

the Pathologist®



Official society partner of *The Pathologist*

In My View
Modernize your
pathology teaching

13

In Practice
Connecting labs for better
patient care

38 – 42

Profession
Survival lessons from
Henry Appelman

44 – 47

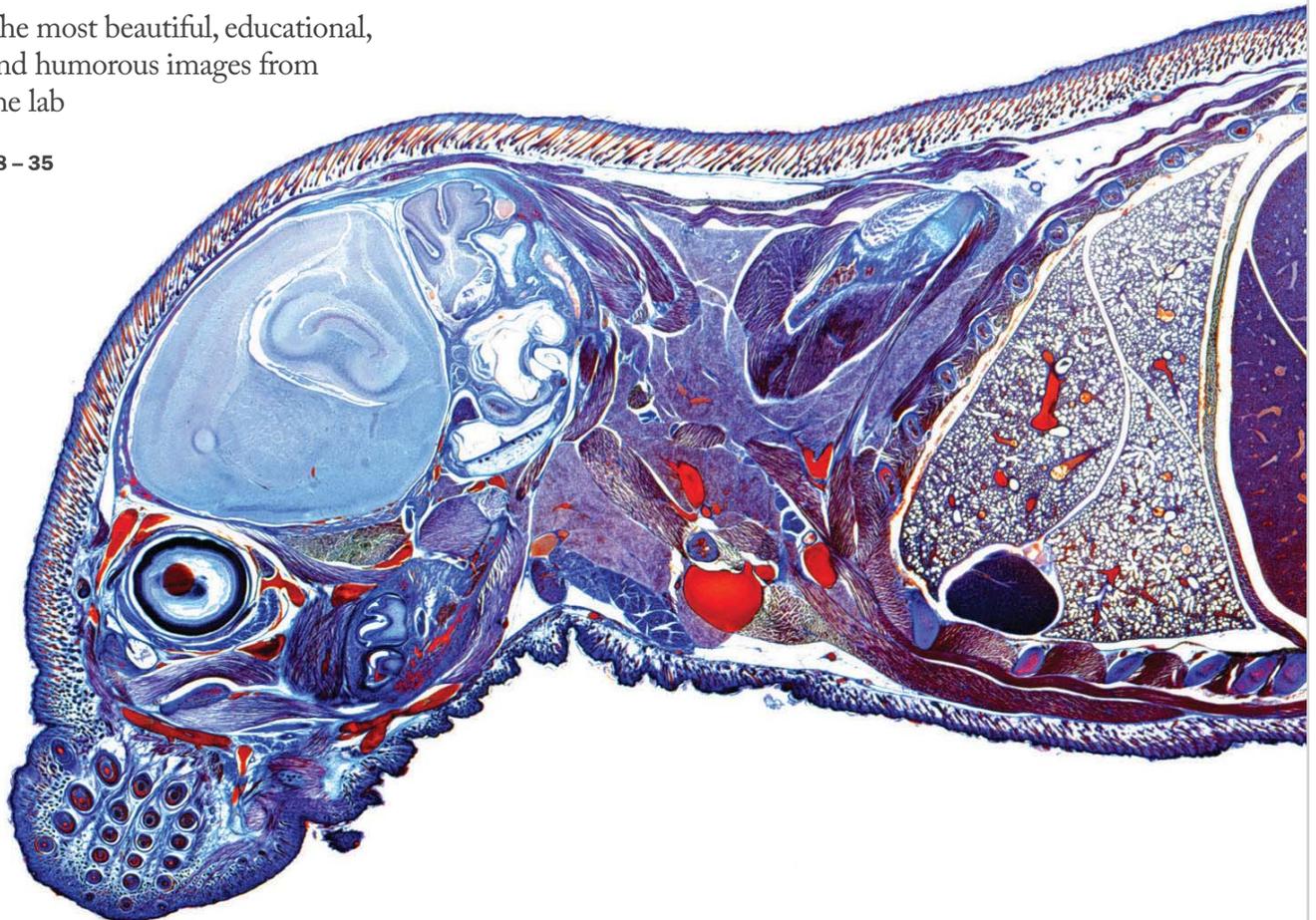
Sitting Down With
Living textbook creator
Nat Pernick

50 – 51

Picture Perfect Pathology

The most beautiful, educational,
and humorous images from
the lab

18 – 35



CAP TODAY Webinar

PD-L1 IHC 22C3 pharmDx in TNBC: from KEYNOTE-355 to real-world scoring

Wednesday, May 19, 2021, 1 PM–2PM ET



Why should you register now for this webinar?

Understand the practical use of PD-L1 IHC 22C3 pharmDx in TNBC, and get tips for high-quality implementation in your lab.

Brought to you by: CAP TODAY

Moderated by: Bob McGonnagle, Publisher, CAP TODAY

Presenters: Corrado D'Arrigo, MD, and Teresa Thomas, MD

What will this webinar empower you to do?

- Understand how to apply the clinically-validated Combined Positive Score (CPS) in PD-L1 testing for TNBC
- Explore how to score real TNBC cases
- Discuss the differences between PD-L1 assays approved for TNBC

Ask questions of our distinguished presenters

Register FREE of charge at

<http://www.captodayonline.com/051921webinar>



Corrado D'Arrigo, MD
Poundbury Cancer Institute for
Personalized Medicine, UK



Teresa Thomas, MD
Poundbury Cancer Institute for
Personalized Medicine, UK

CAP TODAY does not endorse any of the products or services named within.
The webinar is made possible by a special educational grant from Agilent Technologies.



I have always thought of pathology as a visual discipline. How could it not be when so many diagnoses depend on a subtle shift of color in a slide, or on a few too many cells in a visual field, or on the appearance of a microscopic pathogen in otherwise normal-looking tissue?

But it seems I may have underestimated the field. Although the visual aspect is certainly key – after all, our upcoming gallery feature clearly showcases that pathology really is about “the picture of health” – laboratory medicine professionals can accomplish a great deal without ever coming near an image.

Take last issue’s focus on podcasts, for instance. How can so many skilled laboratory professionals convey so much about their discipline without ever actually showing it – and how has an audio-only medium become not only popular, but a valuable educational tool in pathology?

Or consider digital and computational pathology. Despite the emphasis on images, it’s clear that a computer can’t actually “see” anything – and that all of its information comes from 0s and 1s in the ether. Yet, far from being a limitation, this focus on data actually allows algorithms to make distinctions so slight that they are invisible to the human eye.

In a world where artificial intelligences increasingly take the reins and education often takes place at a distance, is visual learning giving way to new approaches? I don’t think so – but it’s clear that even images need to keep up with the times. Students who may once have learned to gross in person may now learn from video tutorials (1) – and, in a few years, may learn via augmented or virtual reality (2). Textbooks that may once have showcased careful drawings of slides and cells now contain glossy full-page photographs; the CDs once included in your textbook purchase have been replaced by software codes that lead you to interactive websites offering an enhanced educational experience. Our pictures move; we can zoom in and out, annotate, and manipulate them. We can overlay them onto real backgrounds and interact with them as though they were real.

The future of pathology is indeed visual – and digital – and so much more.

Where do you think the discipline is headed next? Drop us a line – edit@thepathologist.com – to have your say!

Reference

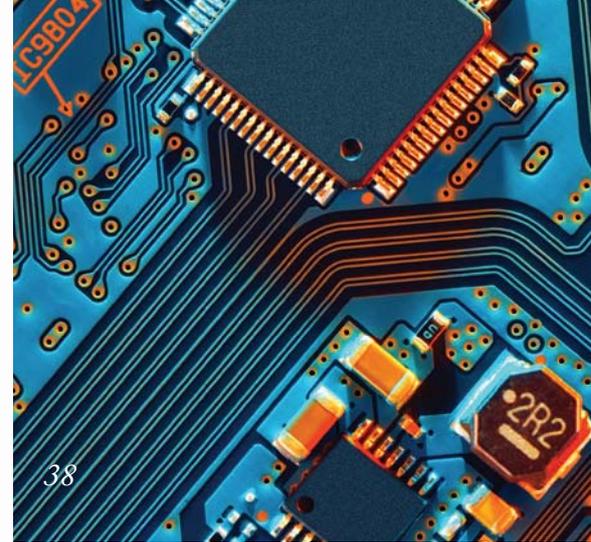
1. M Schubert, “Have You Heard?,” *The Pathologist* (2021). Available at: <https://bit.ly/3s4jFR9>.
2. M Schubert, “Augmented Reality for the Lab,” *The Pathologist* (2020). Available at: <https://bit.ly/30YWYCO>.

Michael Schubert
Editor





25



38



09

03 **Editorial**
A Receptive Field
by Michael Schubert

On The Cover



"Five-Day-Old Mouse,"
by Robert D. Meyer.

Upfront

06 Test your knowledge of hepatitis history or dive into the genetics of glaucoma – this month's Upfront section offers you everything from saving kidneys to sniffing out disease.

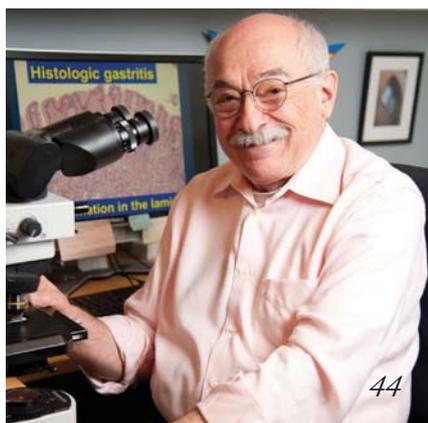
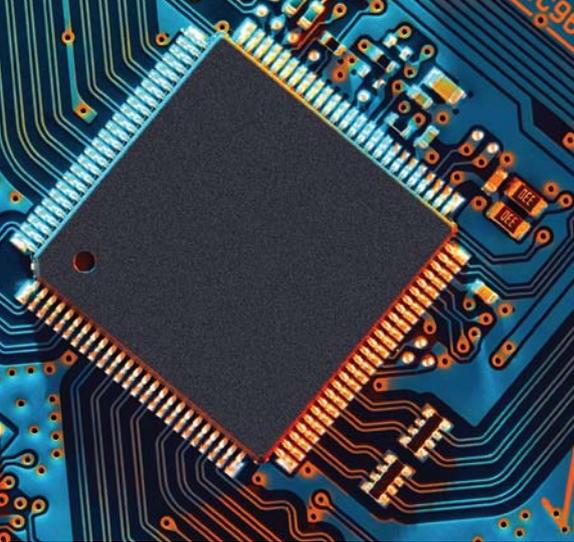
10 Case of the Month

In My View

- 12 All is not well in pathology postgraduate training. **C.N. Srinivas** explores both the excellence of Indian pathology graduates and the gaps in their training.
- 13 **Shivayogi Bhusnurmath** and **Bharti Bhusnurmath** take a close look at the current state of Indian pathology training and offer suggestions for its improvement.
- 14 Single-cell analysis is the way of the future, says **Zachary Pitluk** – and, with advances in technology, it now sits within our grasp.

From The ASCP

- 15 **Educating Patients, Now and Beyond**
The spotlight is on the lab now – but laboratorians must make sure it stays there by participating in education for patients and the general public.



Feature

- 18 **Picture Perfect Pathology**
We asked our readers to share their best and most beautiful pathology images – from the sublime to the hilarious – and you responded in droves. Here, we share some of the highlights of your year in pictures.

In Practice

- 38 **Breaking Siloes, Building Networks**
Tom Lewis tackles the touchy subject of variation between laboratories and discusses how the Getting It Right First Time program, assisted by improvements in seamless data transfer, has helped.



Profession

- 44 **Peer-to-Peer with Henry Appelman**
With one of the longest careers in pathology today, Henry Appelman knows what it takes to succeed – both in a career and in life. Here, in an interview with Ivan Damjanov, he shares his experiences, his learning, and his words of wisdom to colleagues.

Reports

- 16 **Let's Do It Ourselves**
- 36 **Ahead of the Rest**

Sitting Down With

- 50 **Nat Pernick, Founder and President of PathologyOutlines.com, Bingham Farms, Michigan, USA.**

Feel free to contact any one of us:
first.lastname@texerepublishing.com

Content Team

Editor - Michael Schubert
Olivia Gaskill (Associate Editor)

Commercial Team

Publisher - Lee Noyes
Sally Loftus (Associate Publisher)
Danny Crowe (Business Development Executive North America)
Paul Longley (Business Development Executive)

Design Team

Head of Design - Marc Bird
Hannah Ennis (Senior Designer)
Charlotte Brittain (Designer)

Digital Team

Digital Team Lead - David Roberts
Peter Bartley (Digital Producer Web/Email)
Abygail Bradley (Digital Producer Web/App)

Audience Team

Audience Growth Strategy Manager
- Brice Agamemnon

CRM & Compliance

CRM & Compliance Manager - Tracey Nicholls
Hayley Atiz (CRM Assistant)

Commercial Support Team

Internal Systems Manager - Jody Fryett
Dan Marr (Campaign Reporting Analyst)

Commercial Services

Commercial Service and
Social Media Manager - Matt Everett
Kevin O'Donnell (Marketing Executive)
Alice Daniels-Wright (Video Project Manager)
Jess Lines (Project Support Coordinator)
Lindsey Vickers (Sales Support Project Manager)
Jennifer Bradley (Sales Support Coordinator)

Marketing Team

Marketing Manager - Katy Pearson
Jo Baylay (Marketing Executive)

Accounts Team

Kerri Benson (Accounts Assistant)
Emily Scragg (Accounts Apprentice)

Human Resources

Human Resource Manager - Tara Higby

Management Team

Chief Executive Officer - Andy Davies
Chief Operating Officer - Tracey Peers
Senior Vice President (North America) - Fedra Pavlou
Financial Director - Phil Dale
Commercial Director - Richard Hodgson
Content Director - Rich Whitworth

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

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

Distribution: The Pathologist (ISSN 2055-8228),
is published monthly by Texere Publishing Limited, Booths
Park 1, Chelford Road, Knutsford, Cheshire, WA16 8GS, UK.
Single copy sales \$15 (plus postage, cost available on request
info@thepathologist.com). Non-qualified annual subscription
cost is available on request.

Reprints & Permissions - tracy.nicholls@texerepublishing.com
The copyright in the materials contained in this publication and the
typographical arrangement of this publication belongs to Texere Publishing
Limited. No person may copy, modify, transmit, distribute, display,
reproduce, publish, licence or create works from any part of this material or
typographical arrangement, or otherwise use it, for any public or commercial
use without the prior written consent of Texere Publishing Limited.
The names, publication titles, logos, images and presentation style appearing
in this publication which identify Texere Publishing Limited and/or its
products and services, including but without limitation Texere and The
Pathologist are proprietary marks of Texere Publishing Limited. Nothing
contained in this publication shall be deemed to confer on any person any
licence or right on the part of Texere Publishing Limited with respect to any
such name, title, logo, image or style.

Disease-Sniffing Snout-Device

Machine-based cancer detection system mimics the canine nose

Though prostate cancer is the second-highest cause of cancer death in men, early biomarker detection methods – specifically, the prostate-specific antigen screening test – lack sensitivity and specificity. We need to reduce false positives and false negatives – but how? The answer may lie in our four-legged friends. Trained canines have been shown to reliably detect and diagnose cancer by smell. Granted, dogs in the lab would be a logistical nightmare and not feasible for mass testing – but that’s where researchers at Massachusetts Institute of Technology (MIT) come in.

Using urine samples from patients with or without prostate cancer (confirmed by biopsy), they tested whether the cancer could be detected by trained sniffer dogs, molecular volatile organic compound (VOC) analysis by gas chromatography-mass spectroscopy (GC-MS), or microbiota profiling (1). Canine olfaction reliably distinguished between prostate cancer samples and biopsy-negative controls, whereas VOC



Upfront

Research
Innovation
Trends

and microbiota detected qualitative differences between the groups.

From this, the team trained an artificial neural network to mimic canine olfactory diagnosis – distinguishing between biopsy-positive and biopsy-negative samples based on the GC-MS data both alone and combined with canine olfaction data. “We knew that the sensors are already better than what the dogs can do in terms of the limit of detection, but what we haven’t shown before is that we can train an artificial intelligence to mimic the dogs,” said Andreas Mershin, a research scientist at MIT and author on the study (2). “And

now we’ve shown that we can do this – we’ve shown that what the dog does can be replicated to a certain extent.”

This multiparametric approach lays the groundwork for the development of machine-based diagnostic tools that mimic canine olfaction – and, given the dogs’ keen sense of smell, it has the potential to improve diagnostic efficacy in a field where unreliable results run rampant.

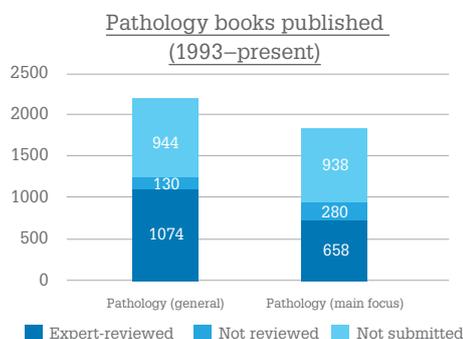
References

1. C Guest et al., *PLoS One*, 16, e0245530 (2021). PMID: 33596212.
2. *MIT News* (2021). Available at: <http://bit.ly/307Y10K>.

INFOGRAPHIC

Pathology by the Books

Data visualizations from the world of pathology book publishing



Specialty pairings: pathology and...





RESEARCH ROUNDUP

The latest breakthroughs in pathology and laboratory medicine research

Prior Expectations

Cognitive bias may affect forensic pathologists' decisions; research shows they are more likely to determine the cause of death as "homicide" rather than "accident" for Black children compared with white children, and to exhibit biased decisions when given non-medical information about the child's and caregiver's race (1).

Paleopathology Perspectives

A paleopathological study of 69,379 skeletons has found a decline in prevalence of tuberculosis, treponematoses, and leprosy over time, but only after an early increase in disease-related skeletal changes. This may be caused by the initial host-disease contact period and decline due to co-adaptation of the pathogen and host (2).

Dissolvable Digestion

Researchers have developed a rapid digestion workflow for PAGE separation of proteins, overcoming the limitations of the GeLC-mass spectrometry workflow (which requires overnight enzymatic digestion in gel) and reducing serum sample preparation and quantification

times of inflammatory biomarkers to only five hours (3).

Heart to Heart

Protein-protein interaction networks have been found to distinguish hypertrophic cardiomyopathy patients from dilated cardiomyopathy patients, suggesting underlying differences between the two (4). Individual network features were also associated with heart failure and health outcomes, exhibiting potential for individualized treatment options.

Finding Fragments

Urine cfDNA has a high volume of DNA fragments, but is poorly understood. Now, researchers have found that urine tumor cfDNA contains more aberrant fragments that end within recurrently protected regions – showing that it could be an indicator of cancer and a potential supplement to plasma cfDNA (5).

Dealing with Delirium

Delirium is common in elderly adults, particularly after surgery – but what causes it? A proteomic analysis has identified novel markers of risk and progression, finding that CHI3L1/YKL-40 is associated with the postoperative state (6). The protein has also been linked to aging, mortality, and onset and progression of Alzheimer's disease.

See references online at: tp.txp.to/res-rup

Now That's Smart

Portable smartphone microscope detects biomarkers at low concentrations

To detect low-level biomarkers, we must amplify their signals – but, though fluorescence-based tests have advanced greatly, they still require costly equipment that may be inaccessible in resource-limited settings or at the point of care.

Researchers at Munich's Ludwig Maximilian University have used DNA origami nanostructures to develop addressable nanoantennae with cleared hotspots – pairing DNA probes with gold or silver particles to amplify fluorescence signals. Using those nanoantennae, they built a portable smartphone microscope to successfully detect fragments of antibiotic-resistant *Klebsiella pneumoniae* DNA.

"Our technology could be utilized for diagnostic tests even in areas in which access to electricity or laboratory equipment is restricted," said Viktorija Glembockyte, joint first author of the study (2). "We have shown that we can directly detect small fragments of DNA in blood serum using a portable, smartphone-based microscope that runs on a conventional USB power pack."

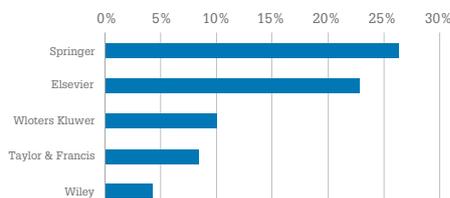
See references online at: tp.txp.to/amp-bio

Average list price

Pathology (general)
US\$162.04

Pathology (main subject)
US\$160.58

Top publishers (by volume)



Top lead authors/editors

- ➔ Vinay Kumar
- ➔ Ivan Damjanov
- ➔ Emanuel Rubin and Raphael Rubin
- ➔ Liang Cheng
- ➔ Pranab Dey

Credit: Doody Enterprises

One Giant Leap for Diversity

A new study offers a comprehensive genomic dataset that more fully represents global diversity

It's no secret that genetics has a diversity problem. And the issue hasn't gone unnoticed – in recent years, there have been a number of efforts to sequence genomes from populations other than the largely European, largely Caucasian references we've had to date. But diversity isn't solved in a day and studies that focus on a single alternative population are also not the answer. That's why researchers from the University of Maryland School of Medicine performed advanced sequencing and mapping on 64 complete human haplotypes representing 25 different populations from around the world (1).

One unique aspect of the study is that each genome was assembled without reference to previous composites – meaning that the genetic differences represented in the haplotypes better represents true human diversity. That applies not only to “normal” variations between genomes, but also to a broader

range of disease-causing alterations. “We've entered a new era in genomics where whole human genomes can be sequenced with exciting new technologies that provide more substantial and accurate reads of the DNA bases (2),” said author Scott Devine, Associate Professor of Medicine at the University of Maryland and a faculty member at the Institute of Genome Science. “This is allowing researchers to study areas of the genome that previously were not accessible but are relevant to human traits and diseases.”

Take, for instance, cystic fibrosis. Many newborns are screened for the disease at birth – but standard screening panels often miss the less common variants that arise in non-white patients (3). A fuller understanding of the diversity of causative mutations across ethnicities could ensure that more

patients are diagnosed at a young age, ensuring earlier – and potentially more effective – treatment.

“[This] landmark new research demonstrates a giant step forward in our understanding of the underpinnings of genetically-driven health conditions (2),” said E. Albert Reece, John Z. and Akiko K. Bowers Distinguished Professor and Dean at the University of Maryland School of Medicine. “This advance will hopefully fuel future studies aimed at understanding the impact of human genome variation on human diseases.”

References

1. P Ebert et al., *Science*, [Online ahead of print] (2021). PMID: 33632895.
2. D Kotz (2021). Available at: <https://bit.ly/30VoFLV>.
3. I Schrijver, *The Pathologist* (2016). Available at: <https://bit.ly/38T4W3R>.



Catching Cast-Off Kidneys

Ratio of IL-10 to TNF α may predict kidney transplant rejection

Despite kidney transplants' offering new hope for patients with end-stage kidney disease, up to 35 percent of kidneys are rejected within 10 years (1). This may

be the result of long-term immune system damage in the transplanted kidney – but, right now, our ways of finding out are either invasive or limited predictors of rejection.

University of Pittsburgh researchers recognized the need for less invasive immunological biomarkers and investigated the ratio of IL-10 to TNF α (2). In examining patients three months after transplant, they found that a low ratio was a strong predictor of

rejection within the first year and progressively worse renal function and decreased allograft survival within five years.

Anti-TNF α treatment for high-risk patients restored the ratio and, ultimately, regulatory function – demonstrating its potential as a therapeutic intervention for patients with predicted renal allograft rejection.

See references online at: tp.txp.to/c-off-kid

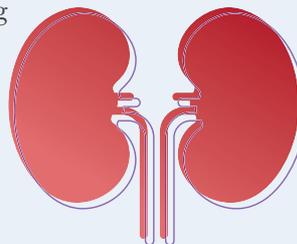




IMAGE OF THE MONTH



Jump Around

Researchers at the Francis Crick Institute have compared the spike protein structures of SARS-CoV-2, the bat coronavirus RaTG13, and a coronavirus from Malayan pangolins to understand the origin of the COVID-19 pandemic (1). They found that the pangolin-CoV spike protein is more similar to that of RaTG13 than SARS-CoV-2 (except for the receptor-binding domain). However, the team also found that spike proteins from pangolin-CoV can bind strongly to both human and pangolin ACE2 receptors, whereas the RaTG13 was unable to bind with either – suggesting that the pangolin coronavirus could infect humans.

Credit: Francis Crick Institute.

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

TWEET of the month

“Thoughts from today: autopsies in pathology residency matter. Sometimes we are the only ones who can give the families left behind answers and closure. They are not a burden; they are a gift. An opportunity to help a grieving family move forward.”

Kimberly M. Johnson (@K_JohnsonMD)
Read the original tweet here: tp.txp.to/kjohn-twt

Dead Cells Tell Tales

Noninvasive biopsy uses DNA fragments to detect disease

Researchers at Hebrew University have shown that a simple blood test can uncover information about the state of dead cells and, ultimately, detect disease (1). Using cfChIP-seq – sequencing of plasma cell-free nucleosomes – they identified DNA fragments in dying cells to uncover specific pathological changes in patients with metastatic colorectal carcinoma and patients with liver disease.



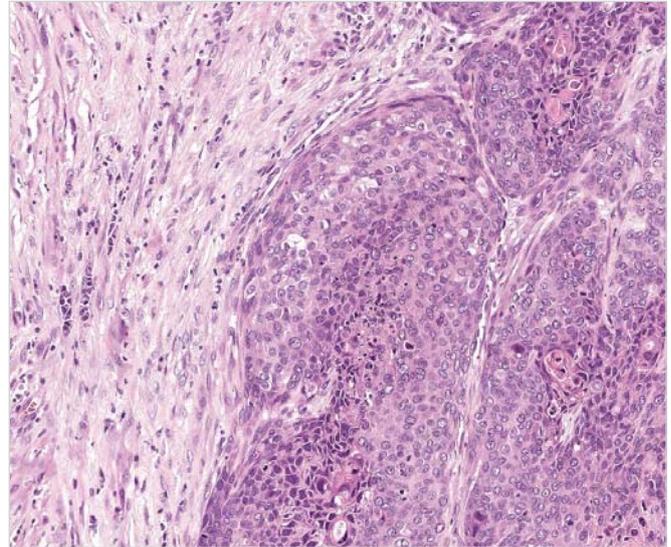
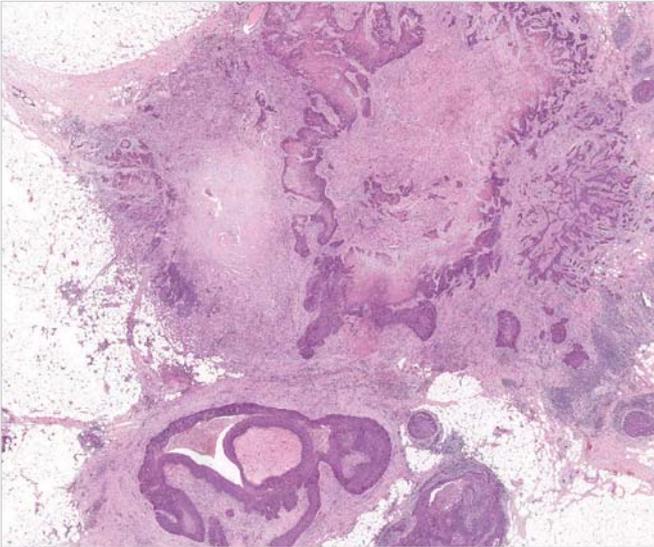
“We understood that if [epigenetic] information is maintained within the DNA structure in the blood, we could use that data to determine the tissue source of dead cells and the genes that were active in those very cells. Based on those findings, we can uncover key details about the patient’s health,” said Nir Friedman, author on the study (2). “We are able to better understand why the cells died, whether it’s an infection or cancer and, based on that, be better positioned to determine how the disease is developing.”

References

1. R Sadeh et al., *Nat Biotechnol*, [Online ahead of print] (2021). PMID: 33432199.
2. AK Leichman (2021). Available at: <http://bit.ly/3bzIRJH>.



CASE OF THE MONTH



A 58-year-old female presented with a right breast mass.

Which of the following immunohistochemical markers is the most specific for this entity?

- a) β -catenin
- b) p63
- c) CK7
- d) ER
- e) CK20

Answer to last issue's Case of the Month...

c) *Histiocytic sarcoma*

Histiocytic sarcoma (HS) is a rare malignant neoplasm derived from histiocytes. It most commonly occurs in extranodal locations such as soft tissue, skin, and gastrointestinal tract, but can also involve lymph nodes. Histologically, the malignant cells are usually large, reminiscent of histiocytes, with mild to severe pleomorphism. Varying numbers of inflammatory cells (small lymphocytes, histiocytes, plasma cells, and eosinophils) can be seen in the background. By immunohistochemistry, HS is usually positive for multiple histiocytic markers: CD4, CD11c, CD14, CD63, CD163, lysozyme, PU.1, and CD45. A subset of cases is

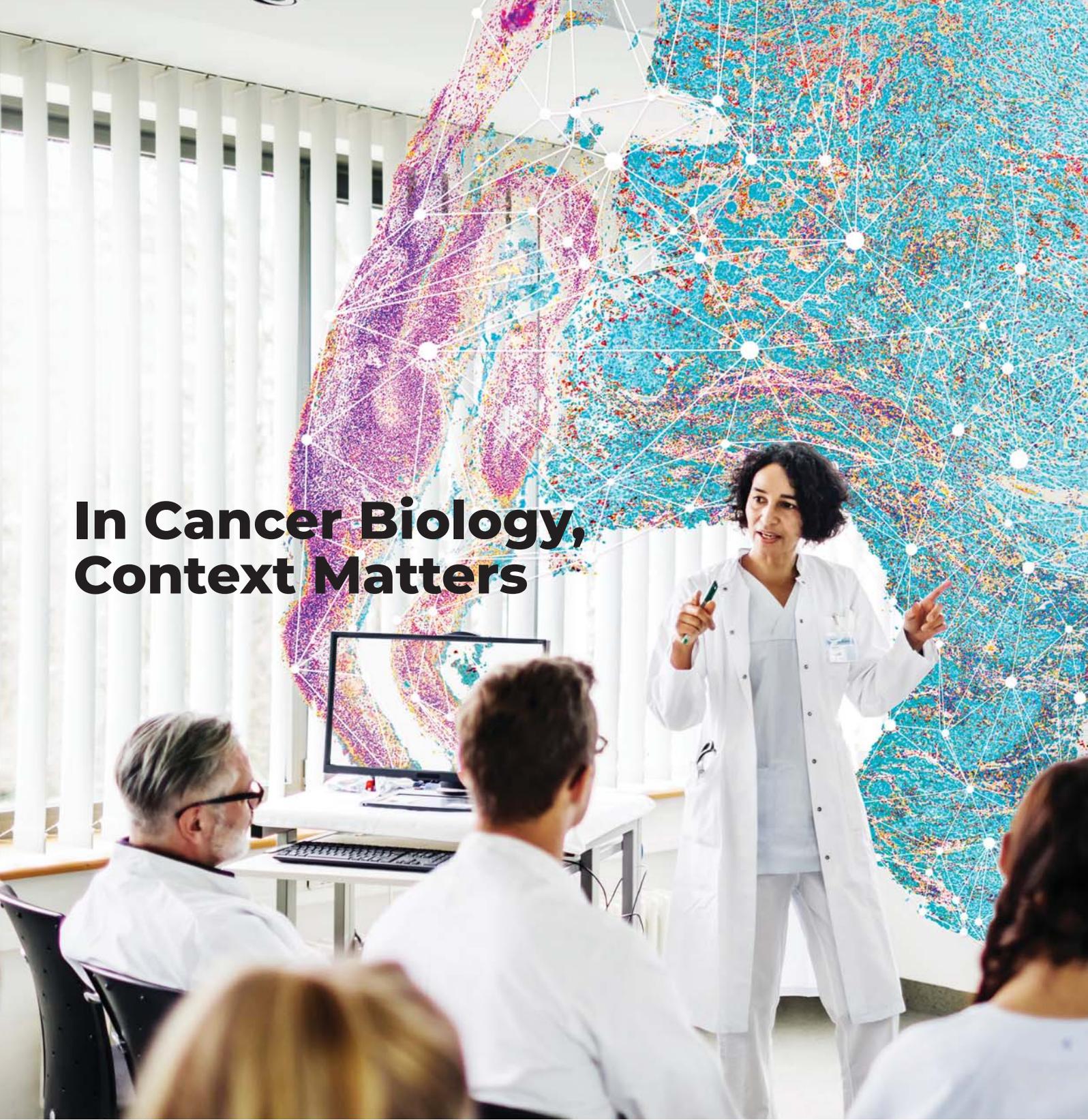
S100-positive; another carries the *BRAF* V600E mutation. It is usually negative for CD1a and langerin (indicative of Langerhans cell sarcoma) and for CD21, CD23, or CD35 (indicative of follicular dendritic cell sarcoma).

Submitted by Kyle D. Perry, Senior Pathologist, Henry Ford Health System, Detroit, Michigan, USA.

References

1. JL Hornick et al., *Am J Surg Pathol*, 28, 1133 (2004). PMID: 15316312.
2. SH Swerdlow et al., *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*, revised 4th edition. International Agency for Research on Cancer: 2017.
3. F Facchetti et al., *Virchows Arch*, 471, 467 (2017). PMID: 28695297.

To register your guess, please go to <http://tp.txp.to/0421/case-of-the-month>
We will reveal the answer in next month's issue!



In Cancer Biology, Context Matters



Transform your approach to immunotherapy biomarker discovery.

Akoya's multiplex immunofluorescence solutions enable the discovery of novel biomarker signatures from a single tissue section. How? By providing greater spatial context. As you immerse yourself in the tumor microenvironment, you'll be able to quantify how cells organize and interact to reliably predict treatment response and disease progression. Learn more at akoyabio.com/cancerbiology.

Postgraduate Training in India

Although Indian pathologists excel worldwide, the educational system leaves much to be desired

By C.N. Srinivas, Director of Laboratory Medicine and Head of Transplantation Immunology and Molecular Diagnostics, MIOT International, Chennai, India

India has numerous medical colleges, both government-owned and private, offering postgraduate courses in pathology, clinical chemistry, and microbiology. A total of more than 1,500 seats are available each year, and students gain entry by taking a national-level examination. Unfortunately, many don't choose these courses out of passion, but rather practicality – perhaps it's the path of least resistance, the one that offers the most flexibility for the future, or the one that promises the best work-life balance. Most neglected of all is clinical chemistry, followed closely by microbiology. In both courses, many seats are left vacant each year.

The teachers in the medical colleges are often more involved in academia and administration than in serving their students. Most are experts in morphology, microscopy, and the mortuary – but few work in the clinical laboratory, and even fewer interact with patients. Although the course curriculum includes a stint in a modern clinical lab with (at least) a complete blood count analyzer, a coagulation analyzer, and similar tools, these facilities are not available at all institutions and students are not always permitted to use them when they are available. Even most libraries are closed cabinet, meaning that interested students can't access reading material to expand their horizons. The unfortunate outcome is that although teachers may have rich experience to share, it often fails to translate into

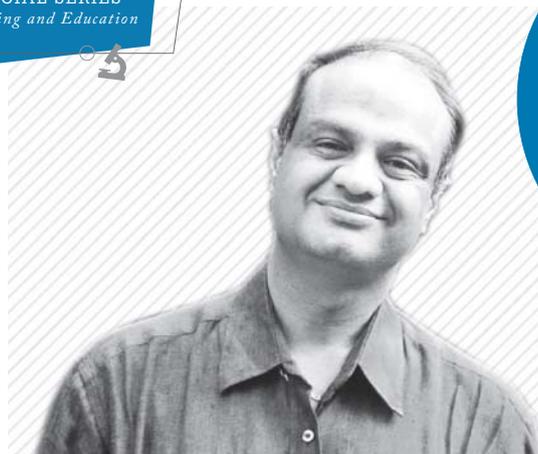
education and training for their students.

But what do students want? With little access to training and resources, many turn to Mother Internet. Siri, Google, and now Alexa have become favored tools among India's medical trainees – and although they diligently use these tools to complete their work, many are not motivated to learn beyond the bounds of their course requirements. And that means essential skills, from grossing to management, may fall by the wayside. Worse still, many are pressed into service by teachers to arrange or attend conferences, market events, and even act as couriers, chefs, tour guides, and chauffeurs to senior examiners. You would be right to ask what such tasks have to do with a student's education, but teachers in Indian medical colleges often require them nonetheless – and, if the tasks are satisfactorily completed, a degree is virtually guaranteed...

In most medical colleges, the entire basic science department is housed in one building. The walls between the departments extend – at least conceptually – to the people who manage, maintain, and dictate the rules. Although medical coursework requires some hours spent in clinical chemistry, microbiology, cytogenetics, and the blood bank, there is little communication between these departments and none at all between the laboratory and its patients. Instead of viewing laboratory medicine as patient-centric, most view it as "specimen-centric." Instead of patients, we have "pieces." Is it any wonder that so few students are interested in pathology?

In My View

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



The road forward? Mentorship offers one possible way to raise the profile – and quality – of pathology in India. A mentorship is a relationship in which one person invests time, energy, and expertise in nurturing the growth of another. Mentors vary greatly in style, but all contribute to the professional and personal growth of junior colleagues through their wisdom, knowledge, and expertise. No one can effectively advance along their career path alone – and without effective mentorship, it can be difficult to deal with the professional and personal issues that arise. Trainees, in particular, want to feel that they are "part of the family" academically, intellectually, and socially. By helping trainees and faculty members build relationships, departments not only cultivate strong mentorships, but also foster the creation of a tight-knit scholarly community.

The modern practice of pathology is constantly reshaped by rapid scientific and technological progress, as well as by market forces. Pathologists must expand their role as consultants to remain part of the clinical care team. Skills that made us successful yesterday will not be sufficient to guarantee success tomorrow. To move with the times, our education system must include:

- Patient care skills: not just diagnostic competency, but also the provision of advice to treating physicians.
- Medical knowledge: integration of biochemical, clinical, and molecular sciences into pathology, and integration of patient management

- into all laboratory medicine.
- Professionalism: commitment to provide reliable, ethical laboratory services.
- Management principles: the tasks and tools of management, including leadership skills, conflict resolution, and resource development.
- Laboratory operations: laboratory design, process management,

- technology assessment, contract and acquisition skills, marketing, and financial management.
- Quality assurance and regulations: total quality management, risk management, patient and laboratory safety, error-proofing, and ways of addressing errors when they take place.
- Informatics: both in the laboratory

- and in the wider hospital environment to provide integrated patient support.
- Medicolegal skills: including malpractice concerns, patient safety issues, and ethics

In short, high-quality mentorship and a focus on essential new skills will deliver the education system that India needs and its patients deserve.

Modernize Your Mindset

To provide the best possible pathology education, teachers must be willing to revolutionize their methods

By Shivayogi Bhusnurmath, Co-Chair of Pathology and Dean of Academic Affairs, and Bharti Bhusnurmath, Co-Chair and Professor of Pathology at St. George's University School of Medicine, Grenada, West Indies

We need to drastically overhaul the way we teach pathology to medical students in India. As teachers, most of us do to our students what our teachers did to us. Our teaching is largely geared toward specific facts about specific diseases. For instance, we describe the morphological characteristics that help us make diagnoses – but we don't explore how these diagnoses affect our patients. What signs and symptoms do they produce? Why do we choose certain lab investigations over others? How do the tests we perform help to establish the diagnosis, etiology, extent of disease, or potential complications? Have we chosen the least invasive, most affordable testing options? Does the diagnosis leave anything unexplained?

Questions like these emphasize the role of pathology as the foundation of clinical



medicine. Students are excited to study diseases in context instead of passively memorizing the details of morphologic changes to pass exams. In my view, we as teachers do a great disservice to medical students when we force them to memorize instead of teaching them how to apply pathology in a clinical context. Rather than teaching “pathology,” we should view ourselves as teaching “clinical reasoning based on pathology.” That approach promises to yield logical, science-minded doctors and improve healthcare. After all, our goal is not to make every medical student a pathologist; only a small fraction of each class will choose to pursue our discipline. It's more important to show them pathology's vital role in understanding every aspect of a patient's problems and identifying the best approach to management.

It's also important to abolish the outdated perception of our role as teachers. We're not here just to pass on the details of our knowledge; our lecture notes, textbooks, and online resources can provide those. Our job is to develop interactive lecture and lab sessions in which students interpret

and analyze clinical scenarios and use pathology information to make decisions. Moving students from passive listeners to active participants can take many forms – “clickers” for responding to multiple-choice questions, concept mapping, modified essay questions, flipped classrooms, team-based learning, writing clinical vignettes based on unknown pathology images given to them, and more. It's amazing how well students rise to the challenge if we create platforms like this to spark their intellectual curiosity.

But medical expertise isn't all we have to share. We need to incorporate learning objectives on professional behavior and communication skills for both medical students and residents – and residency training should include a component on business practices in pathology. In India, most of the emphasis in residency training is on surgical pathology, but only a few go on to practice as surgical pathologists. The bulk of practice for most is clinical pathology, which receives little attention during residency training.

Continuing medical education (CME) in India is more like a wedding ceremony than a learning environment. High-level academics are invited to speak about their work and surrounded with celebrations – but no effort is made to determine the target audience, their knowledge level, or their educational needs. There are no measures to determine the impact or sustainability of the CME. The general refrain of residents and junior faculty is

that the topics discussed often have no practical utility for them – and yet the costs are high to subsidize the speakers' travel, accommodations, and entertainment. Why not use online tools to give lectures, slide seminars, or even interactive sessions that interested audiences across the globe can access at a low cost? Events could be

held at convenient times, repeated, or archived and made available on demand. The stumbling block? Faculty reluctance – because we have created an environment where physical appearance and celebration matters. We need to set our egos aside and work for the greater good if we want to create effective, meaningful CME.

The Indian mindset toward pathology education needs to change – from our medical students' first introduction to the discipline all the way to professional development for senior pathologists. Only when we are willing to move out of our comfort zone and grow as educators can we provide world-class training to all pathologists in India.

The Vast Potential of Single-Cell Analysis

Single-cell analysis has great promise... but how can we get there?



By Zachary Pitluk, Vice President of Life Sciences and Healthcare, Paradigm4, Waltham, Massachusetts, USA

It is now four years since a group of scientists met in London to discuss how to create a human cell atlas (HCA) – a collection of maps that describes and defines the cellular basis of health and disease. Research based on this atlas has also helped researchers create more specific maps – such as the COVID-19 Cell Atlas, which could help us in the fight against SARS-CoV-2.

Cell atlases are powerful – but, to unlock insights that will enable us to help specific patients, we need reference datasets of hundreds to thousands of patients to complement population-

scale genomics datasets. This vision of precision medicine is coming ever closer thanks to the technological advances – particularly in the field of data handling and analysis – and single-cell research.

Advances in single-cell genomic analysis provide the industry with greater insights from clinical trials – for example, by allowing scientists to look further into specific molecule responses to different therapies. Of the many single-cell genomic analysis methods, scRNA-seq is the most widely used. This approach involves labeling biomolecules that originate from individual cells, allowing high-throughput molecular analysis at the single-cell level. In 2013, scRNA-seq was Nature's Method of the Year. It earned the accolade a second time in 2019 due to its ability to sequence DNA and RNA in individual cells (1), allowing extrapolation of the biological differences between cells.

Massively parallel single-cell genomics assays can now profile hundreds of thousands of cells, meaning that researchers can gain more insights than ever before on certain cell characteristics and behaviors. The uptick in spatial single-cell analysis puts a further onus on technology development to preserve the contextual information of imaging so that researchers can augment individual cellular responses with regional and sub-regional information.

Technologies to profile DNA and proteins in single cells – as well as combinations of DNA, RNA, and proteins in the same cell – provide important additional layers of information to accelerate precision medicine. The advent of single-cell nucleus

RNA sequencing (snRNA-seq) has allowed the extension of single-cell transcriptomics analyses to human diseases in which live tissue is not obtainable (2).

Computational algorithms have also emerged (and continue to evolve) to determine cell types, states, transitions, and locations – allowing single-cell analysis to extract more targeted insights from specific biomarkers. But there are 300 different cell types in the human body, which itself compromises 37 trillion cells. And precision medicine research relies not just on the number of cells (because cells from one patient cannot be biological replicates!), but on the number of patients. It's clear that these data must be stored and processed at scale to be effective.

Single-cell analysis may help us uncover never-before-seen physiological interconnections between tissues. With the understanding that exosomes and even naked nucleic acids can be used for intercellular communication, the need to quickly profile responses at the cellular level are even greater. The ability to find gene expression fingerprints and distinct cell types that may look unrelated, but might be corresponding with each other, could transform the way we diagnose and treat disease. If the full potential of single-cell analysis is realized, we will be able to navigate the physiology of humans from the molecule up – an exciting future that now sits tantalizingly within our reach.

See references online at: tp.txp.to/single-cell

Educating Patients, Now and Beyond

The lab has taken center stage in patient education – and it must stay there

By E. Blair Holladay

Education has always been a critical aspect of pathology and laboratory medicine. Our learning about our profession may start when we enter school – perhaps even before – but, once it starts, it never truly ends. Even after we graduate, no matter where we are in our careers, we are continually learning. As new professionals, we learn how to do our jobs and do them well. As seasoned pathologists and medical laboratory scientists, we learn how to augment our skills to ensure we can provide high-quality patient care. As laboratory professionals on the brink of retirement or even beyond, we learn how to share knowledge with the next generation to sustain our workforce.

This past year, we have spent more time educating than ever before – at all levels of the profession. Not only have we educated ourselves, but also, critically, our patients. In the wake of the COVID-19 pandemic, the task of educating patients on the virus (and now the vaccine) has fallen on every member of the healthcare team – not least the lab. Pathologists and medical laboratory scientists are at the center of the testing and research bringing us out of the pandemic – which puts us in a unique position to lead public education around COVID-19 and makes it our duty to provide the knowledge our patients need to make informed decisions.

With the recent authorization of three COVID-19 vaccines, for example, the



knowledge we hold as pathologists and medical laboratory scientists is more in demand than ever. The American Society for Clinical Pathology's podcast, *Inside the Lab*, recently recorded an episode discussing vaccine safety (1). Our hosts were joined by two members of the laboratory team and one of our ASCP Patient Champions, each of whom brought a unique perspective to the discussion on why they opted for the vaccine, safety data from the medical community, and how to encourage vaccination among people – both patients and professionals – who are hesitant. I encourage you all to listen to this dynamic episode, which showcases the critical role the laboratory plays in patient education.

We're turning a corner on COVID-19 but, just as we never stop educating ourselves after each corner turned in our career, we cannot stop educating others when we reach our post-pandemic "new normal." Pathologists and medical laboratory scientists have stepped

"This past year, we have spent more time educating than ever before – at all levels of the profession."

forward in this challenging time to support the health and education of our patients – and this is just the beginning. As the laboratory is central and ever-present in patient health, so too must it be in patient education.

References

1. American Society for Clinical Pathology, "COVID-19 Vaccine Safety" (2021). Available at: <https://bit.ly/3vEKPQX>.

Let's Do It Ourselves

A global expert consensus is emerging: by retaining oncology biomarker testing in-house, healthcare management and patient care benefit significantly

Over the last decade, precision oncology therapies dependent on biomarker-based diagnostics have proliferated. The personalized nature of these new treatments, which often exploit the specificity of the immune response, bring hope to many oncology patients. But medical advances typically raise practical questions even as they provide therapeutic answers – and the rise of molecular pathology is no different. Although still relatively new, this field is rapidly progressing – no longer just the province of academic medical centers, but a recognized discipline on its way to becoming routine practice. And this evolution is generating decision points for healthcare providers: not least, whether

“Remarkably, our thought leaders all agreed that in-house biomarker testing, as opposed to outsourced testing, is associated with key benefits.”

to outsource biomarker testing to centralized laboratories or implement it in-house. What is best for the system – and what is best for patients?

This debate is vital for the future of both molecular pathology and the patients themselves. Therefore, during 2020, we hosted a virtual panel debate (now available to view on demand at LINK) and conducted a series of interviews with experts in the field. Each of these individuals brought their own unique perspective and experience, but all were united in their passion for patient care and for molecular pathology; it has been a privilege to listen to them. Furthermore, it has been fascinating to observe the concordance between independent experts working in different parts of the world, under different healthcare systems. Remarkably, our thought leaders all agreed that in-house biomarker testing, as opposed to outsourced testing, is associated with the following key benefits.

1. Time savings: this in turn permits faster and more optimized treatment decisions.
2. Biopsy economy: this “tissue saving” allows additional future tests to be performed if required.
3. Improved coordination of patient care: this is particularly important in the context of multidisciplinary teams and supports the delivery of flexible, truly personalized medicine.
4. Development of local expertise: this is essential if biomarker-driven precision medicine is to reach its full potential.



Below, we provide some key expert insights, which represent a shared consensus view held by all our interviewees, irrespective of their nationality or the healthcare system that employs them.

Alain Mita, Medical Oncologist, Co-Director of the Experimental Therapeutics Program, Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai, Los Angeles, California, USA



Turnaround time is one of the big advantages of in-house testing. I recently had an elderly patient with lung cancer who was not a candidate for chemotherapy, so we needed to decide between immunotherapy and targeted therapy. We didn't want to make the wrong decision, because the sequence of treatment matters; the risk of side effects from targeted therapy is much higher after immunotherapy. The decision had to be made quickly, so we did an in-house panel and chose a treatment right away. I don't know what would have happened if we had waited three weeks for results from a central lab.

Tanya Ahmad, Consultant Medical Oncologist, London, UK

Delays in availability of test results are potentially clinically harmful, especially for lung cancer patients, who often present in the advanced stages of disease and with comorbidities that affect their suitability for treatment. Also, an inadequate test result or a lost sample

could be the difference between starting treatment within days or within weeks – and, because patients need to be relatively fit for certain therapies, rapid deterioration can mean they miss the opportunity for treatment entirely.

Michael Vieth, Professor of Pathology, Chairman of the Institute of Pathology, Klinikum Bayreuth, Germany



When a clinician asks us to perform a specific test, our first step is always to identify the most suitable methods. By carrying out all testing in-house, we can adjust these methods to best suit each individual sample while maintaining regular communication with our clinicians to align testing with clinical needs. This benefits the patient because we can provide the treating oncologist with an immediate response, asking for further samples or information if necessary.

Fernando López-Ríos, Director of Pathology and Targeted Therapies Laboratory, Hospital Universitario HM Sanchinarro, Madrid; Professor of Pathology and Molecular Pathology, Universidad CEU, San Pablo, Spain



It is important to preserve as much as possible of the precious patient biopsy samples. If you do your testing in-house, you can decide on the test flexibly, based on amount of sample available. By contrast, the



centralized labs perform the same large test (a panel of over 500 genes) on all samples, and sometimes do not get any result due to insufficient tumor material. This can result in delays and possibly re-biopsies.

Rui Manuel Reis, Coordinator, Molecular Oncology Research Center, Barretos Cancer Hospital, Barretos, São Paulo, Brazil

In-house testing allows us to discuss results with clinicians during meetings of multidisciplinary tumor boards. This helps them better understand the findings, ask questions, and plan the best treatment for each patient, ultimately leading to better care and outcomes.

Wei Song, Director, Clinical Genomic Laboratory, Englander Institute for Precision Medicine; Assistant Professor of Pathology and Laboratory Medicine, Weill Cornell Medical College; Assistant Attending Pathologist, New York-Presbyterian Hospital, New York, USA

We regularly participate in multidisciplinary tumor boards and have numerous telephone conversations with clinicians. This level of interaction is not possible when sending out tests to a central lab. Furthermore, my experience of communicating with central labs is that the people I speak to usually

“Pathology departments not using these techniques will be left behind, so pathologists must develop expertise with the new testing methods, and with molecular pathology in general.”

are not trained pathologists and lack the expertise to address my questions.

Ruthy Shaco-Levy, Professor, Head of Pathology, Soroka Medical Center, Clalit Health Services; Head of the Israeli Pathologists Association, Beer-Sheva, Israel

Pathology is one of the fastest-developing fields in medicine, and molecular pathology is one of the fastest developing areas in pathology. Soon, molecular pathology will likely be routine for confirming the diagnosis and prognosis of most tumors. Pathology departments not using these techniques will be left behind, so pathologists must develop expertise with the new testing methods, and with molecular pathology in general.

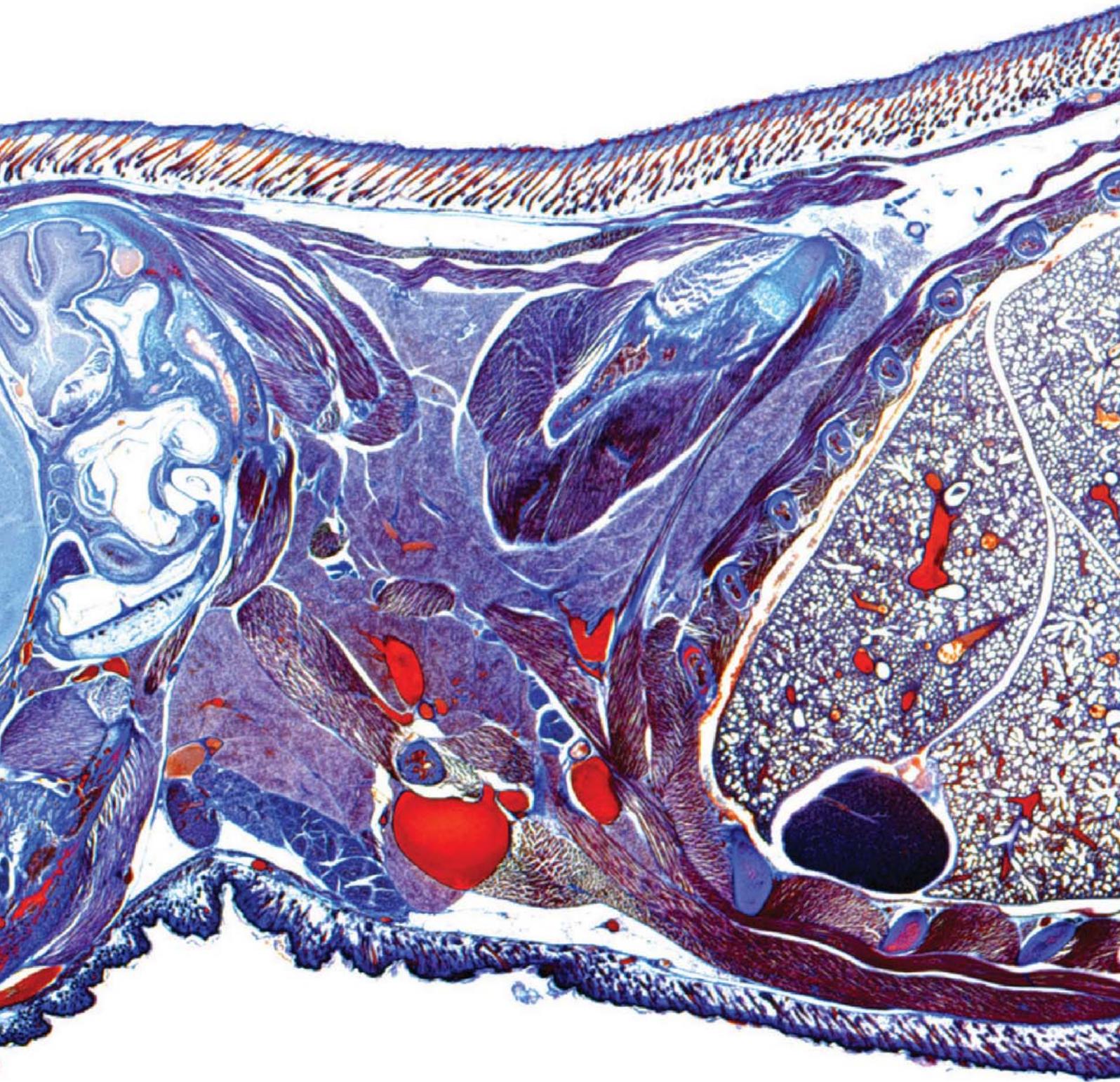
Complete interviews are available as a free e-book: www.oncomine.com/cgp

PICTURE

Perfect

PATHOLOGY

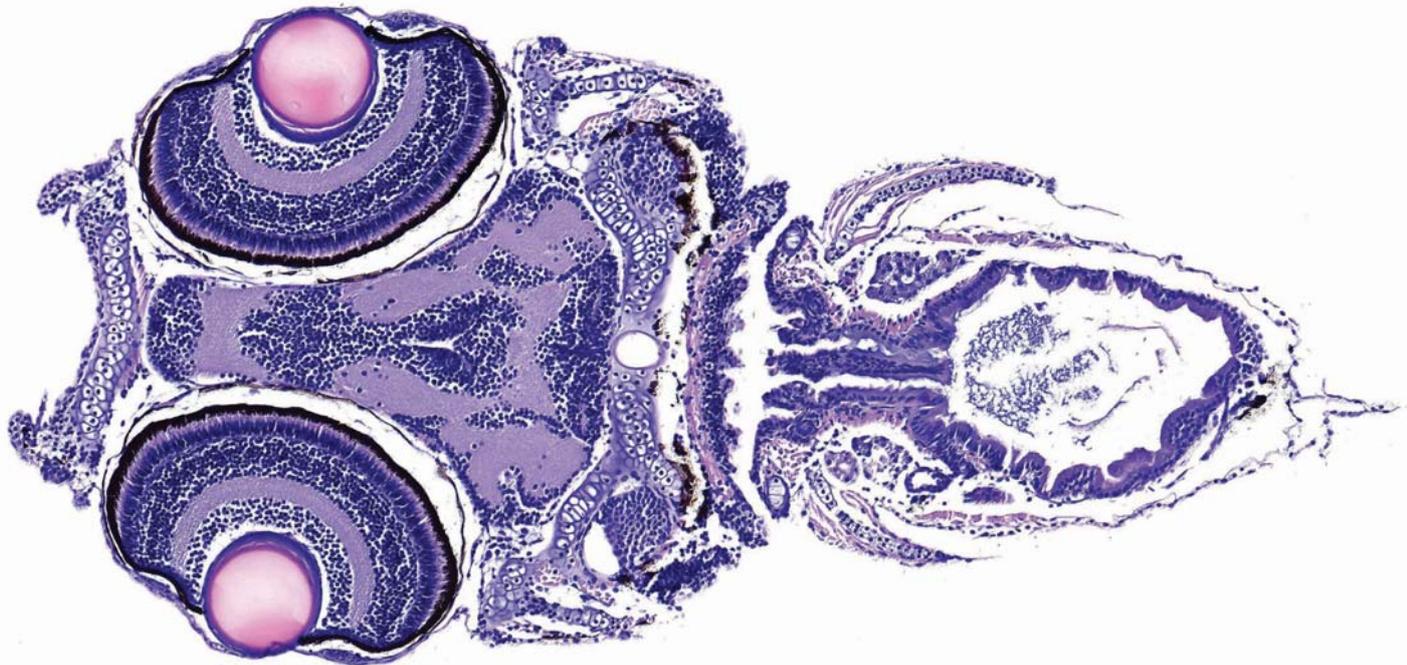
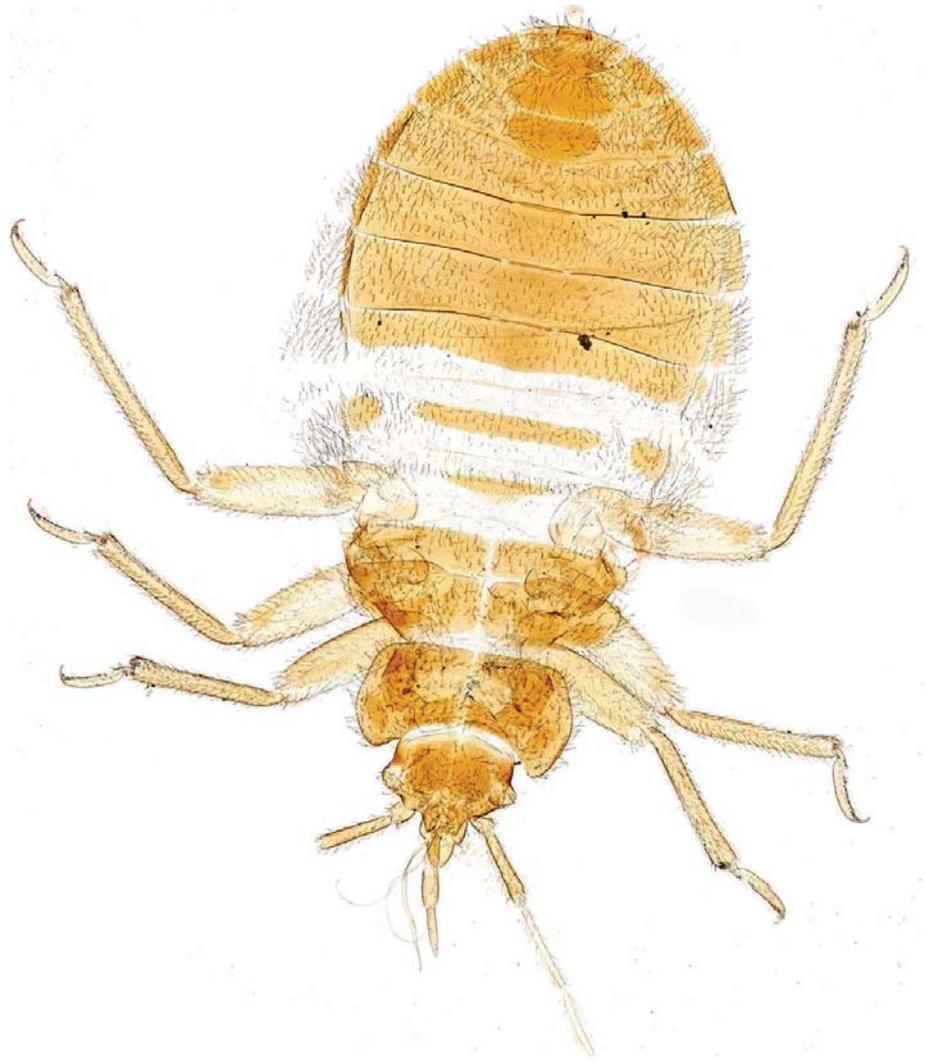
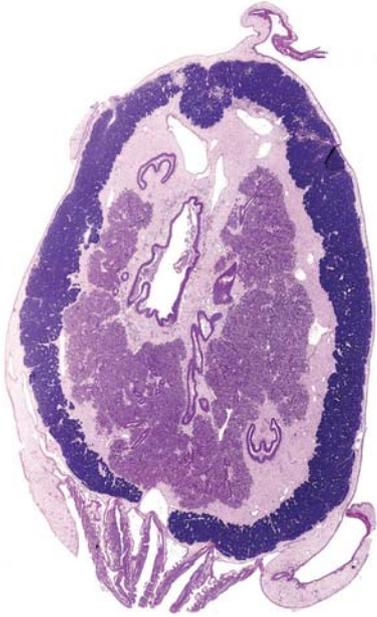




Five-Day-Old Mouse

Scanned with PathScan Enabler III.

*Robert D. Meyer, Meyer Instruments,
Houston, Texas, USA.*



Fish Gonad

Far, far left: Scanned with PathScan Enabler 5.

Bug Out

Far Left: A bedbug (*Cimex lectularius*). Its primary hosts are humans and it is one of the world's major "nuisance pests." These arthropods were scanned using a 20x/0.75 N.A. Olympus objective on a Glissando slide scanner. Z-stacks were created and the final extended depth-of-field images were obtained using their software.

Zebrafish

Bottom left: Scanned with MoticEasyScan Pro 6.

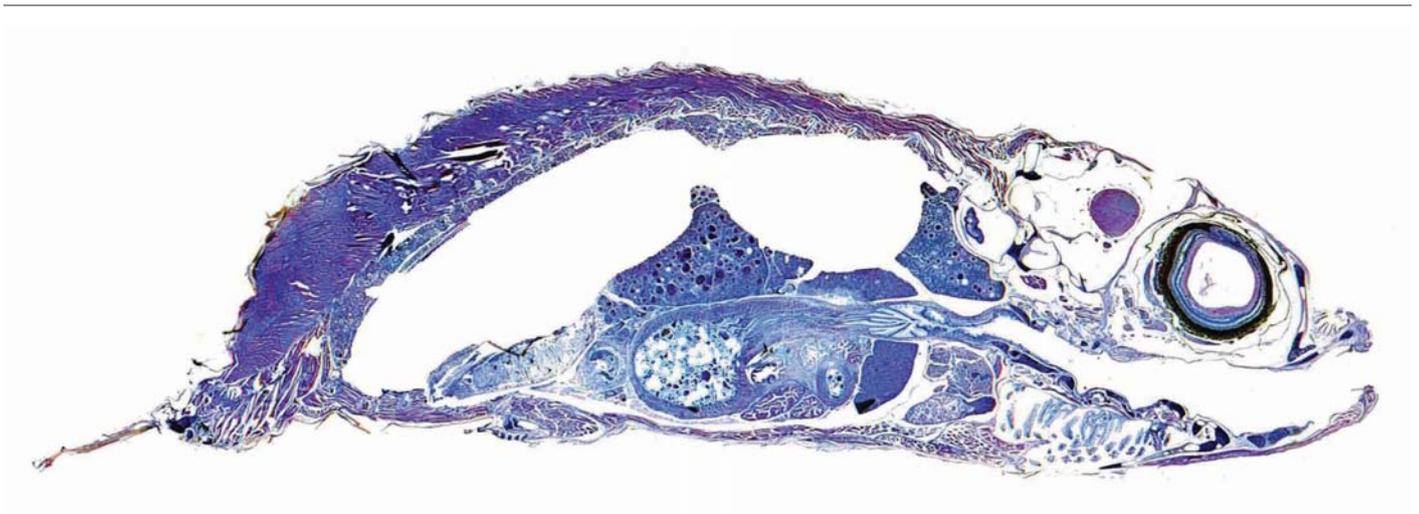
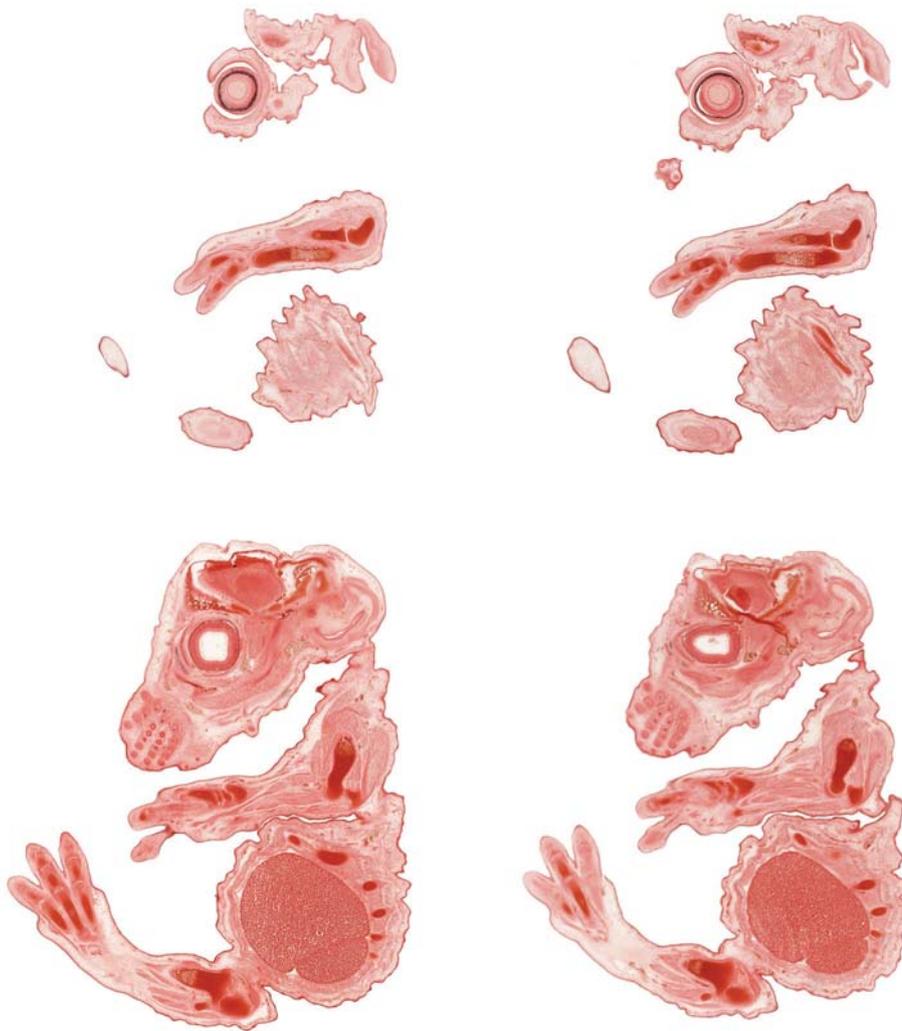
Mice Five by Five

Left: Serial sections of an embryonic mouse scanned with the PathScan Enabler IV.

Tetra

Bottom: Scanned with MoticEasyScan Pro 6.

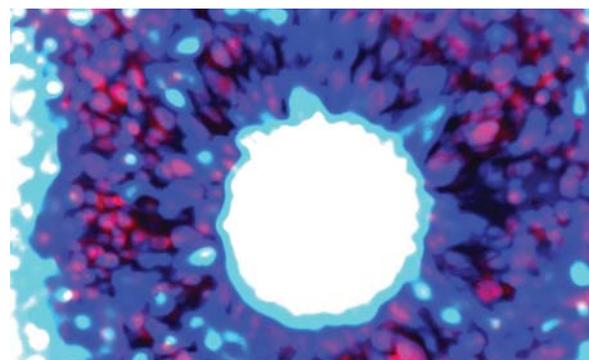
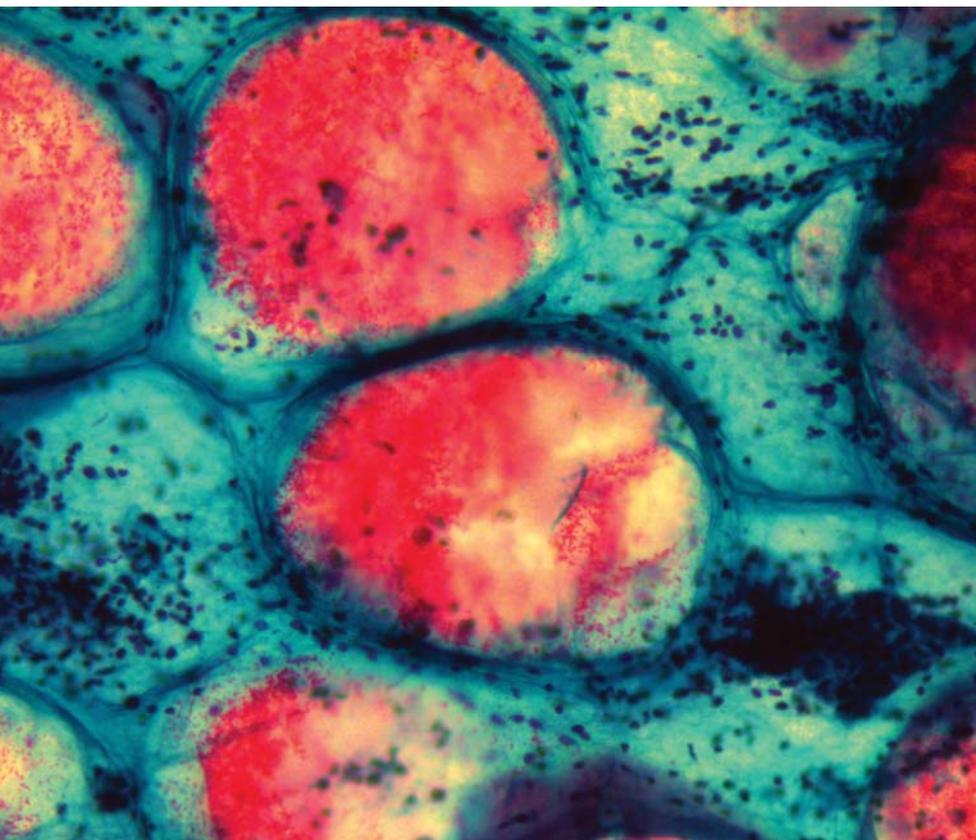
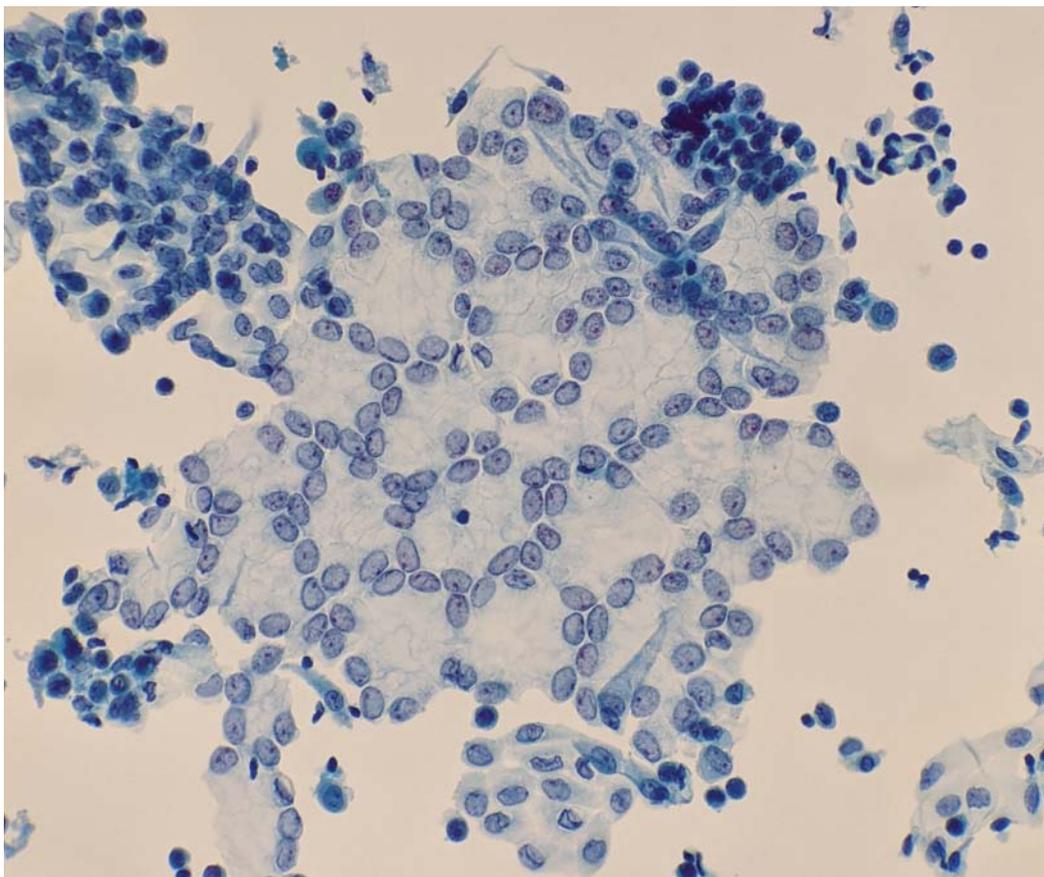
Robert D. Meyer, Meyer Instruments, Houston, Texas, USA.



A Truly Microscopic Geometric Phenomenon

Top right: I took this photomicrograph of a beautiful cytology from a pelvic wash today because I was stunned by the mathematical arrangement of this group of cells - a truly microscopic geometric phenomenon!

Dana Razzano, Yale School of Medicine, New Haven, Connecticut, USA.



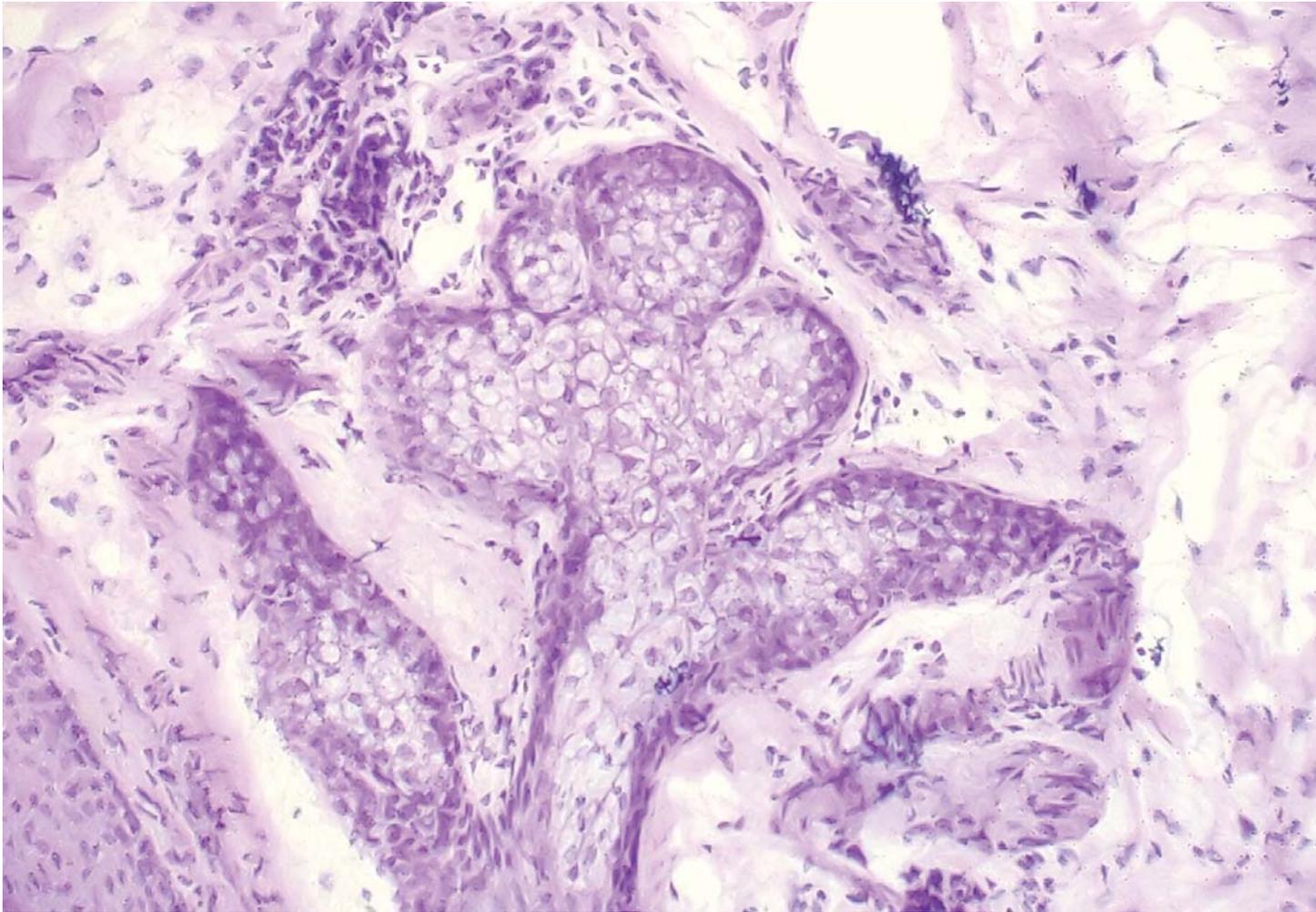
Multicolored Daisy

Right: Fine-needle aspiration of a thyroid gland nodule (colloid).

Stones

Bottom left: Fine-needle aspiration of a lipoma (fat globules).

Smaroula Divani, Department of Clinical Cytology, Volos General Hospital, Volos, Greece.



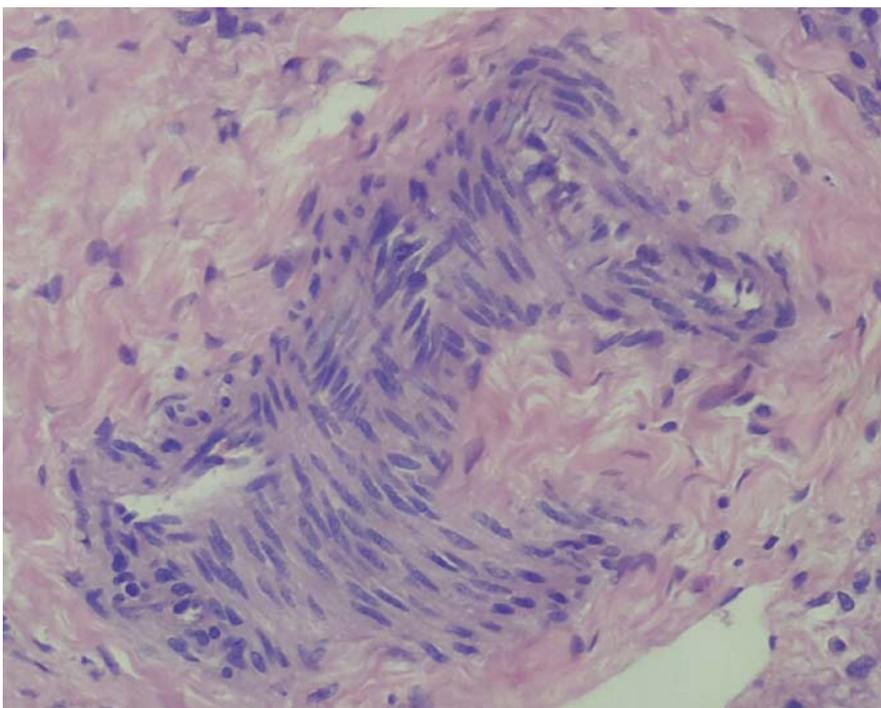
A Sebaceous Flower

Top: Normal skin of the upper lip.

My Laughing Horse

Bottom: A benign soft tissue neural tumor.

Roshan Chinoy, Prince Aly Khan Hospital, Mumbai, India

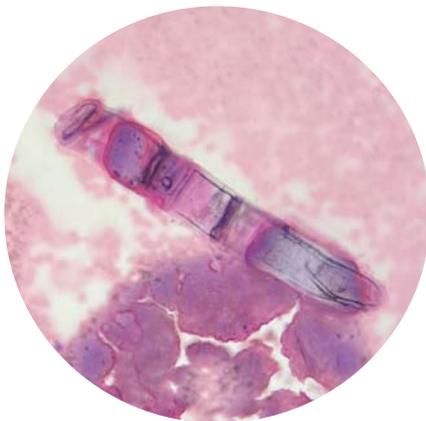




I Heart Pathology

A heart-shaped blood vessel in a lung.

Katie Saunders, Department of Pathology and Laboratory Medicine, University of North Carolina Hospitals, Chapel Hill, North Carolina, USA.



Marry Me

“I found this in peritoneal liquid and it reminded me of a finger... now I’m engaged!”

Luis Antonio Delgado Soler, Hospital Central Militar de México, Mexico City, Mexico.



Blooming Bird

This specimen is a breast mass (fibroadenoma).

Rico P. Lasaca, Divine Word Hospital, Tacloban City, Leyte, Philippines.



The Cat in the Hat

This is a bronchial biopsy from a 46-year-old female with a histopathologic diagnosis of nodular lymphoid hyperplasia. Hematoxylin and eosin stain.

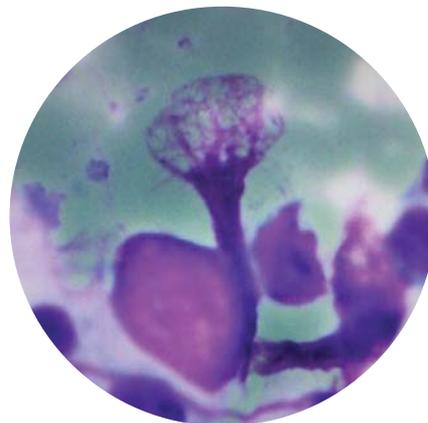
Felipe S. Templo, Jr., Division of Laboratory Medicine, Philippine Heart Center, Quezon City, Philippines.



Waxy Cast

This is a photomicrograph of a waxy cast in urinary sediment from a patient with chronic kidney disease.

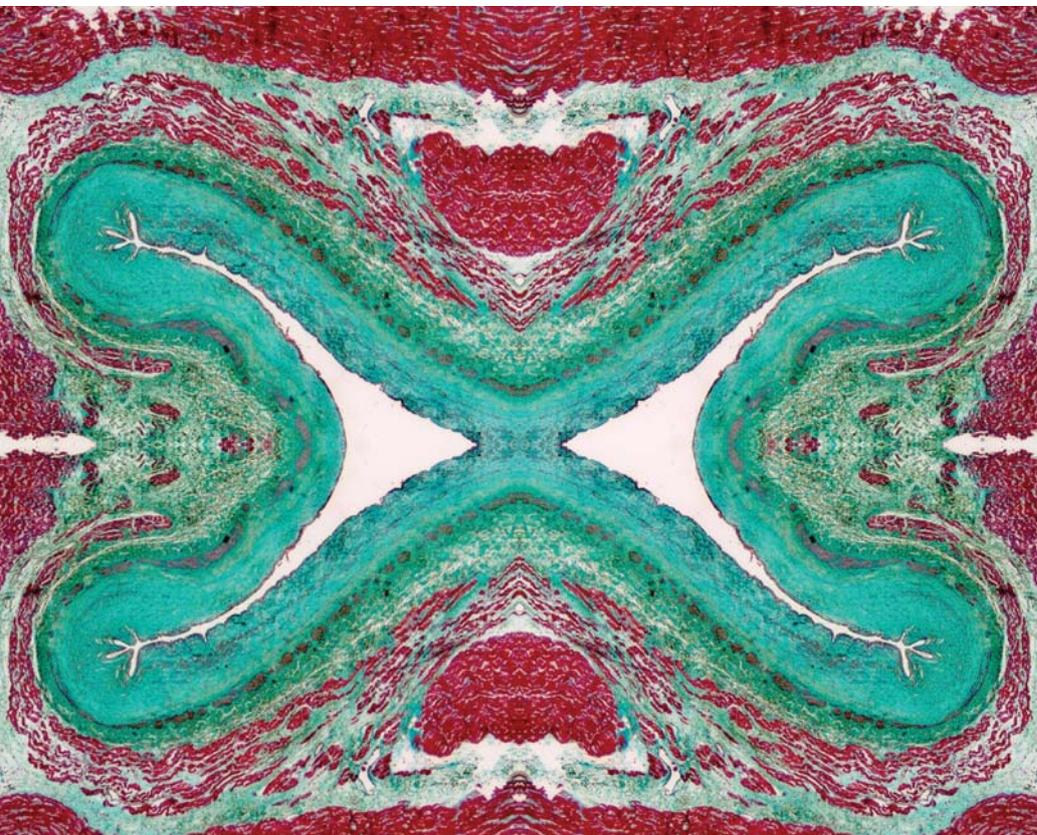
M. Jane McDaniel, Physician Assistant Online Program, Yale School of Medicine, New Haven, Connecticut, USA.



Microflora, Genus Rosa

Macrocytic transformation to garden flora in a pleural effusion.

Beth Doughty, University of Colorado, Anschutz, Colorado, USA.



The Heart Vessel

Top: Masson stain.

Myocardium

Bottom: MSB stain.

*Kseniya Ruksha, Belarusian State
Medical University, Minsk, Belarus.*



Zen Microscope

Top left: A designer microscope on a background of watercolors.

Ribcage Pop Art

Bottom right: Various special stain patterns of bone used to design ribcages.

*Nikita Dasan, Saifee Hospital
Mumbai, India.*





Castleman Candy

Left: Lollipop lesion pattern of Castleman disease.

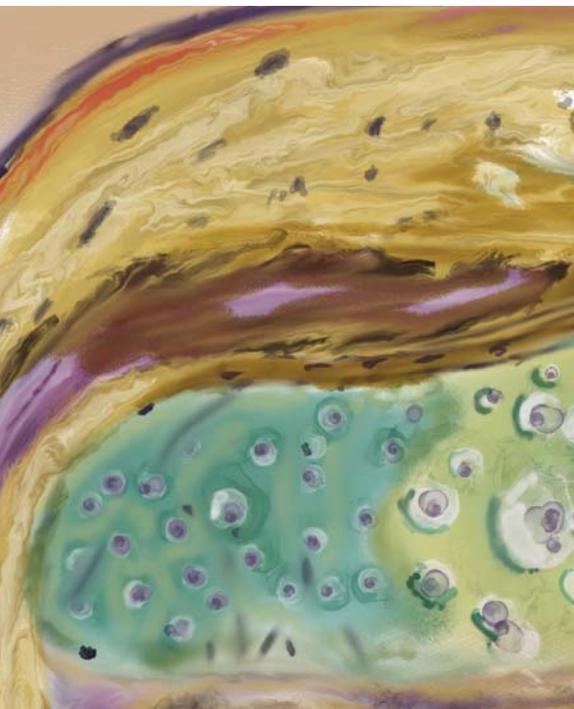
“Path” to Fashion

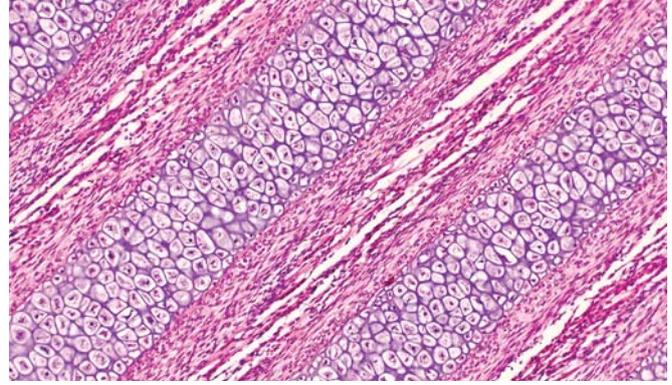
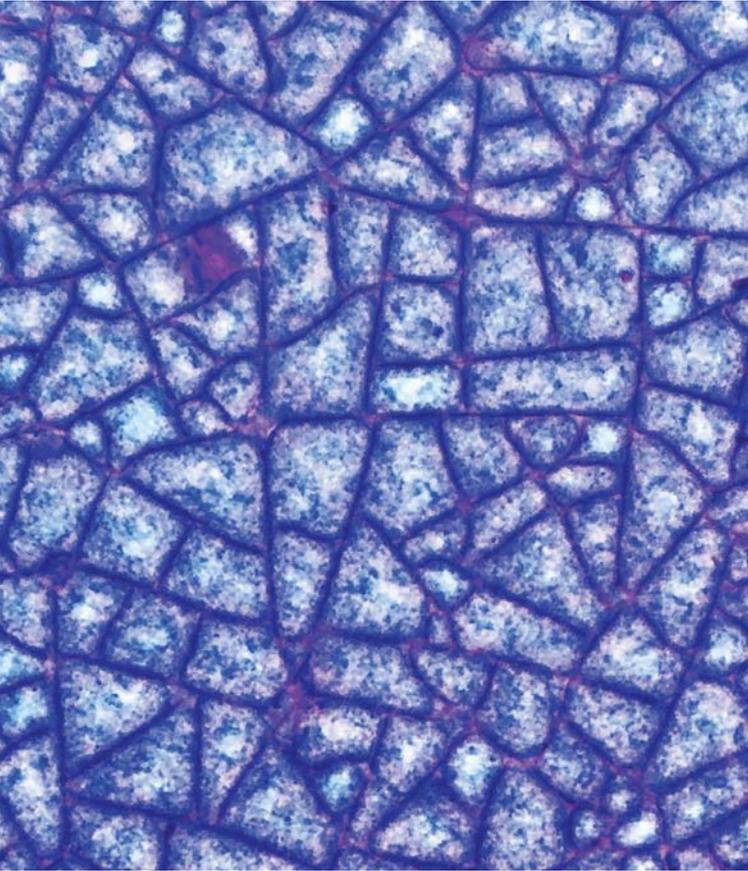
Far left and bottom right: A combination of various patterns seen in special stains with fashion.

Movat's Muse

Bottom middle: A fluid ink depiction of Movat's pentachrome stain (bronchus).

*Nikita Dasan, Saifee Hospital
Mumbai, India.*





In a Cage

Top right: Normal histology of an embryonal thoracic wall. I love the alternating textures of chondroid and soft tissue/muscular layers. It is vibrant, like waves of different tissues flowing in a living being.

Geometry

Top left: This was a quick shot of the broken surface of embedding medium. I played with filters to create images we are familiar with: a bird's-eye view of a city, a street map, or dry soil...

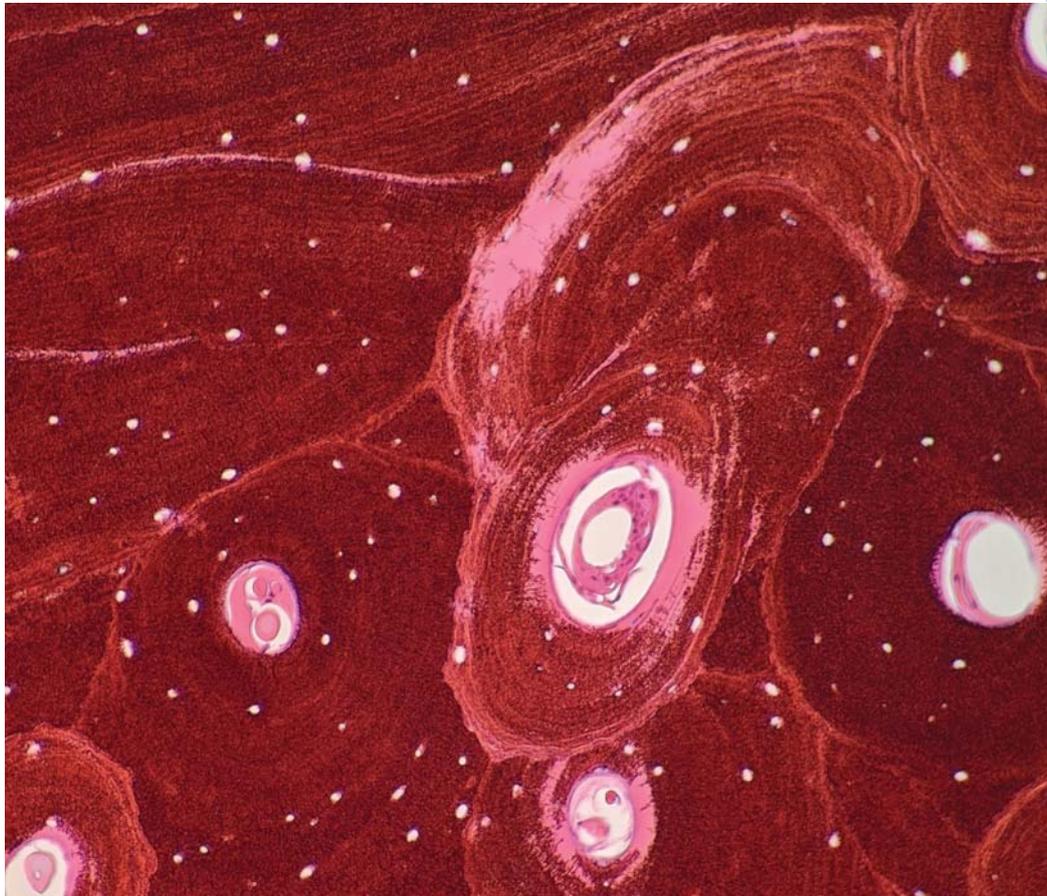
Sanjai Shab Hauschild, Medizinisches Versorgungszentrum für klinische Pathologie, Klinikum Darmstadt, Germany

Into the Microscopic Galaxies

Bottom right: I had always considered the microscopic examination of tissues, cells, and their processes a whole different universe. When I looked at this section of bone, the lacunae in the haversian canals shone out brightly, like stars from a different galaxy. It gave a more literal meaning to the pathologist's "microscopic universe." Like marine biologists dive deep into the ocean to discover beautiful and little-known creatures, we pathologists dive deep into slides to unravel the secrets of diseases.

This bone, however, looked different (not pink) because of processing artefact. Sometimes beauty is serendipitous (as long as we're open to seeing it)!

Swati Bhardwaj, Icahn School of Medicine at Mount Sinai Hospital, New York, New York, USA.





***The Challenges of
a Military Medical
Scientist on the
Global Stage***

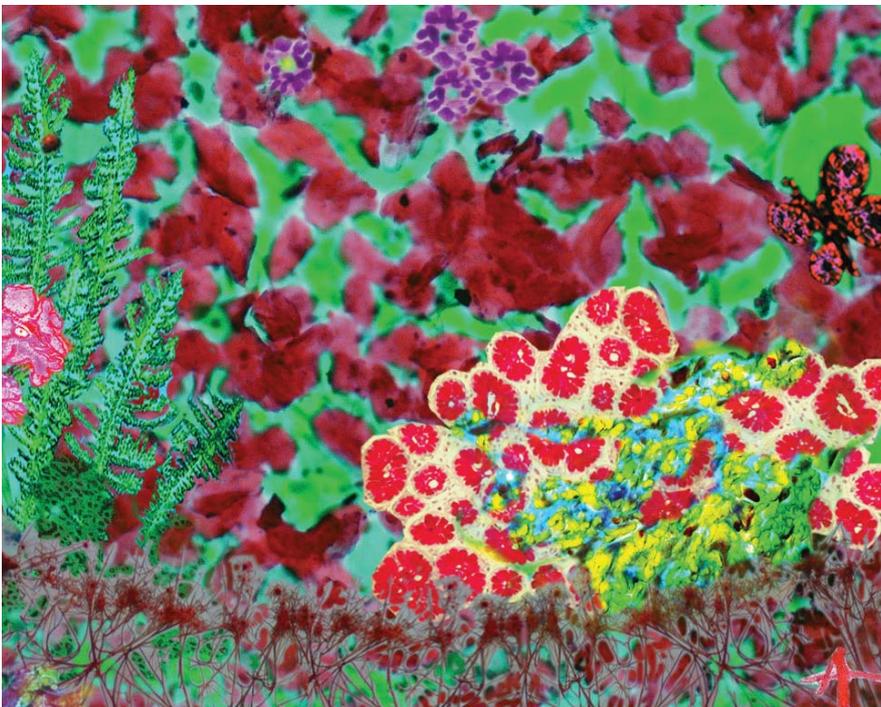
Top: Left-right-left, step-by-step, after balanced decisions are met, medical ethics are all we have left. Pictured: Major (US Army, Retired) Lionel Lowery II.

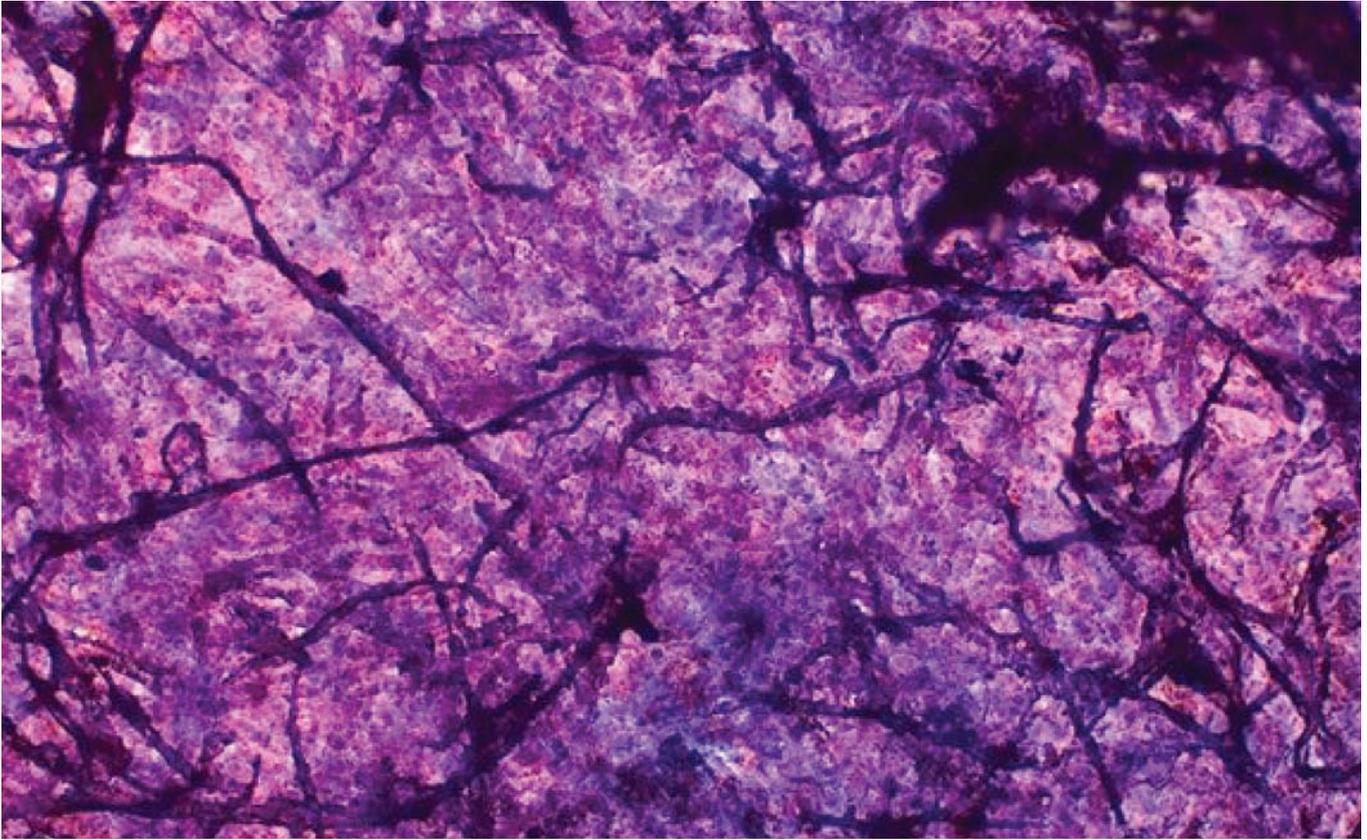
Lionel Lowery III.

Spring on Planet Earth

Left: Dreamscapes through a microscope lens. Eternal cells released in blue skies and green fields, celebrating the coming of spring.

*Anna Batistatou, Department of Pathology,
Faculty of Medicine, School of Health
Sciences, University of Ioannina, Greece.*





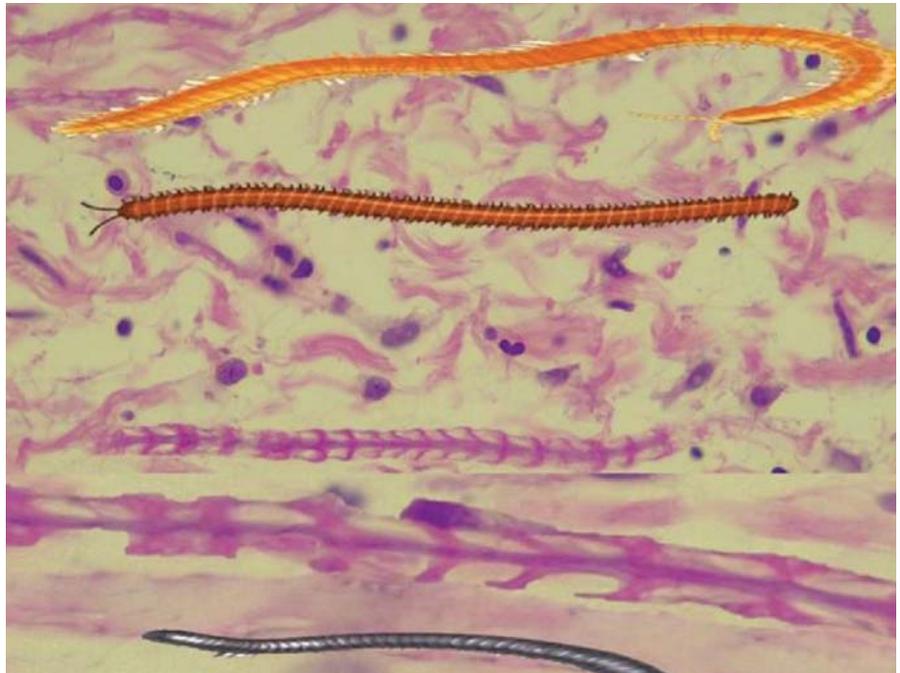
The Forest

Top: Artifacts of a conventional Pap smear.

Centipedes

Right: Neurofibroma neck injury (Schmidt-Lanterman incisure).

*José Miguel Cruz-Arias, Pathologist,
Santo Domingo, República Dominicana.*



Renewal

Top left: I created this painting shortly after recovering from breast cancer. Cancer has taught me to be “in the moment” and to appreciate relationships and the beauty that surrounds me. “Renewal,” on the shores of Lake Michigan, illustrates that feeling. The painting is also for my stepdaughter, who lost her battle to non-Hodgkin’s lymphoma in 2013. I was very involved in her care and miss her spirit and joy. My goal now is to appreciate, be “in the moment,” and enjoy the beauty that surrounds me.

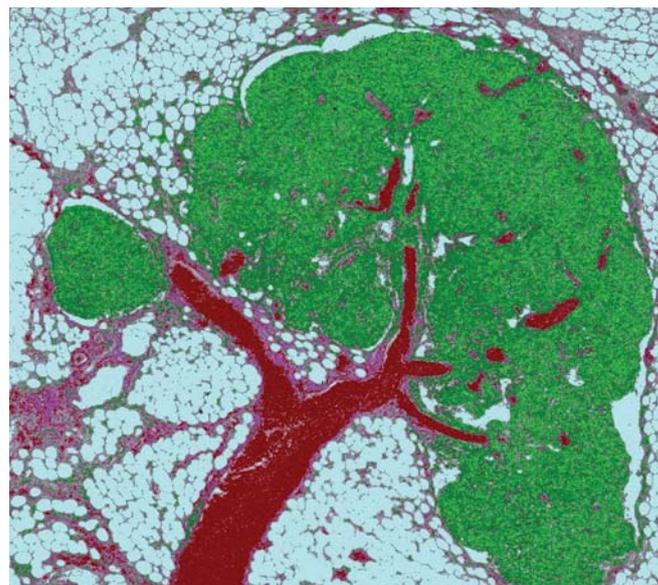
Michele Mitchell, Patient Champion, American Society for Clinical Pathology.



Green Tree

Top right: Pop art is a movement changing traditional art by including objects from popular and mass culture to create a different style. One of the best-recognized pop artists, Andy Warhol, inspired me. He changed the whole art scene by using elements of everyday life to portray reality in unconventional ways. Some of his work was a revolt against the loss of the value of art in pop culture, which allowed mass production of art along with many other things.

Sülen Sarioğlu, Chair of Molecular Pathology, Dokuz Eylul University, İzmir, Turkey.



Mr. Bones’ Outlook on Life

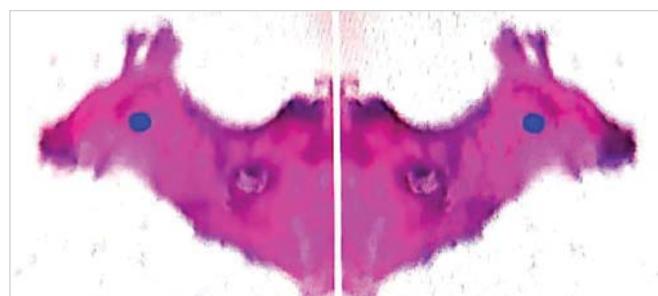
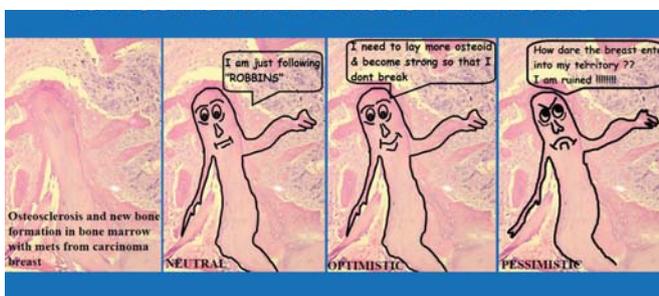
Bottom left: Osteosclerosis and new bone formation in bone marrow with metastases from breast carcinoma.

Sushma Belurkar, Department of Pathology, Kasturba Medical College, Manipal, Karnataka, India.

Mirror Image

Bottom right: Two sides of a calf’s head emerge in this cropped and enlarged image of a bone section.

Syed Salahuddin Ahmed, Delta Hospital Ltd., Dhaka, Bangladesh



Ear Resection Sketch

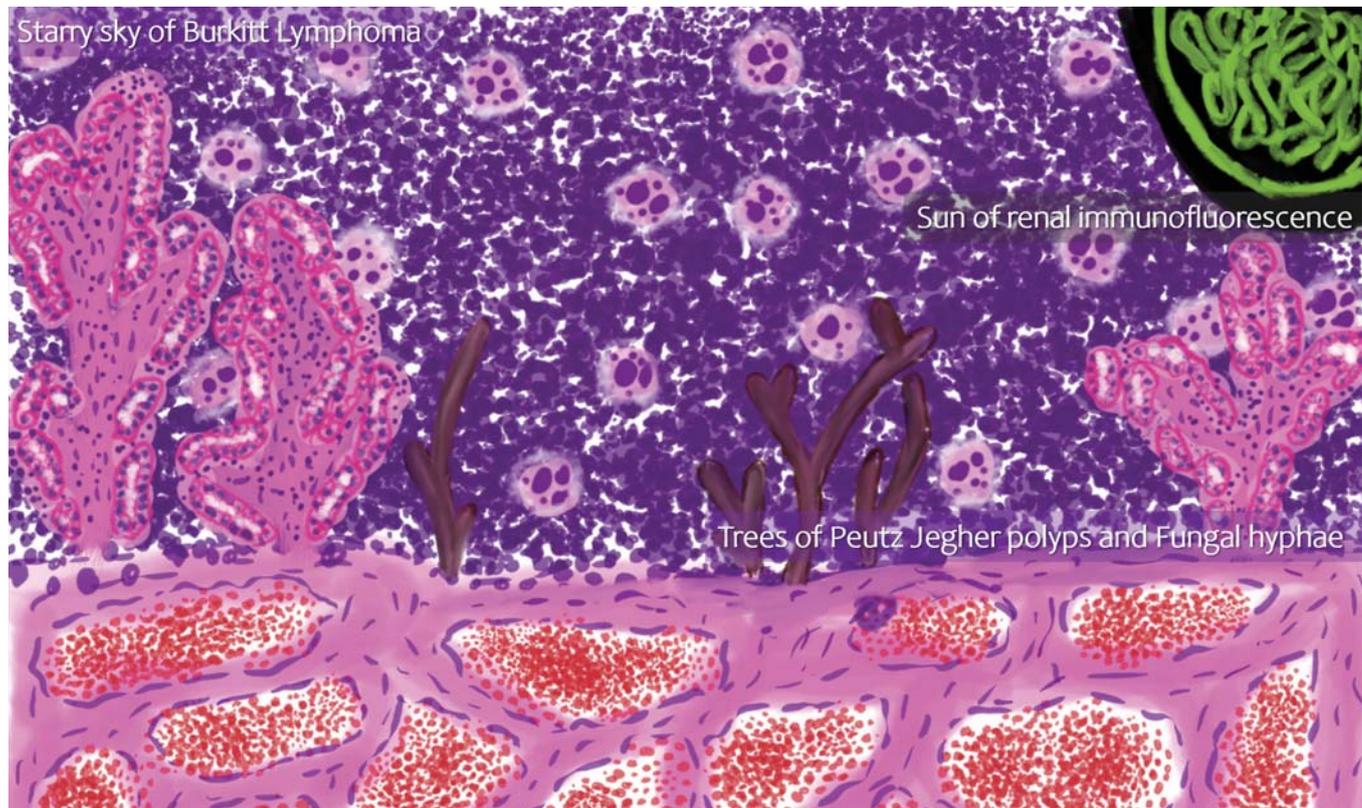
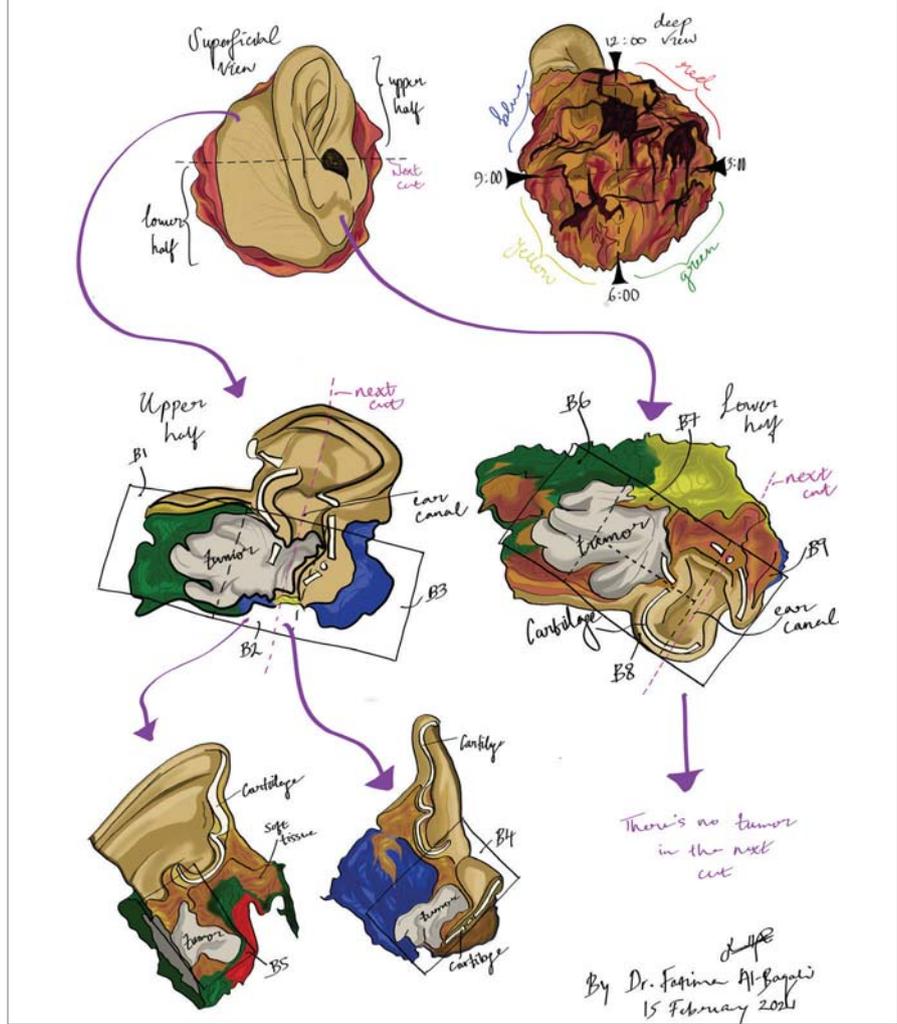
Right: I recently had the pleasure of grossing an ear resection specimen. I also had the utmost fun drawing a digital sketch of the specimen to make it easier to orient signing out the case and to detail where sections are taken from. The sketch took 15 hours and was made using an iPad.

Fatima A. Al-Baqali, George Washington University Hospital, Washington, DC, USA.

A Pathologist Sees Art Everywhere

Bottom: This image was made using the Sketchbook app on a Microsoft Surface Pro device.

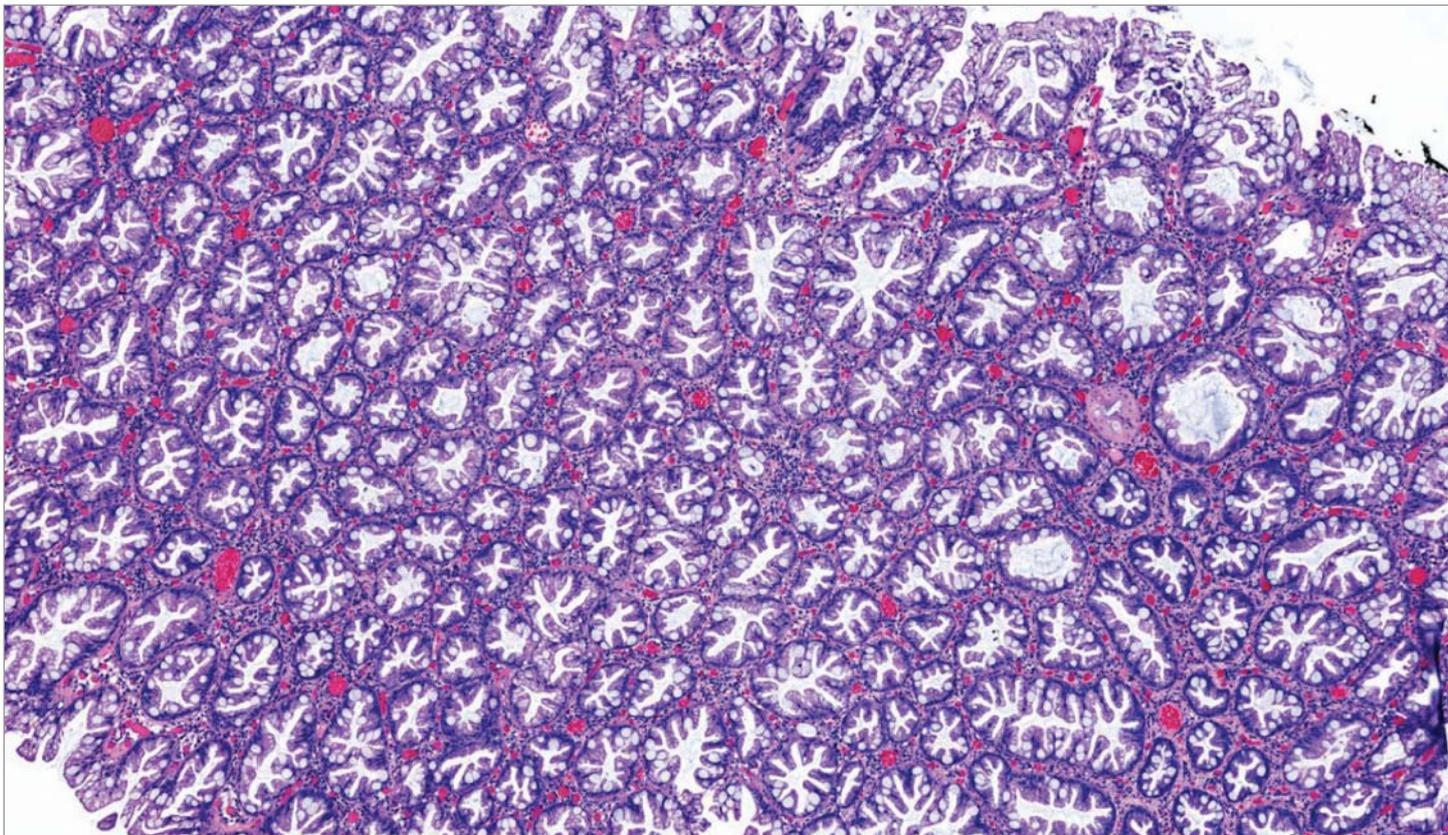
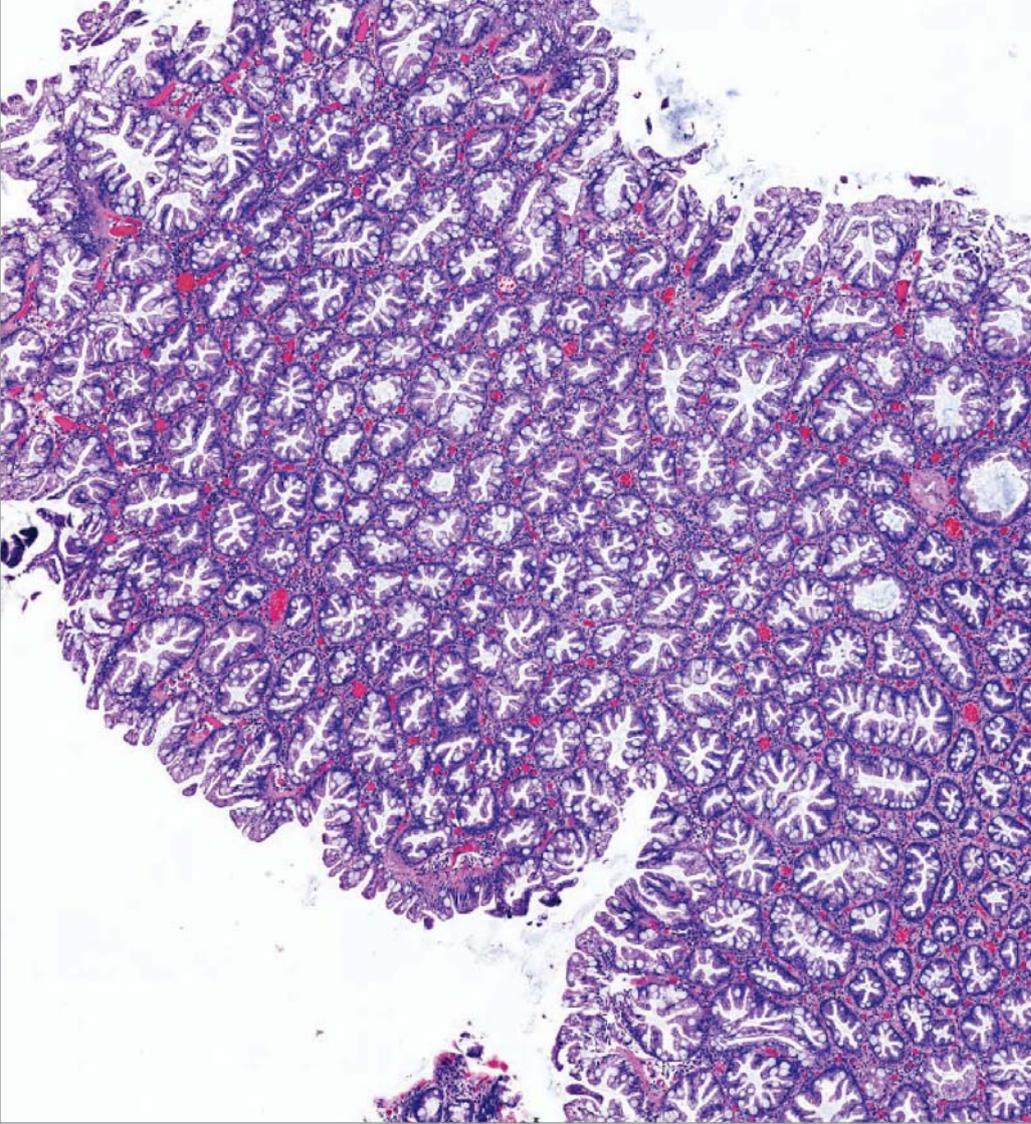
Deeksha Sikri, Department of Pathology, St. George's University, True Blue Campus, Grenada, West Indies.

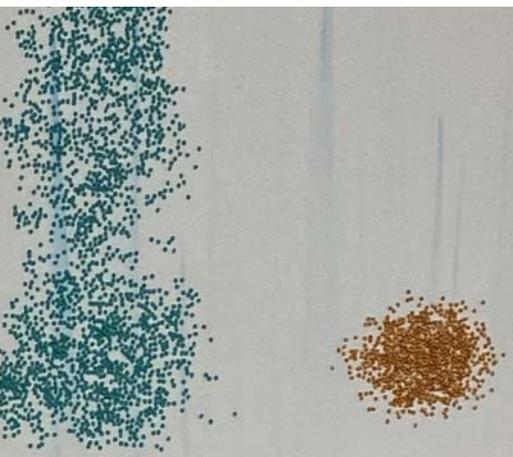
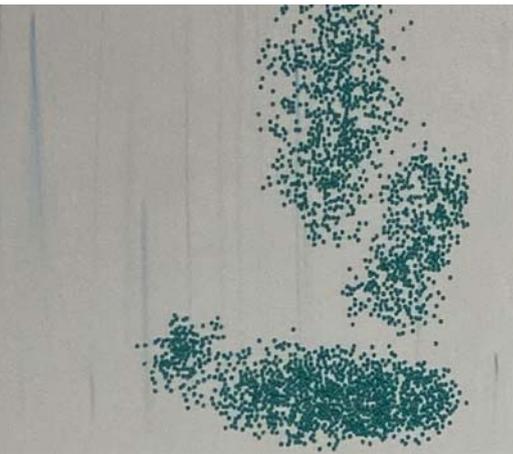


Snowflakes or Trilobites?

Asymmetrical glands and crypts appear as falling snowflakes with snow goblet cells or trilobites crawling through the lamina propria of this sessile serrated lesion.

Adam L. Booth, courtesy of an anonymous ascending colon biopsy.





In a Land Where Beads CAN be Cells

Top and middle left: An interpretation of ISHAGE gating on apheresis product using mixed media (beads on painted canvas).

Lindsay N. Hoffman, Quality Control Testing Laboratory, Stem Cell Program, UC Davis Health, Sacramento, California, USA.

Flying Disc

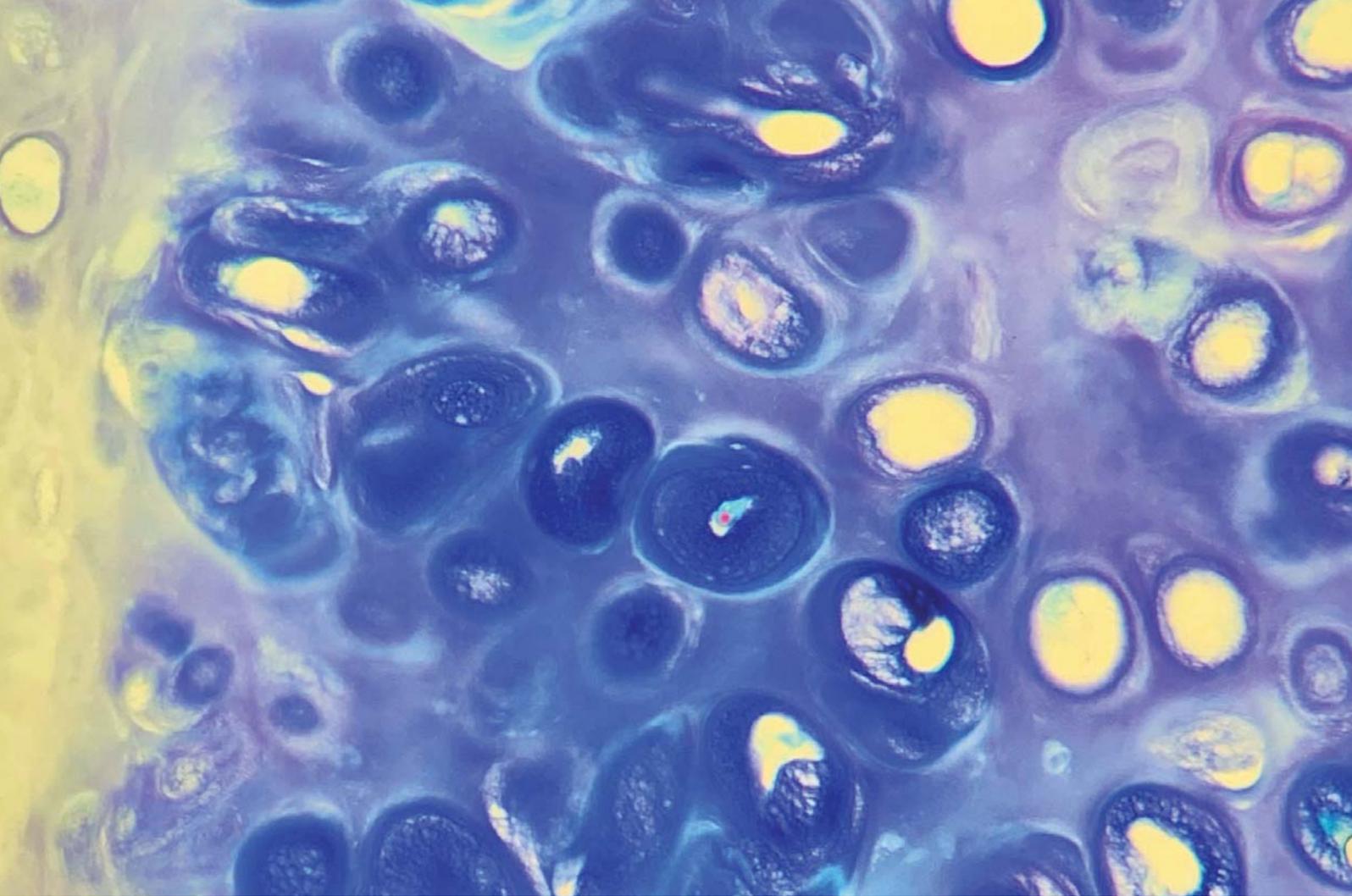
Bottom left: A photomicrograph of a follicle.

Pavlos Skoufogiannis, General Hospital of Volos, Greece.

Kleb-She-Ella

Top right: I find a superhero (or villain) character pose online that I like, replicate the image as a sketch, and change or modify as I draw. I color the characters based on what I know about how microbes grow on various agars or look under the microscope. Kleb-She-Ella is matched with the pink mucoid color on MacConkey agar.

Natalie Renier, UCSF Medical Center, San Francisco, California, USA.



Deep Blue Cartilage

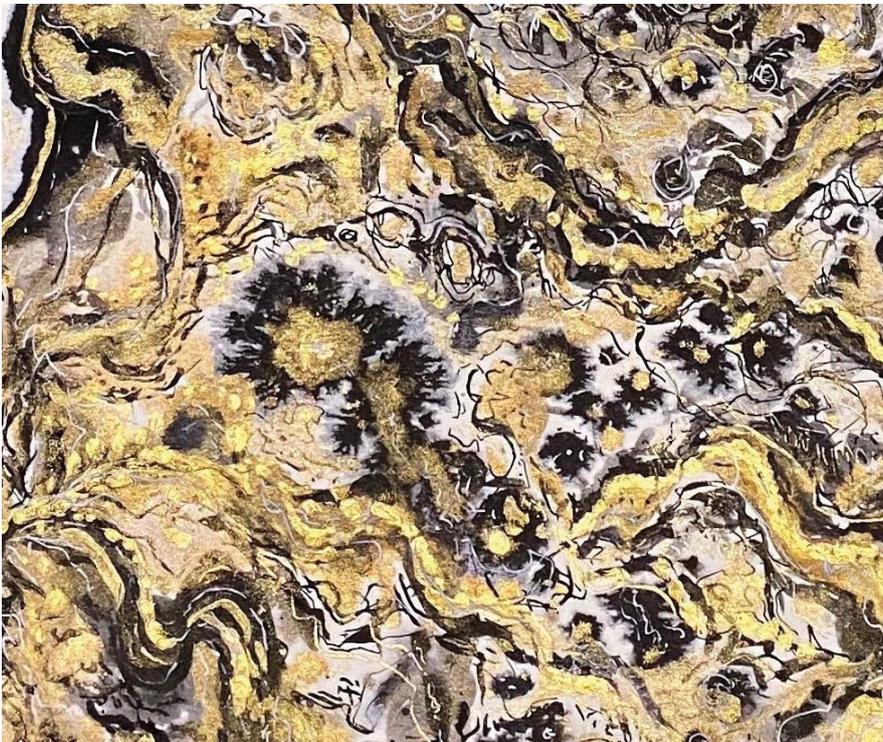
Top: Normal cartilage, Fite stain.
Picture taken with iPhone X.

*Janira M. Navarro Sanchez, John A.
Burns School of Medicine, University of
Hawaii, Honolulu, Hawaii, USA.*

After Cajal

Bottom right: Inspired by Santiago
Ramon y Cajal's numerous drawings of
the central nervous system. Watercolor
and India ink on paper.

*Lily Mahler, University of Alabama
School of Medicine, Birmingham,
Alabama, USA.*



Ahead of the Rest

Spatial phenotyping supports researchers from bench to bedside

The use of immunohistochemistry (IHC) and immunofluorescence (IF) has grown rapidly over the past decade – especially in recent years. Though research capabilities and technologies have advanced alongside them, for some labs, the choices can be overwhelming. “Beginners in the field may be caught between excitement for a bright future – and confusion,” says Joe Poh sheng Yeong, a research immunopathologist at Singapore General Hospital. But one clear route to that bright future lies in multiplex IF.

Multiplex IF opens the door to spatial phenotyping, which enables labs to “not only identify several cell types within a single sample, but also categorize whether a particular cell is expressing several biomarkers – allowing us to recognize specific phenotypes,” says Matt Humphries, scientific lead for Tissue Hybridization and Digital Pathology at Queen’s University Belfast. “This high level of cell profiling could hold significant prognostic information at a basic diagnostic level, while addressing the failures of treatment regimens in clinical trials – particularly in immuno-oncology.”

An unmet need

Current immunotherapy response rates are poor – fewer than 20 percent across several cancer types. “This could be improved with personalized medicine, which is what we strive for as a community of immuno-oncology researchers,” says Yeong. “But resource-limited areas still face accessibility and technical challenges, slow turnaround times, and cost limitations.”

That’s not all; prior to the rise of spatial phenotyping, predicting treatment response relied mostly on next-generation sequencing (NGS) and transcriptomic analysis. “Though these techniques are essential for gaining high quality subvisual

data, the loss of spatial arrangement of influential cell types is a significant drawback,” says Humphries. “Retaining the morphological landscape can help us identify key phenotypes that can impact tumor progression or patient survival – even with phenotypes that are expressed at very low levels.”

Big data challenges

Big data generation in biomarker research also presents a challenge. Clinicians are expected to analyze hundreds to thousands of samples, with single whole-slide multiplex IF images sometimes as large as 100 GB. “It is unrealistic to expect the human eye to assess and quantify an image containing hundreds of thousands of data points and report these with a high degree of accuracy and reproducibility,” says Humphries, “especially within the timeframe that diagnosticians have to assess a single slide.”

There is a growing need to simplify this wave of big data that will inform biomarker discoveries in cancer research. “Accurately quantifying the number of cells expressing two biomarkers within a certain proximity to tumor cells could take a clinician many hours to complete – but this is something computational pathology can do rapidly and reliably,” says Humphries. But where does the responsibility for driving it forward lie? “Laboratory medicine professionals will need to authorize such analysis – but this high-level information could be invaluable to an oncologist deciding on a patient’s treatment course.”

Clear advantages

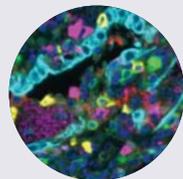
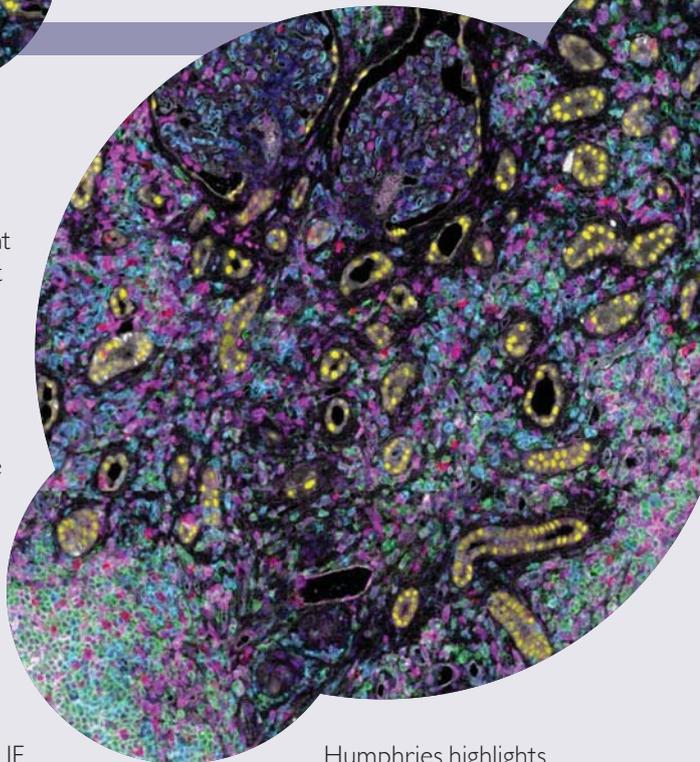
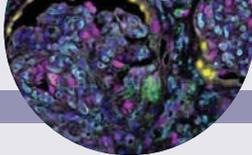
Predicting immunotherapy outcome is fundamental for providing patients with the best possible treatment and, although there are various methods to choose from, spatial phenotyping is particularly advantageous because of the reduced need for larger numbers of tissue slides.

Humphries highlights that “human tissue – whether used for research or clinical diagnosis – is precious and can be a finite resource if predicting immunotherapy response requires the assessment of several biomarkers.”

He continues, “Not only does this require several slides to analyze individually (which may be limited if the tissue is a small diagnostic biopsy or a precious tissue microarray research resource) but, because each successive slide is stained and reviewed, the topography of the tissue changes as you progress through a specimen.”

How can multiplex IF overcome this? “Spatial phenotyping can capture all these biomarkers and their cellular landscape in one slide,” says Humphries. “Furthermore, multiplex IF can identify cell types that co-express biomarkers with potential prognostic value. It is in the proximity of these phenotypes where spatial analysis is valuable – this level of data could strongly indicate immunotherapy response.”

“The advantages are tremendous,” agrees Yeong. “I doubt anyone working in cancer immunotherapy





can deny that. We can investigate phenotypes that require us to identify more than one marker and save the tissue for investigating two markers on one slide – and do so in a way that is compatible with most digital pathology analytical software for comprehensive interpretation, such as high-dimensional and spatial analysis. It also has strong potential and compatibility for clinical translation.”

Leading the charge

When considering what the future may hold for early adopters of spatial phenotyping with multiplex IF, Yeong believes they have much to look forward to. “Labs will not have to outsource to a third-party lab – just like those who adopted molecular testing and NGS all those years ago. Instead, their in-house researchers will have the knowledge to understand and interpret the data.” On the other hand, he says, “If the lab is a part of an Academic Medical Center or National Cancer Centre, oncologists and surgeons will no longer need to worry about this part of immunopathological monitoring – which, nowadays, is like having an indispensable arm in most large trials and studies.”

Humphries adds, “Laboratories undertaking spatial phenotyping with multiplex IF will quickly realize the huge wealth of information contained within a humble tissue slide. As the possibility for more nuanced data extraction grows, so too will the need for clear, objective analysis goals to have a meaningful impact on patient survival.”

Don't get left behind

Labs that do not incorporate spatial phenotyping into their research risk stunting their growth. “They will continue to deliver the high-quality diagnoses and reporting they are currently capable of – and only that,” says Humphries. Although he understands that caution is to be expected when new technology challenges the status quo, he says, “The laboratories that push the envelope with these new methods will truly reap the benefits, and there will be a point of critical mass when industry, national health agencies, and patient needs will drive adoption. This can already be seen in recent medical history with the introduction of techniques and technologies such as IHC, high-throughput auto-staining platforms, and digital pathology.”

But it's not all doom and gloom for those not yet making the leap – there are groups dedicated to helping labs adapt.

“I am a part of a task force called the JEDI council. Our goal is to make the knowledge of standardization and quality control of staining, imaging, troubleshooting, analysis, interpreting, and reporting more accessible,” highlights Yeong. “And there are more – many other global task forces and committees are already helping in this effort.”

Moreover, labs can start small on their path to spatial phenotyping. “We started tentatively with small panels that we designed to confirm

our observations in single-plex analysis – one of these was in an esophageal adenocarcinoma cohort demonstrating a dual-positive phenotype that could have prognostic value,” says Humphries. “But, as our panels have grown, so too has our in-house technical proficiency and our confidence in panel design and application.”

Parting wisdom

For pathologists and laboratory medicine professionals out there – wherever they may be in their spatial phenotyping journey – Yeong and Humphries have a key message. “We have seen the field of oncology evolve from the ‘H&E-only’ era to IHC, molecular testing, and now cancer immunotherapy – but there is more to come,” says Yeong. “We need collective effort and shared wisdom to use multiplex IHC and IF to move the field forward and overcome cost limitations and slow turnaround times.”

Humphries agrees that now is the time for labs to adopt spatial phenotyping and set an example for others to follow. “Don't forget to engage in conversations around new technologies as early as possible. Without your expert and uniquely placed opinion, early adoption of new technologies will take far longer,” he says. “As a translational scientist, my goal is to support pathologists and laboratory medicine professionals in the brilliant job they are doing. If new ways of working can augment specialist clinical skills, save time, and improve patient care, I would hope this is a positive pathway that all scientists would want to embrace.”

Joe Poh sheng Yeong is Research Immunopathologist at Singapore General Hospital, Singapore.

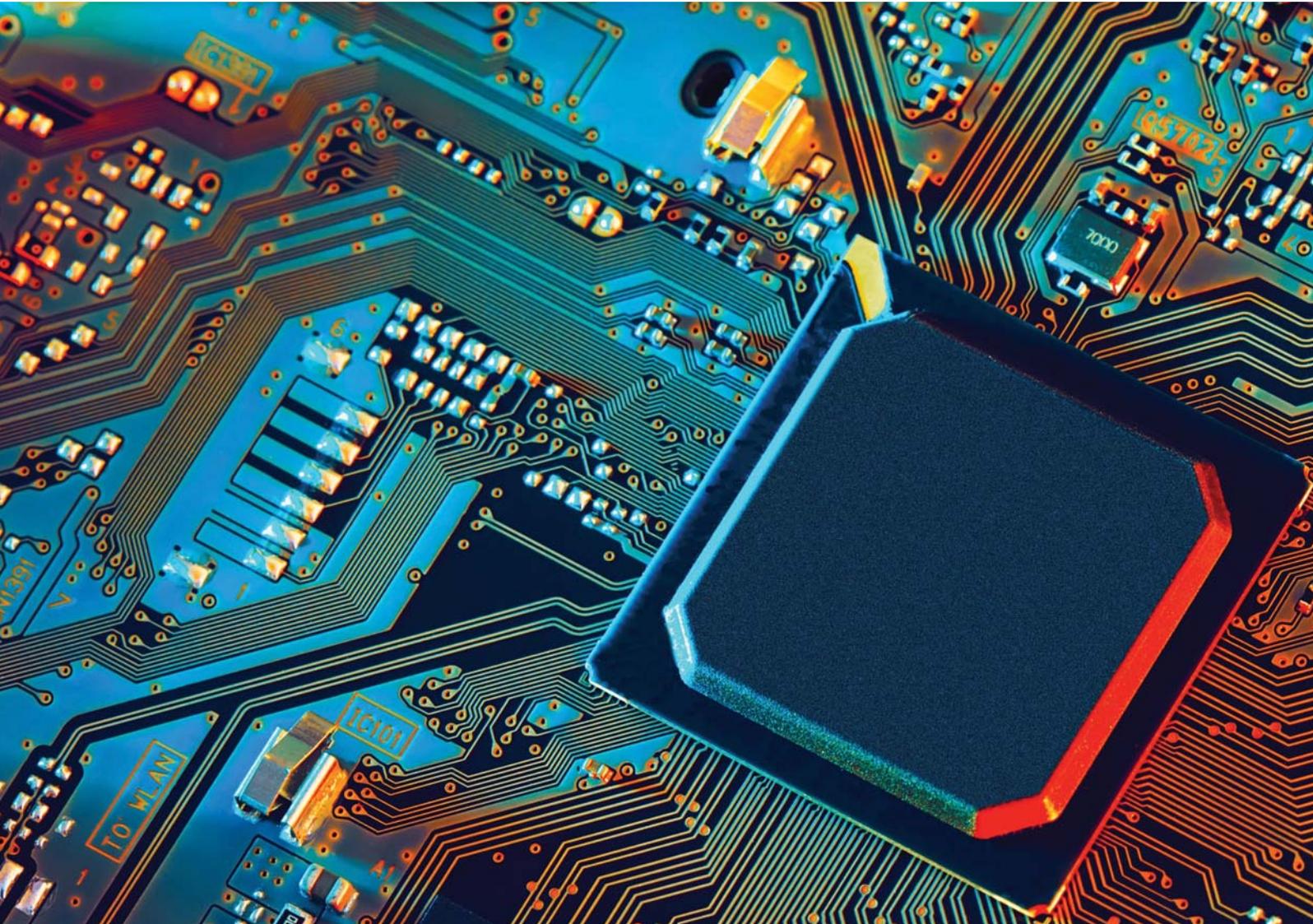
Matt Humphries is Scientific Lead for Tissue Hybridization and Digital Pathology at Queen's University Belfast, Belfast, Ireland.



Breaking Silos, Building Networks

Improving patient care through seamless data transfer

Michael Schubert interviews Tom Lewis



What is Getting It Right First Time (GIRFT) and how does it interact with the clinical lab?

The program was started by an orthopedic surgeon who noticed significant variation in approaches to orthopedic surgery across the country – specifically with respect to infection rates after hip surgery. Data in hand, he went around showing people the discrepancies and using them to open up discussion – what constitutes acceptable variation? What is unacceptable?

The key to starting these conversations is not to be dogmatic about “right” and “wrong,” but to challenge people who are doing things differently. He started by designing a data pack from different sources – questionnaires, hospital episode data, national datasets, and more. When trusts come to us for support, we send them their own individual data pack, which benchmarks their responses to the national averages.

Next, we do a “deep dive” – an open discussion about the data with the three clinical leads and relevant stakeholders from the host organizations. It tends not to be a compliance-driven approach and can take you into all sorts of unexpected areas, which is what I like about it. It’s about learning from best practice and, when the approach is at its best, it’s learning from excellence.

On the laboratory side, trusts are of high quality; of course, there is some variation across the country, but it’s marginal. The real variation lies in the pre- and post-analytical phases of the service pathway, which have been neglected because pathologists have traditionally said the pre-analytical phase is not their job. As part of the GIRFT program, we have tried to show people that pathology is an end-to-end pathway – from the moment a decision is made and a specimen needs to be collected to the actions taken as a consequence of the results.

Tell us about GIRFT – its implementation, the reasoning behind it, and what makes it so valuable...

Nowadays, you can’t work in isolation from other laboratories – no lab can deliver all of the testing patients need. We’re moving toward a network model with more formal agreements between labs and more specimens moving between sites. To achieve this, you have to make sure the pathway is seamless; the patient should not see any difference. We should be completely agnostic about where a test is done; what matters are the test specifications and whether it is undertaken as point-of-care, in a local lab, or sent away to a national or international authority. As a service user, you should be completely blind to that – and, at the moment, there is far too much variation when a specimen leaves the laboratory. This is partly due to timeliness, so the logistics are not great.

The main problem is the integration of requests and results. Many labs still send specimens away with a paper request or receive results on paper, which is slow and labor-intensive because people must transcribe the information on both ends. As a clinician, this worries me. It’s dangerous. We see avoidable transcription errors too often – a risk we should not tolerate. To overcome it, we need to adopt an integrated approach that is connected to the electronic patient record and seamless from order to result.

What successes have you seen so far?

We are a fairly small district general hospital that mainly performs a core set of tests. I believe our focus should remain on that core repertoire, even if we can do other analyses (which we often can), to avoid quality issues. We should send low-volume tests to other labs. This fits the pathology network model that seems to be developing, but involves time and effort to safely request and repeat samples.

“The National Pathology Exchange (NPEX) has brought us to the point where nearly all of our biochemistry samples are sent electronically to our largest local laboratory.”

The National Pathology Exchange (NPEX) has brought us to the point where nearly all of our biochemistry samples are sent electronically to our largest local laboratory. We immediately felt the benefits of this approach – there was one fewer person required per day for entering results, it’s more cost-effective, and it’s faster. National data laboratories who use NPEX have significantly faster turnaround times than those who don’t.

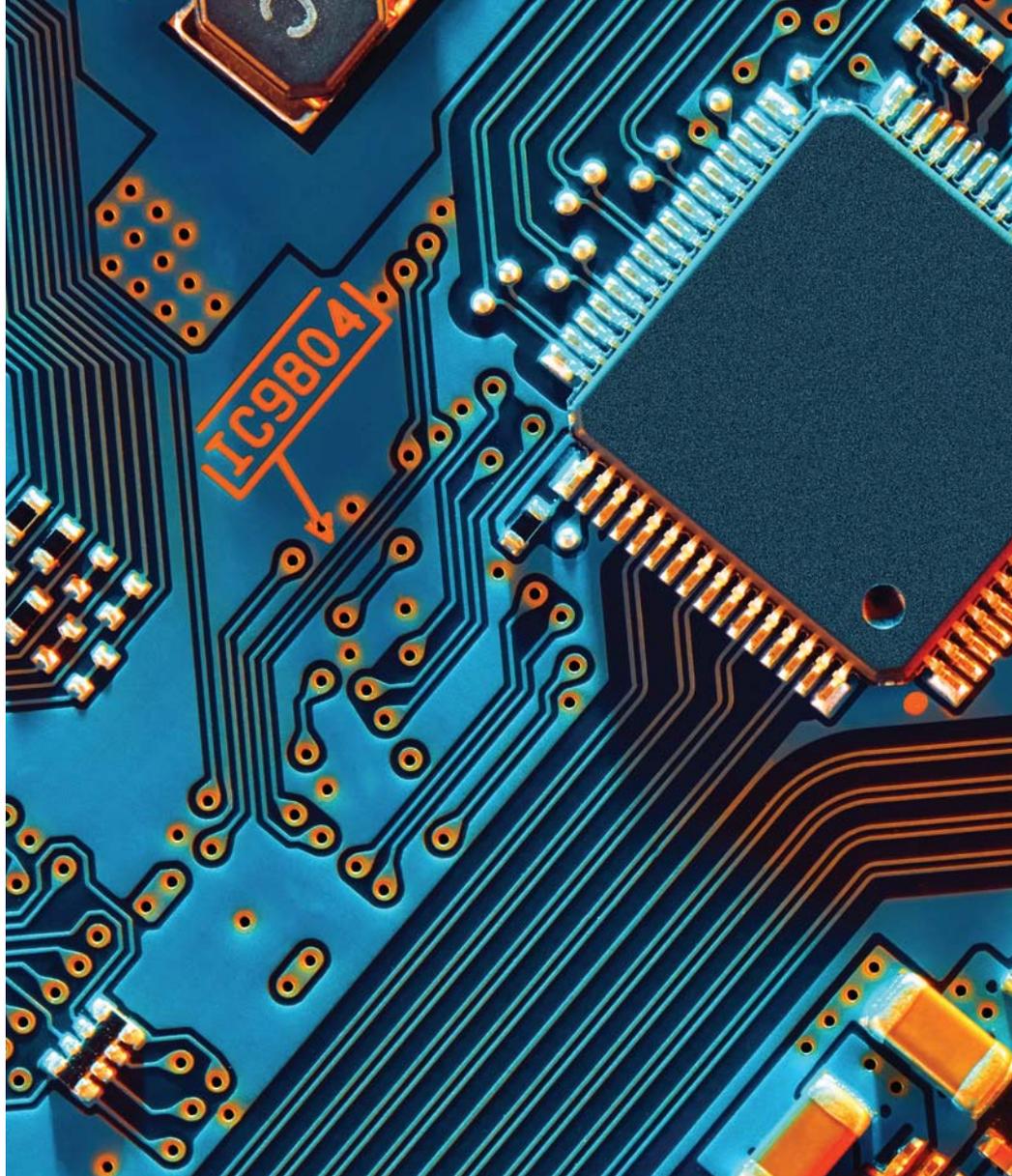
We don’t have much data on technical safety because it’s difficult to capture such rare events, but the approach is a safer way to avoid transcription errors. We are aware of people who have received life-changing – incorrect – diagnoses based on transcription errors, an avoidable problem we are trying to address.

What challenges might labs face in implementing these new large-scale approaches?

As a clinician, I don't see a lot of the challenges – I just expect them to be resolved. The initial setup requires someone at both ends (receiving and referring) to understand how NPEx works and how it interfaces with the laboratory information management system (LIMS). Once over that initial hurdle, it is relatively easy to adopt new tests into the system and it becomes business as usual.

Some specialties – particularly microbiology – have been slow to adopt this system. Our results are more complex (or we treat them as such), so mapping within laboratory systems presents a greater challenge than for other fields. Because of this, we have to be imaginative about how results are managed in our system, but most of us don't have the time, cognitive space, or sometimes even expertise for that kind of innovation.

“At the start, we relied almost entirely on the larger Royal Devon and Exeter Hospital for testing and, although we still rely on them somewhat, we now deliver a large amount of local testing ourselves.”



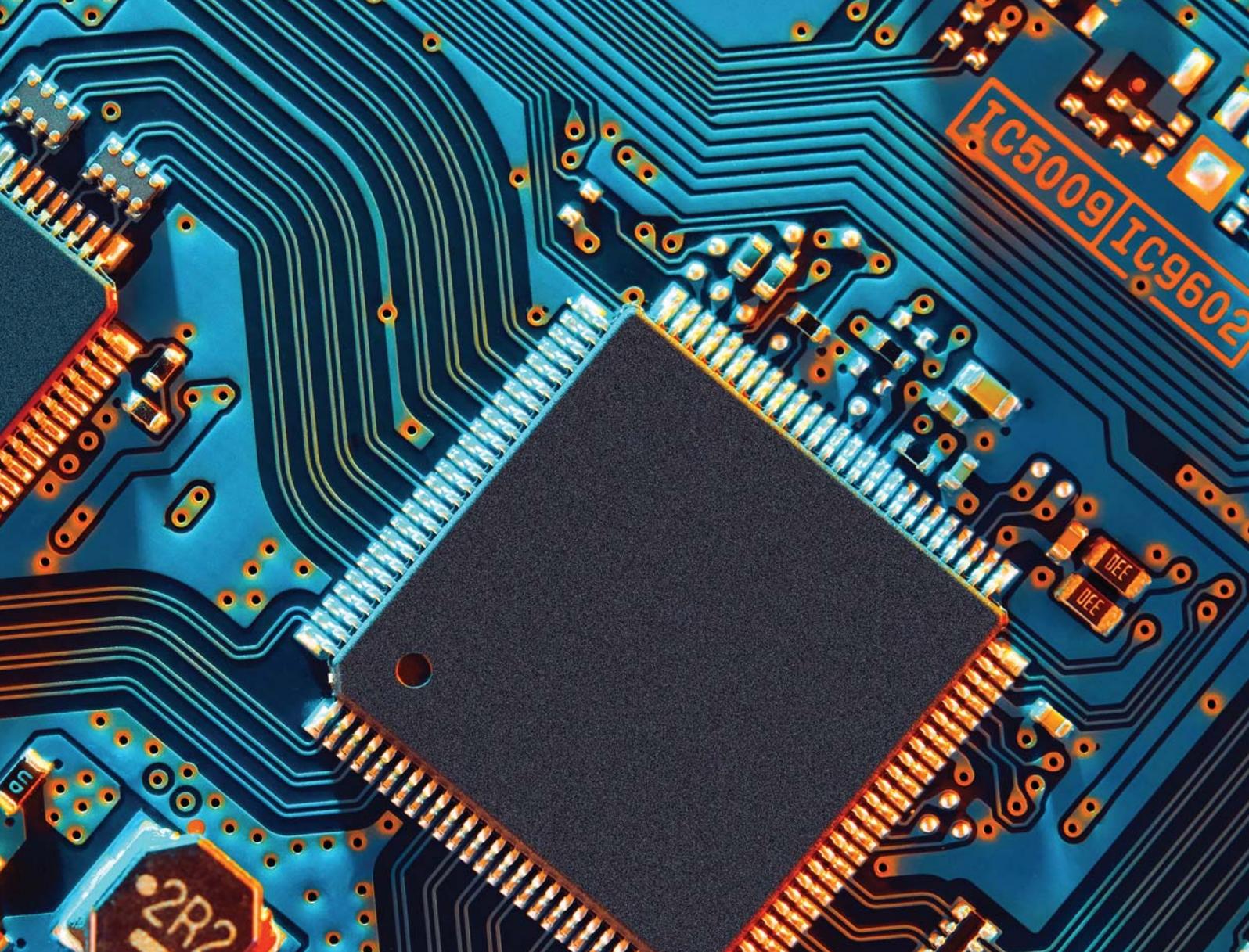
Because biochemists understand the results and how LIMS communicate with each other, they are best suited to help us to overcome these challenges. Recently, I spoke to our Lyme disease reference unit about how they might report complex results to us. It was interesting to hear their biochemist talk us through it; she was very aware of the outstanding issues and how we might solve them. All it takes is a willingness on both sides to invest time upfront and listen to each other.

Has the COVID-19 pandemic influenced how you deal with these challenges?

The pandemic has been a major

catalyst for our implementing NPEx in microbiology. When it hit the UK in February 2020, there was a clear need to “ramp up” testing, but I was skeptical about our ability to rapidly meet this need. At the start, we relied almost entirely on the larger Royal Devon and Exeter Hospital for testing and, although we still rely on them somewhat, we now deliver a large amount of local testing ourselves. If we compare this to where we stood earlier in the year, we can recognize and appreciate just how far we have come.

Without electronic result management, we could not have had that initial reliance on larger local hospitals – and without NPEx delivering results, the hospitals



would not have received our specimens and turnaround times would have been too slow. There was such unanimity of purpose when the pandemic hit that implementation was relatively easy. Within a day, we had NPEX set up and our turnaround times improved significantly – specimens taken in the emergency department in the morning were reported back to our LIMS by midday. We already had good logistics in place but, without NPEX, the necessary testing would have been undeliverable.

COVID-19 has also opened the door for us to consider why we don't use NPEX for other tests. We should be doing this across the board. There's no reason for us to deliver less crucial tests – such as

chlamydia – on-site but, because they are high-volume tests, it has been easier for us to do them ourselves. There's always room for improvement and NPEX opens up new ways of thinking about our ability to network, the tests we are doing, where we are doing them, and when.

Are there any tests following in the footsteps of COVID-19?

We have some hepatitis tests following that route, but that might be it for now. Right now, most people are only thinking about COVID-19, so trying to shift the focus to other areas is challenging. We have recently trained a new staff member to help expand our efforts and get back to normal life – or

what the new version of normal might be – because we know that, if we invest this time upfront, we'll see significant downstream gains.

How can programs like NPEX and GIRFT help labs cope with increasing amounts of data?

The increasing amount of data is not a problem – it's an opportunity. At the moment, data aren't comparable across the UK, which makes it difficult to set benchmarks; NPEX can help drive a commonality of data structure. We conducted a nursery school data analysis with GIRFT, but we really need people who can extract information and wisdom from large datasets. It would be interesting to explore how NPEX could



Tom Lewis participating in an NPEX User Group 2019 panel at Royal College of Pathologists.

improve the national data repository as well as data transfer.

NPEX is a new way of working and we do really see it as a non-negotiable – it isn't a nicety that we should be adding onto the pathway, it is a core essential deliverable. Others will say you need a common LIMS – if you are in the same laboratory network, you are on the same LIMS and the problem is solved. But that's difficult to achieve and, depending on IT infrastructure constraints, a common LIMS may even be impossible. You can speed this process up by combining existing LIMS (using NPEX

as the glue), but it can be frustrating when people believe a common LIMS will be the answer to their problems – and it isn't.

If labs get on board, what lies in their future?

We hope to achieve a distributed network designed according to function. For instance, you might have a distributed network of national labs that deliver complex testing and a secondary network underneath that of less complex testing, DGH units, and point-of-care testing. NPEX could be the glue for such networks, which rely on the ability to move data around

the system.

That didn't happen with the COVID-19 testing rollout, which might have worked much better if all of our testing capabilities were combined. It would have given us the opportunity and resilience to move data around and to stop seeing the lab as the focus of the pathology service – and, instead, put the patient at the center of our efforts.

Tom Lewis is Consultant Microbiologist at North Devon NHS Trust, Devon, UK, and Pathology Lead for Getting It Right First Time.

YOUR NEXT STEP IN EDUCATION

*Brought to you by Texere Publishing,
the parent company of The Pathologist*

^{the}**Pathologist Educator**

*You need to stay on top of new developments in pathology
and laboratory medicine. It can be hard to find the time
to search for CME, hone your diagnostic skills, and
take in the latest tips and tricks for training – all while
keeping up with your routine work.*

*The Pathologist Educator takes the effort out of
staying informed.*

TEXERENEWSLETTERS.COM
/PATHOLOGIST-EDUCATOR

SUBSCRIBE



Profession

Your career
Your business
Your life

Peer-to-Peer with Henry Appelman

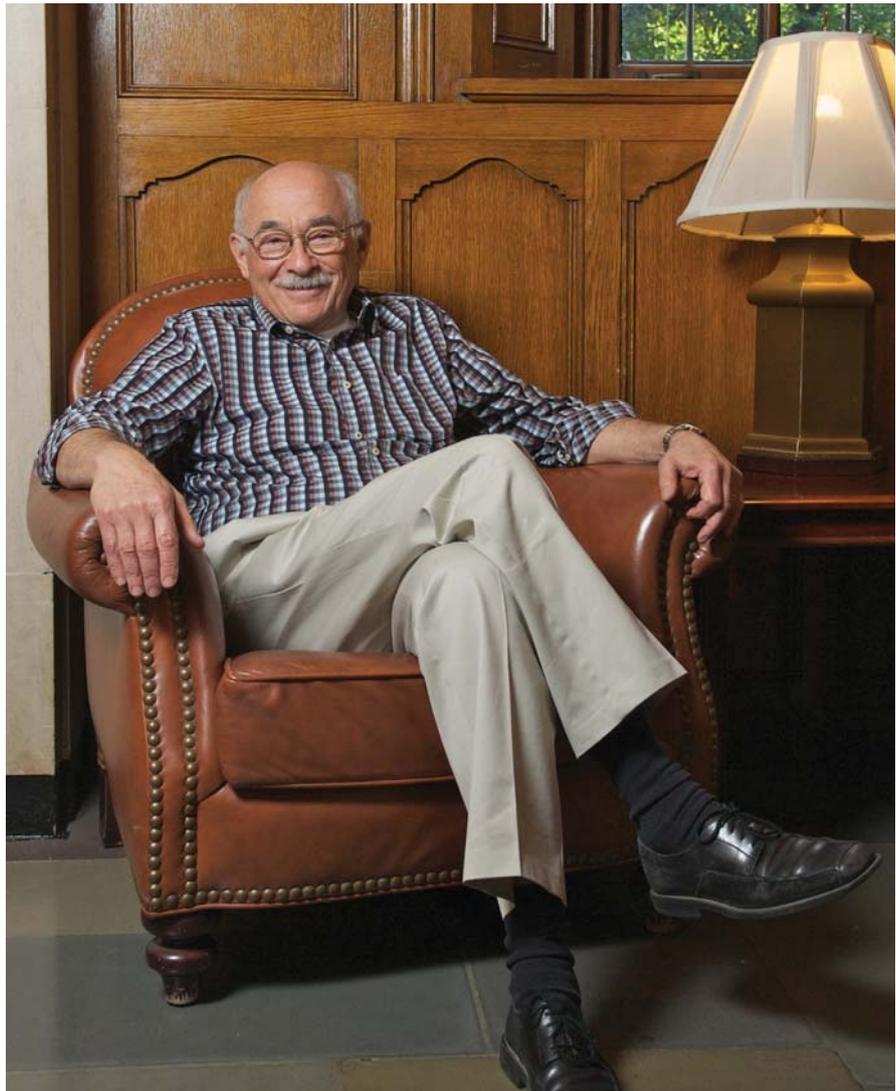
A GI pathologist known for his sense of humor shares his tips for surviving pathology... and life

Ivan Damjanov interviews Henry Appelman

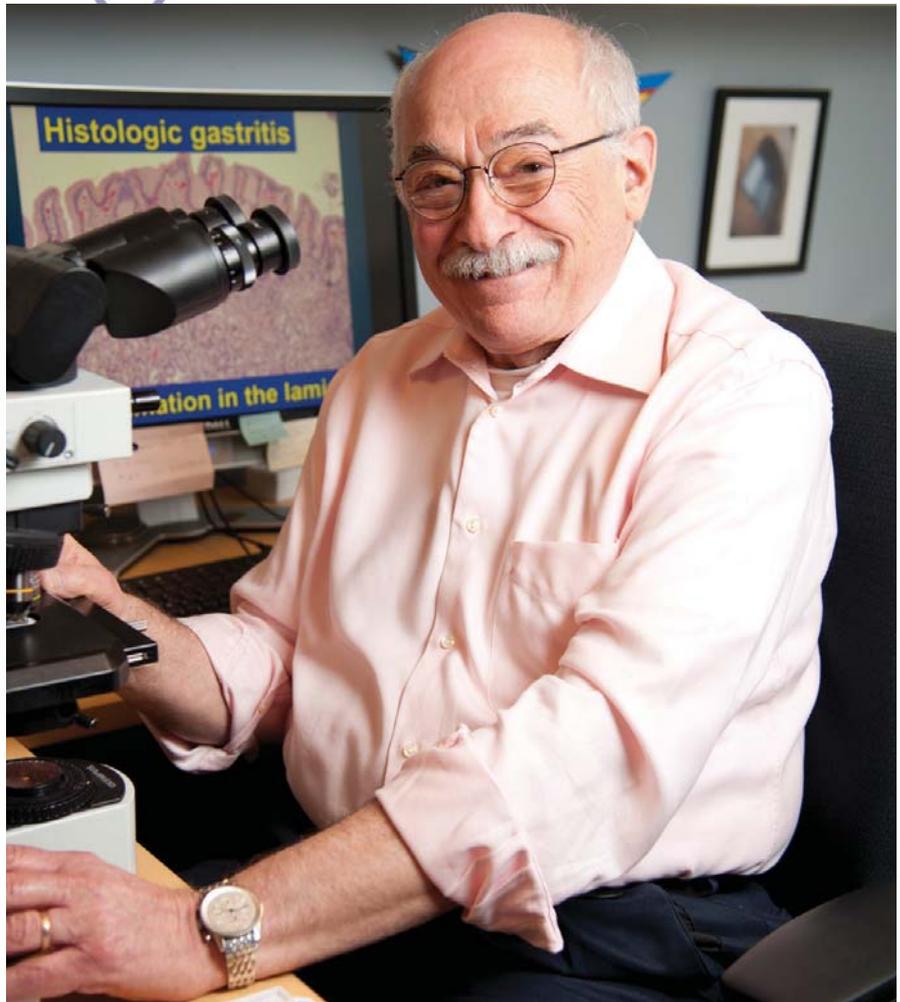
Henry Appelman has spent most of his long professional life at the University of Michigan School of Medicine in Ann Arbor. Even at 85 years old, he shows up every morning at his microscope in the surgical pathology department, signing out more than 5,000 routine gastrointestinal (GI) biopsies per year – not to mention innumerable outside consultations. Teaching residents and fellows, traveling the country as an invited lecturer, and writing books and papers has kept him busy for most of his life and he doesn't see himself quitting anytime soon. How does he manage it – and what keeps him going?

At your age, you might be one of the oldest practicing academic surgical pathologists! When will you give up your practice?

I will be 85 in December and I think I signed out around 5,000 cases last year – although I don't know the number for certain. I have no idea how many people my age are still signing out, but probably very few. When will I stop? When it is no longer interesting, when I find that I am losing my diagnostic capabilities,



“My work is still exciting and intellectually challenging. Every day, there are new things to learn and new experiences to try to understand. Besides, I have fabulous, brilliant, accomplished colleagues...”



when I am too physically limited to function... or when my colleagues have had enough of me!

In the meantime, my work is still exciting and intellectually challenging. Every day, there are new things to learn and new experiences to try to understand. Besides, I have fabulous, brilliant, accomplished colleagues who teach me new things daily. I see no reason to give all these things up before I reach senility and develop dementia.

Do you still see many cases in consultation – and are they more fun than routine work?

We have a busy consultation practice, so we split the consult cases among our group of seven GI pathologists, each of whom covers the consultation service for a week at a time. It does not matter

to whom a case is addressed. Before the COVID-19 pandemic hit, we received 3,500–4,000 consult cases a year and the numbers were steadily going up.

Which type of case is more “fun?” I am partial to the routine cases because of the far better clinical interactions. Too many consultation cases come with inadequate clinical and laboratory data for us to offer appropriate interpretation and help for the contributors. Unfortunately, many of the contributors get little or no information from the clinicians who send them specimens, especially biopsies. In contrast, in our routine practice, I established a system years ago in which every gut biopsy is

accompanied by a copy of the endoscopy report, which serves as the accessioning form. This means that, for every biopsy performed in our endoscopy centers, we pathologists know the reasons for the examination, the endoscopic findings, the clinical impressions, and the recommendations for treatment and follow-up. For liver biopsies, we have immediate access to the laboratory data and clinical findings for every patient on our electronic clinical database. These features make dealing with routine in-house cases both easier and more pleasant for us – and, as a result, we can do a much better job for the patients and for our colleagues in gastroenterology.



We see over 20,000 in-house cases each year and, because of our specialized gastroenterology service, they are enriched for inflammatory diseases. That makes these cases both interesting and challenging – appealing features for any pathologist.

Are you as fast at signing out cases now as when you were younger?

I have no idea; I've never timed myself. My work gets done on time, which is all that really matters. No clinician has ever yelled at me for being too slow with a case!

What inspired you to become a GI pathologist?

It was purely accidental. I finished my

residency in 1966 at the beginning of the Vietnam War and immediately had to go into the army. Like most of my contemporaries, I was in a plan sponsored by the Department of Defense that allowed resident physicians to finish our residencies without being drafted into the service – but then required us to spend the next two years working at our specialties in service facilities. I was assigned to serve my country at the Armed Forces Institute of Pathology, at that time the premier consultative pathology service in the world. The Institute was divided into specialty branches defined by body sites. I was assigned to the branch that covered skin and GI cases, neither of which

particularly interested me during my pathology residency. (This was before the advent of endoscopy and biopsy using fiber-optic technology, which came into common use several years later when GI biopsies became the common tissue for diagnosis.) This gave me the chance to work with one of the giants in both skin and GI pathology – Elson Helwig, a brilliant diagnostician and fabulous mentor.

When I started in the Skin and GI Branch, 90 percent of the cases were skin samples. Of the 10 percent that were GI specimens, most were resections. The branch had three pathologists and three dermatologists who were essentially doing dermatopathology fellowships.

The pathologists and dermatologists shared the skin cases, but only the pathologists handled GI cases. Because the AFIP was a consultation service, we received samples from all over the US as well as from other countries – meaning that both skin and GI cases were often challenging. It was the two years I spent at the AFIP, doing GI research and handling the most challenging and interesting clinical cases imaginable, that inspired me to become a GI pathology expert when I left the army – and that’s exactly what happened.

You’ve seen the rise of immunohistochemistry, molecular biology, and other techniques that have revolutionized surgical pathology. How do you answer your junior colleagues when they ask, “How did you practice pathology without these techniques?”

When I started in pathology, things were pretty primitive compared with today’s techniques. But I bet that, a few years down the road, what we have today will seem pretty primitive compared to the newest approaches. For anatomic pathology, we had a battery of special stains, but not much else – so we relied on careful gross analysis and detailed microscopic diagnosis. We also did not know about the many diseases and variations we do now, so there was much less to learn!

Many leading pathologists were your residents and fellows. Are they good because they were smart and talented, because they had a drive to succeed, or because you taught them so well? Undoubtedly a combination of all three. They were smart and capable to begin with. Then they decided what type of practice was best for them, looked around, and discovered the keys to success. Finally, I probably did motivate some of them. All they had to do was

to watch me and see how much fun I was having doing all the things I do! I suspect this was probably my greatest contribution to their success.

What makes a good surgical pathologist?

That depends on your definition of a “good surgical pathologist.” Obviously, you must master the understanding of tissue changes, including how they interact and what combinations of changes are needed for diagnoses, because we rarely diagnose any disease from a single microscopic change. You must also recognize the clinical significance of every diagnosis and know how to communicate effectively with clinicians.

Can you teach someone to become a good surgical pathologist?

I can teach them what I do and how I do it. I had role models growing up – especially Murray Abell, the best diagnostician in our department, and Jim French, a role model for a department chairman whom I emulated at the beginning. Over the years, I gradually developed my own approaches, but I probably kept using a lot of what I gained from my original role models. I hope my students will do the same.

How long does it take you to recognize a talented future pathologist?

Interesting question. Selection for our residency program has been pretty competitive over the years, so our trainees tend to be talented, highly capable, and highly qualified. Most of them are terrific future pathologists right from the start. Some are better at certain things than others – for instance, microscopic aptitude, literature review, lectures, or handling clinical laboratory problems. One of the things I look for in a trainee is curiosity and willingness to question me in diagnoses and concepts. However, overall, our trainees have done

wonderfully in whatever type of practice they chose, which makes me proud to say that I had a part in their training.

People love your seminars and presentations. How many do you still give per year – and how did you get your reputation as a “funny guy?” I used to give eight to 10 lectures and seminars a year outside my institution. As many as four were given during courses sponsored by national organizations such as the American Society for Clinical Pathology and the United States and Canadian Academy of Pathology. As I have grown older, the number of invitations for lectures and seminars has decreased as young, energetic, and entertaining GI pathologists have emerged. It’s appropriate for the invitations to go to them now and I’m pleased to see them receiving the honors.

I have never tried to teach anyone to present in my style. Everyone has to develop a style with which they are comfortable. Personally, I have a love of life and of the people in it, and I have developed a sense of humor about both. I also find that some of the things we do and say in our business are hilarious – or ridiculous – so I tend to make fun of them in my presentations. This is especially true of anything that has specific numbers of diagnostic or prognostic importance attached to them – for instance size, number of positive nuclei, or number of mitoses per square mile!

Henry Appelman is M.R. Abell Professor of Surgical Pathology, Gastrointestinal and Hepatobiliary Pathology and Program Director of the GI Pathology Fellowship, Department of Pathology, University of Michigan, Ann Arbor, Michigan, USA.

Ivan Damjanov is Professor Emeritus at The University of Kansas, Kansas City, Kansas, USA.



SAVE THE DATE

ASCP 2021 Annual Meeting

Join us this fall
in Boston!

October 27–29, 2021



ASCP 2021

ANNUAL MEETING

OCTOBER 27-29 | BOSTON, MA

Save the Date!

www.ascp.org/2021

Spotlight on... Technology

PathScan® Combi: Slide Scanner Dedicated to FISH on Tissue

The most common FISH scanner in France to manage up to 5,000 slides yearly. With the additional bright field scanning feature, you can easily define the area of interest on an H&E or IHC slide and match with a FISH one. The onboard image analysis module manages every kind of probe and allows the automation of FISH activity from slides to reports.

www.excilone.com



PTLab Software for Full-Color Slide and Cassette Printing

PTLab was designed for use with Signature-series printers. Templates can be designed that define the required information on slides or cassettes, including fixed and variable fields. Information contained in 2D barcodes on the vial or other containers is automatically printed on the number of slides or cassettes ordered for a given study.

<https://dtm-medical.eu>



Enable In-House Comprehensive Genomic Profiling (CGP)

TruSight™ Oncology 500 assays enable in-house CGP across 523 genes from blood or tissue biopsy samples. Assays from Illumina are designed to identify pan-cancer biomarkers in guidelines and trials, including tumor mutational burden (TMB) and microsatellite instability (MSI).

For Research Use Only. Not for use in diagnostic procedures.

tp.txp.to/tso500



Professional grossing tables perfectly suited to your lab

GrossPath – the special worktable that ensures a pollution-free environment for histological slide preparations. Buy it, set it up, and power it on: thanks to its generously proportioned active-carbon air recirculation system, it is ready for immediate use! Hazardous vapors are vacuumed downward; formalin concentrations are significantly below maximum allowable concentrations throughout the extraction zone.

tp.txp.to/Kugel/GrossPath



Creating a Living Textbook

Sitting Down With...Nat Pernick, Founder
and President of PathologyOutlines.com,
Bingham Farms, Michigan, USA

How did you end up in the world of pathology?

My first love was computers. I started programming in the early 1970s, initially with an Olivetti programmable calculator to keep score in bowling. After my calculus teachers taught me BASIC, I started working for Wang Laboratories as a programmer. Then, I got a job from my girlfriend's uncle – creating a LIS for his clinical laboratory. Because I also loved science, my girlfriend convinced me to consider medicine. I attended medical and law school at the University of Michigan with a planned career in the promised new field of “computers and medicine,” which was never established. I practised law for several years, but didn't find it exciting. Eventually, while talking to some medical school classmates at a summer camp, the idea of becoming a pathologist took hold because I like to understand how things – and people – work.

How have you combined your experience in medicine and law throughout your career?

As a law student, I clerked in a healthcare legal department and was told that I would look back on my medical school education as “a complete waste of time.” After many law firm interviews, I decided to work for myself. I did all types of law, but ended up handling debt collection, primarily for the State of Michigan – things like student loans and taxes. Today, my legal background is helpful for the business aspects of PathologyOutlines and understanding how the world works.

You are best known for your website, PathologyOutlines.com. What inspired you to create such a resource for pathologists and laboratory medicine professionals?

The inspiration for the website started with David Grignon's unknown conferences coupled with John Sinard's book, *Outlines in Pathology*, which

residents constantly updated by taping sheets of paper into the book. After residency, I decided to compile all of my books, atlases, handouts, and notes into an online database that would be readily accessible to me and anyone else who might find it useful. My “mission” was to help pathologists, including myself, do a better job by making the information we need fast and free to obtain. I started writing, initially with the thyroid chapter, at the same summer camp where I had first made the decision to pursue pathology.

How did you set up PathologyOutlines.com?

A friend who designed websites set up the main structure. I wrote chapters in Microsoft Word, saved them in HTML, and uploaded them. It was quite simple at first. At some point, I realized that it made sense to invite people much smarter than I to write for the site. Later, Debra Zynger suggested starting an editorial board – and helped me set it up, because I did not speak “academic.”

I consider this textbook an almost impossible task due to its vast scope – but my philosophy for difficult tasks is simple: start and keep going. I think it is successful because I can say two things many others have difficulty with: “I don't know” and “I was wrong.” This is necessary, in my opinion, when doing something that has not been done before. I asked a lot of people for advice and made a lot of mistakes, but I learned from them and kept things moving in the right direction. It also helped that I am an idealist, committed to the cause, and don't care as much about money as others.

Have you noticed any trends in subjects of interest for pathologists over recent years?

For jobs, Debra Zynger and I analyzed our advertisements and found trends towards molecular, dermpath and GI

jobs (1). I write papers on *How Cancer Arises Due to Complexity Theory* (2) and personally think that biologic networks, complexity theory, and self-organized criticality will become “hot topics” as we move toward curative strategies for adult cancers.

You have an extensive CV and a busy website. How do you balance your personal and professional lives?

I try to compartmentalize my time for the website, research, and personal life but it often gets jumbled. I have found that vacations – even just long weekends – are a good opportunity to “restart” my life by planning each day the way I want it to be. That way, the “new normal” is established by the time I go back to work. I have also learned from others that starting the day at 4:00 a.m. (when I can do it) makes me more productive.

If you hadn't become a doctor – and then moved into running PathologyOutlines.com – what would you be instead?

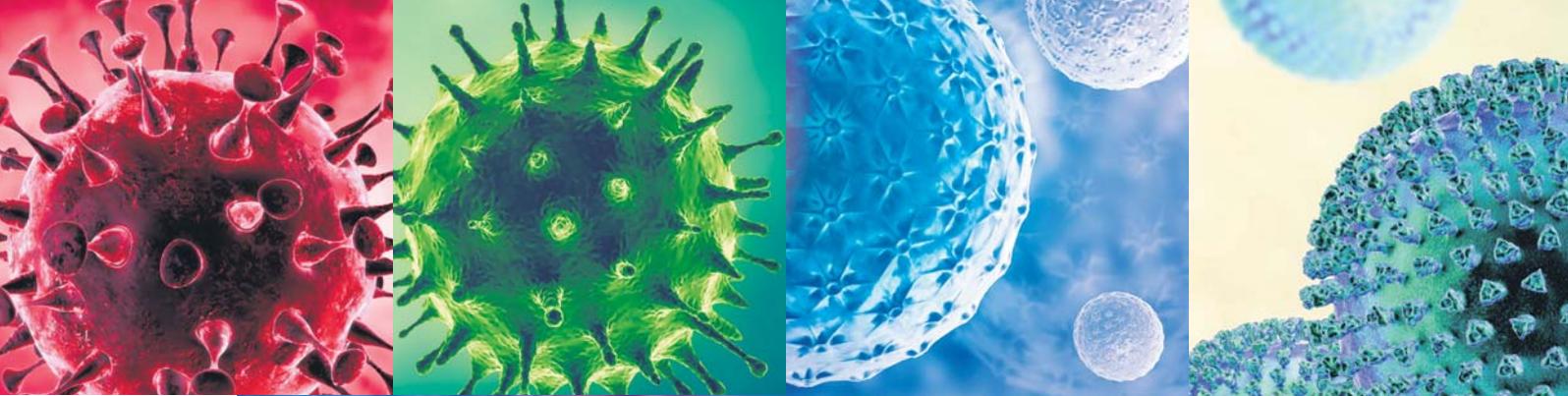
I loved computers and was very happy doing that. In fact, I worked as a programmer to pay for medical and law school and even as a resident.

What advice would you give to pathologists and laboratory medicine professionals who are just starting out in the field?

Act in the best interest of the patient, even if it causes trouble for you personally in the short term. Also – try to get along with everyone... even the difficult people.

References

1. DL Zynger, N Pernick, “Understanding the pathology job market: an analysis of 2330 pathology job advertisements from 2013 through 2017,” *Arch Pathol Lab Med*, 143, 9 (2019). PMID: 30785304.
2. N Pernick (2021). Available at: <https://bit.ly/3jQKr7u>.



1 sample 4 targets detected simultaneously

**RESP-4:
COVID-19, Flu A, Flu B, RSV**

**Amplidiag® RESP-4
Batch testing**

**Novodiag® RESP-4
On-demand testing**

CE-IVD

CE-IVD ongoing



Advantages :

- Batch or on-demand molecular testing for diagnostics of **the most common Winter respiratory infections**
- Distinguish between **viruses responsible for similar symptoms** : SARS-CoV-2, Influenza A, Influenza B, RSV
- Secured supply chain and manufacturing capabilities to answer potentially high demand

Please contact us for more information or visit www.mobidiag.com

MOBIDIAG

Mobidiag Ltd. (UK)
+44 333 305 7506
sales@mobidiag.com