly fun opportunity!

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Proteus spp.
Pseudomonas aeruginosa
Serratia marcescens
Staphylococcus aureus
Streptococcus agalactiae
Streptococcus pneumoniae
Streptococcus pyogenes

Atypical Bacteria (qualitative)
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Legionella pneumophila
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