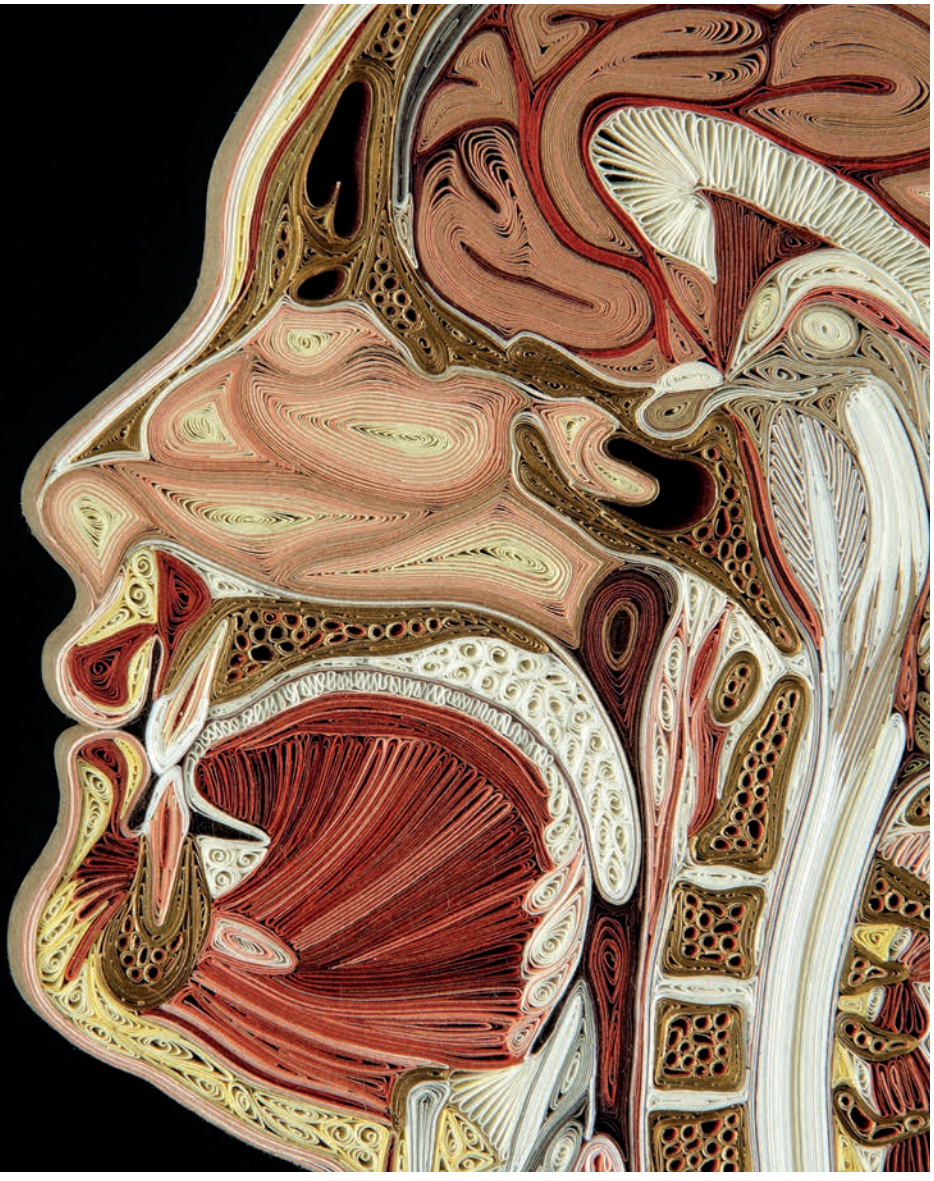
JULY 2018 # 44

the Pathologist™

Portraits of Pathology

The beauty of pathology and laboratory medicine – as shown by those who practice it

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Case of the Month

This malignant salivary tumor was surgically removed from the parotid gland of a 67-year-old man.

Tumors of this type express the receptors for which hormone?

a Androgen

b Estrogen

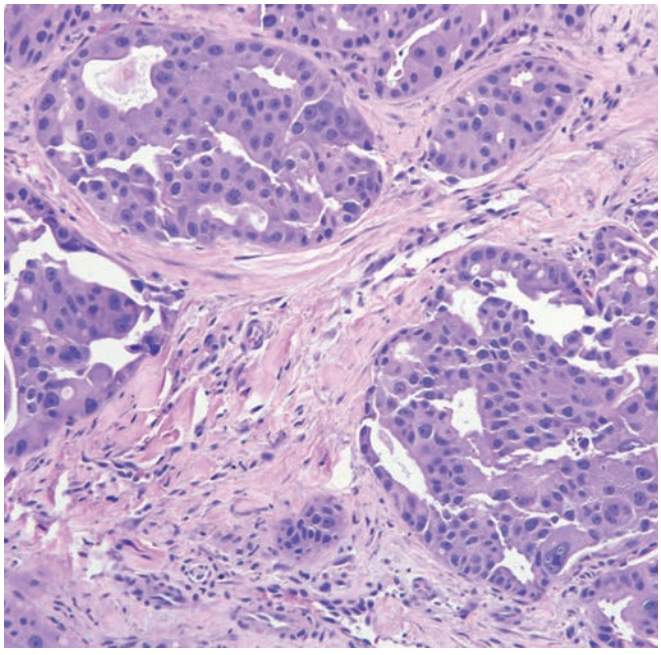
c Inhibin

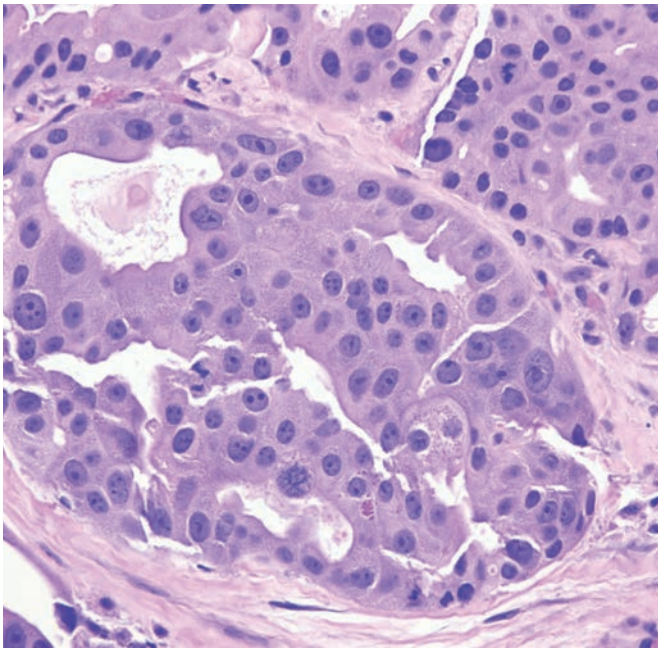
d Prolactin

Answer to last issue's Case of the Month…

C. Cytokeratin CK7

This microphotograph demonstrates the typical features of extra-mammary Paget disease. Tumor cells scattered in the epidermis have clear cytoplasm and are easily recognized even without special stains. Vulvar Paget tumor cells react typically with the antibody to CK7, which does not, however, react with the adjacent normal epithelial cells. In approximately 20 percent of extra-mammary Paget cases, tumor cells also react with the antibody to CK20.





To register your guess, please go to http://tp.txp.to/0718/case-of-the-month
We will reveal the answer in next month's issue!

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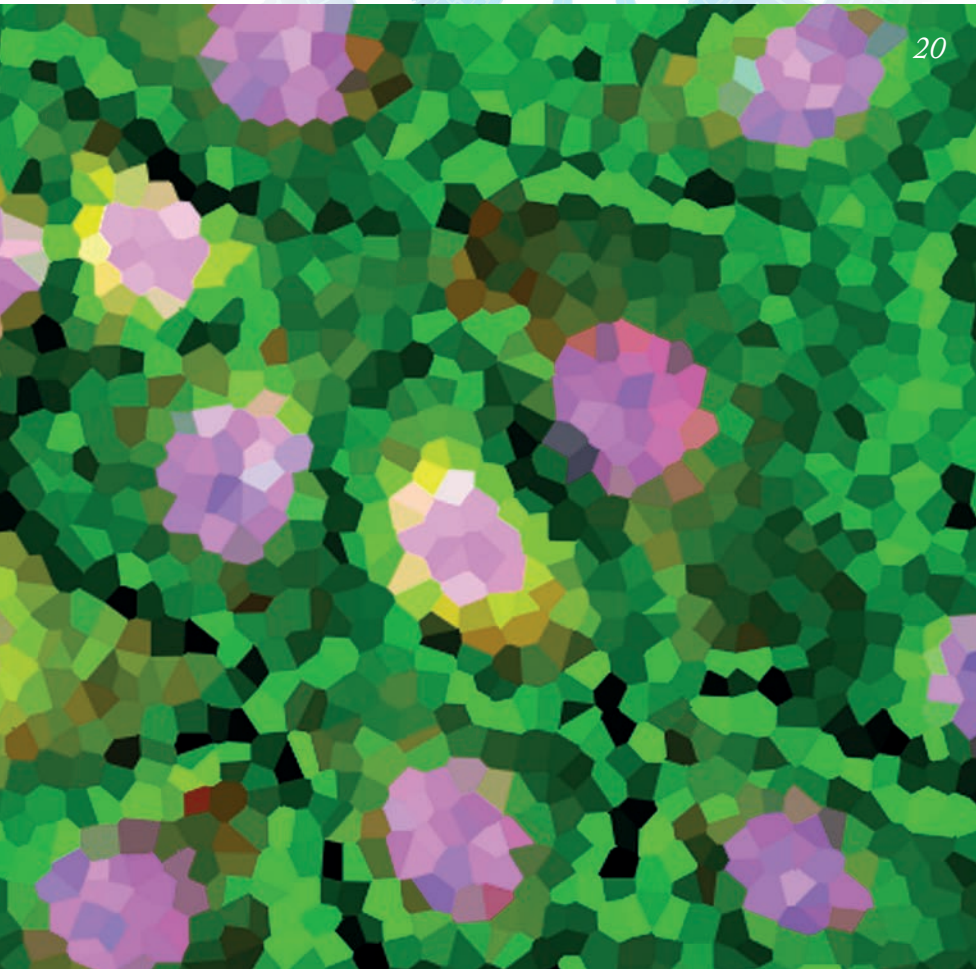
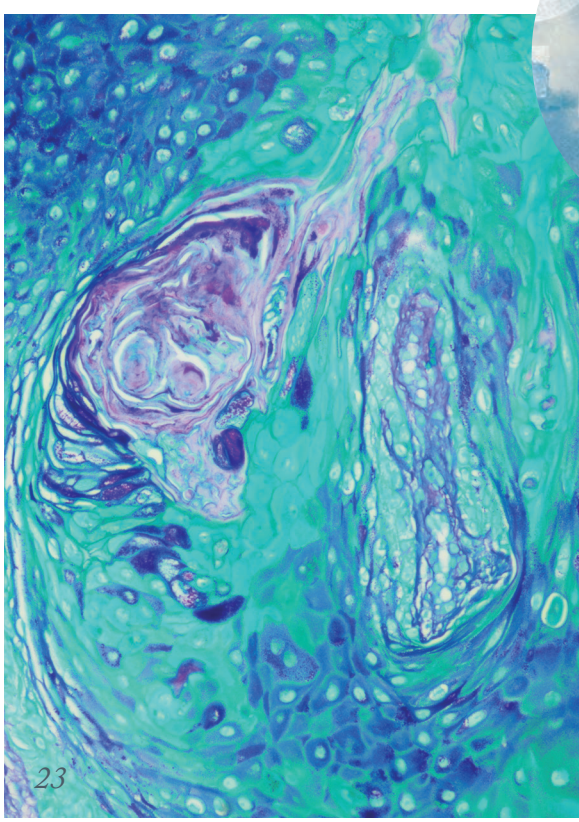


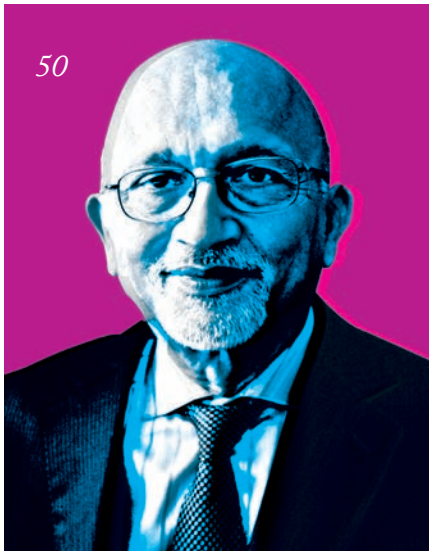


Upfront

In My View

On The Cover

"Head and torso" by Lisa Nilsson. A representation of a human midsagittal section made of mulberry paper.



Features

In Practice

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Sitting Down With

the Pathologist

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Power to the People

Bringing the pathology community together – first through a gallery feature, then through The Power List

Welcome to The Pathologist's third annual image gallery special feature!

Each year, I look forward to this issue, because I get to enjoy the full scope of our readers' visual creativity. And I do mean creativity – the images we receive range from educational slides to gorgeous artistry to hilarious #PathArt. Some are designed to showcase particularly good examples of conditions, or to highlight a rare disease some pathologists might otherwise never see. Some are created as jokes to share amongst others in the pathology community, either in person or via social media. And some are simply inspired by the beauty of a particular type of tissue, stain, or slide – an inspiration that may be explored in pencils, paint, or paper.

Whatever the source, all of these images have one thing in common – they inspired someone to create, capture, and share them publicly. One of the things I enjoy most about the gallery feature is seeing people's eagerness to share what they've made, and to suggest other images and other pathologists who might be interested in submitting. And I see that same community spirit in our other special feature: The Power List.

What's The Power List? If you aren't already familiar with it, it's our way of honoring those who work hard to advance and advocate for the field of pathology and laboratory medicine. Candidates are nominated by our readers and the final selection is made by an independent panel of expert judges – finally, the top 100 are profiled in a special issue of The Pathologist. Do you know someone you'd like to nominate? All candidates are welcome – just let us know their name, institution, and why you think they belong on The Pathologist's 2018 Power List!

Nominate here: *tp.txp.to/powerlist2018*

Michael Schubert
Editor

Upfront

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

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

Email: edit@thepathologist.com

The Flamingo Spreads Its Wings

A pragmatic new approach to light sheet microscope technology could change the game for facilities with fewer resources

For many biologists, there's a bittersweet irony to the cutting-edge heights of modern microscopy. "Accessing microcopy technology has always been an issue within the research area," explains Susi Power, a member of the Flamingo development team at the Morgridge Institute for Research. Not all who dream of an expensive built-in commercial microscope can afford it – and even those who can must make peace with the knowledge that the technology may rapidly become outdated. Yet the notoriously long waiting lists of institutional facilities mean that scope-less users with time-sensitive samples are often left with no way to look at them, and it's not always practical for delicate samples to travel to distant sites. Enter the Flamingo.

Developed by a team of medical engineering researchers, the Flamingo is a light sheet microscope that condenses massively complex technology into a 3D in vivo imaging device weighing just 40 pounds (1). Portable and compact, the microscope can be dispatched to any lab globally for up to three months – a service the team offers entirely free of charge to counter the accessibility problems so many investigators face. "The Flamingo is part of the novel 'involv3d' initiative, which aims to make collaborations and communication between remotely situated scientists easier," says Power. "Sharing a microscope is our contribution to this, and we think it will be a great start." And the cooperation works both ways: "The feedback on the microscope after the short-term rental period will be our profit, because it will tell us how we can improve our technology, so that users can gain the most from it."

This collaborative ethos is the foundation of the Flamingo project, named for the microscope's one-legged stand and slim profile. At the moment, there's just one prototype, which travels internationally to raise publicity for the project. The future is looking bright, though; the researchers hope to have a small flock by the end of the year. In the meantime, the project is on tour: "We will present the Flamingo at the SDB Conference in Portland, USA, at the end of July and in Dresden, Germany, for the Light Sheet Conference in mid-August. Additionally, we're working on final adjustments to the software and hardware so that the Flamingo is ready to fly."

Reference

1. *B Mattmiller, "Flamingo: High-powered microscopy coming to a scientist near you" (2018). Available at: https://bit.ly/2lUEHRX. Accessed July 4, 2018.*

Morgridge Institute postdoctoral fellow Rory Power inspects the completed Flamingo light sheet microscope, which can be mailed to biology labs around the globe. *Credit: Jan Huisken*

A Septic Shock

Are the lactate levels of sepsis patients measured according to recommendations?

Sepsis. A diagnosis that strikes fear into the heart of anyone who knows how severe it can be and how quickly it can worsen. And because sepsis is becoming more prevalent, new protocols have been issued for its management; for example, the Centers for Medicare and Medicaid Services' (CMS) Severe Sepsis and Septic Shock Early Management (SEP-1) bundle (1). One recommendation is serum lactic acid level measurement within three hours of severe sepsis presentation, and again within six hours if the initial measurement is elevated. Is this a practical goal – and, if so, why and how should it be implemented? To learn more, we spoke to Matthew Churpek and Xuan (Susan) Han – authors of a study revealing that many patients don't have these measurements taken (2).

What prompted you to look at the use of lactate measurements in sepsis management?

MC: When the CMS SEP-1 bundle was released, we felt that it was a perfect opportunity to better understand the role of standardized lactate measurements in sepsis, and to try to identify the potential benefits and harms of this practice.

Lactate has been studied for some time as a marker for disease severity, and it is traditionally thought that the main cause of elevated lactate is inadequate organ perfusion during states of severe illness and shock. However, recent evidence suggests that other factors, such as beta-2 adrenergic receptor stimulation, may play a significant role in lactate elevations in sepsis.

Recently, identifying patients with high lactate levels and targeting therapies to normalize lactate have become accepted practices, particularly in the management of sepsis – but the evidence for systematic and early lactate measurements in all patients with sepsis and septic shock is limited.

Are we doing enough to standardize sepsis care?

MC: There has been a concerted effort to improve and standardize sepsis care both in the US and internationally, as reflected by various organizations such as the Surviving Sepsis Campaign and recently revised sepsis management guidelines. Numerous studies are ongoing to identify better sepsis treatment strategies and therapeutic opportunities. Despite this, mortality rates continue to be very high.

SH: What I find personally interesting and challenging about sepsis is that not all septic patients are the same. Although clear, systematic standards for sepsis management establish a necessary foundation for care, we have a long way to go in terms of truly understanding this complex disease process so that we can provide more personalized care.

What impact should the lactate test have on sepsis mortality rates?

SH: Our study focused on patients who met the criteria for "severe sepsis" as defined by CMS. Based on the association between delayed lactate draws and increased mortality in our patient population, one could hypothesize that early lactate measurements on high-risk patients could lead to earlier interventions and improved patient outcomes.

Could lactate measurements have diagnostic implications for other diseases?

MC: We frequently see elevated lactates in other forms of shock beyond sepsis, such as hemorrhagic or cardiogenic shock. We also see them as a result of localized tissue ischemia, seizures, liver failure, and certain drugs – to mention just a few causes. In the absence of clear signs of sepsis, an elevated lactate level often forces a clinician to draw a broad diagnostic differential.

Some variability exists in the type of lactate measurements currently performed (for example, rapid point of care lactate measurements are becoming more frequently used in emergency departments), but lactate levels are already commonly measured in most clinical settings. As a result, this kind of testing would be easy and require few additional resources to implement.

What's next for your lab?

MC: We are interested in validating our findings in other hospitals, as well as further investigating which interventions in response to elevated lactate values are most likely to improve the outcomes of these high-risk patients.

References

1. *EJ Septimus et al., "Sepsis National Hospital Inpatient Quality Measure (SEP-1): multistakeholder work group recommendations for appropriate antibiotics for the treatment of sepsis", Clin Infect Dis, 65, 1565–1569 (2017). PMID: 29048513.*
2. *X Han et al., "Implications of Centers for Medicare & Medicaid Services Severe Sepsis and Septic Shock Early Management Bundle and initial lactate measurement on the management of sepsis", Chest, [Epub ahead of print] (2018). PMID: 29804795.*

Faster Fibrosis Diagnosis

A method for the rapid detection of serum biomarkers in liver disease

"Will Peveler wanted to visit my lab to learn about array-based sensing. In the meantime, he started working in William Rosenberg's lab, where he learned about unmet needs in terms of liver disease diagnostics, in particular the lack of point of care (POC) tools," says Vincent Rotello, Professor of Chemistry at the University of Massachusetts. The unmet need – and the high mortality rate associated with liver diseases – inspired a collaborative effort from the UK and US to develop a rapid diagnostic technique for fibrosis (1).

The new test involves obtaining a small amount of blood (approximately 40 μL) via a fingerstick, adding fluorescent-coated polymers, and then using the enhanced liver fibrosis immunosensing platform – a "chemical nose" – to sniff out serum biomarkers of fibrosis such as albumin, immunoglobulin, transferrin, fibrinogen, and alpha-1-antitrypsin. The simple process takes only 45 minutes and is relatively inexpensive – providing a new diagnostic for the developing world, according to Rotello. "Closer to home, the sensor should enable regular monitoring of liver health using minute quantities of blood," he says. "This straightforward testing would identify issues well before symptoms develop, allowing much more effective preventative and therapeutic strategies to be employed."

The technique checks the speed and pricing boxes, but how will it fit into existing workflows? Rotello says it isn't far from being pathologist-ready; the researchers are currently streamlining the platform for clinical and POC use, as well as working toward further validating and implementing their technique in various settings. It's not a one-man job, though, and Rotello emphasizes the effort required of everyone on the team: "This project provides an example where a hammer-builder, such as myself, can find an important nail through collaboration."

Reference

1. *WJ Peveler et al., "A rapid and robust diagnostic for liver fibrosis using a multichannel polymer sensor array", Adv Mater, [Epub ahead of print] (2018). PMID: 29797373.*

Building a Dinosaur (Genome)

Reconstructing the chromatin organization of a common ancestor yields insight into dinosaur (and other) genomes

Most pathologists – and indeed, many members of the general public – are familiar with the human genome. Those involved in research may know their way around numerous other genomes, too: the rat, yeast, the humble nematode. But how many of us can say we know what a dinosaur genome looks like? Until recently, the answer has been: no one. Now, though, a research group at the University of Kent has brought us one step closer to Jurassic Park by using common pathology and translational research tools to reconstruct the potential genome organization of theropod dinosaurs, such as raptors and tyrannosaurs (1).

How did they manage it? First, they used bioinformatics and molecular cytogenetics to extrapolate the most likely genomic structure of the most recent common ancestor of all diapsids (animals with two temporal fenestra, such as lizards, turtles, or birds). Next, they inferred the most likely genomic events throughout the organisms' lineage – from that ancestor to the dinosaurs and then to modern birds. Interestingly, the researchers noted that, although there was plenty of intrachromosomal rearrangement, very little interchromosomal exchange occurred throughout the evolution, meaning that the genome was simultaneously stable and open to a high level of phenotypic diversity.

Does this new knowledge mean we're ready to begin building our own dinosaurs? Not quite yet – but it does contribute significantly to our understanding of how both they and modern organisms evolved, and how they were able to survive and thrive for so long.

Reference

1. *RE O'Connor et al., "Reconstruction of the diapsid ancestral genome permits chromosome evolution tracing in avian and non-avian dinosaurs", Nat Commun, 9, 1883 (2018). PMID: 29784931.*

Real-Time Tumor Analysis

Look out! Here comes the SpiderMass

How can we make cancer surgery more efficient? At the moment, there's approximately a half-hour waiting time built into the procedure so that pathologists can inspect the excised tissue to make sure all the cancerous matter has been removed. Now, a research group from France is adding to a growing list of mass spectrometry-driven tools that aim to speed up the process.

"We started by developing a technology to enable in vivo mass spectrometry analysis to target applications for medicine," says Isabelle Fournier, Professor of PRISM Laboratory at Université de Lille. "In our first prototype, we demonstrated that we could perform in vivo analysis with mass spectrometry without being invasive – using the system, SpiderMass, to analyze our skin (1). The technology we developed is based on using the endogenous water of biological tissues as a MALDI matrix." They dubbed the process Water Assisted Laser Desorption Ionization – or WALDI. Initially, the system was used to detect lipids and metabolites – but, in a recent study (2), the researchers expanded their remit, using SpiderMass to detect and analyze peptides and proteins from cancer biopsies in real time.

Fournier says, "The advantages of the technology are to enable easy analysis of various raw samples without any preparation. The samples can be easily screened dynamically by moving the [SpiderMass] handpiece above the surface of the sample." But biopsy tissue isn't the end of the line for SpiderMass. Fournier and her colleagues also hope to analyze peptides and proteins noninvasively in vivo soon.

The team believes that such real-time technologies are a big clinical step for diagnostics and prognostics. With use by pathologists at the bench, in the lab, or directly in a surgical theatre, the process is relatively flexible. Plus, there's room for improved accuracy and further adaptability. Fournier explains, "For diagnostics, the system will rely on the creation of databases of molecular profiles that will be used to build up classification models that can be interrogated in real-time."

An added bonus to the technique is the speed at which the team expects it to be clinically ready – less than a year. "We recently moved a prototype to the vet surgery room for testing," says Fournier. "We plan to finish our POC in the next few weeks – although we are currently testing the [in vivo] surgical applicability of the system using lipids and metabolite profiles, but not proteins yet."

References

1. *B Fatou et al., "In vivo real-time mass spectrometry for guided surgery application", Sci Rep, 6 (2016). PMID: 27189490.*
2. *B Fatou et al., "Remote atmospheric pressure infrared matrix-assisted laser desorption–ionization mass spectrometry of proteins", Mol Cell Proteomics, [Epub ahead of print] (2018). PMID: 29653959.*

In My View

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

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

Contact the editors at edit@thepathologist.com

My Path to Path

The value of the pathology post-sophomore fellowship

By Albert Sy, MS-III, The University of Arizona College of Medicine–Tucson, Arizona, USA

When I started medical school three years ago, most of my understanding of a pathologist's (any pathologist's) job stemmed from watching CSI: Miami. In other words, I had no idea what a pathologist really was. Yet as I continued my medical journey, I became increasingly attracted to the specialty. I am not sure if it was the vibrantly colored histology, the complex pathology, or the humorous references to food when describing gross pathologic specimens – but, whatever the cause, I became so curious about the field that I decided to apply for the Pathology Post-Sophomore Fellowship (PSF) position at The University of Arizona. During this fellowship, I spent a whole year in the role of a pathology resident. I previewed my own cases, dictated final diagnoses, participated in frozen sections, presented at tumor boards, and even lived out the CSI fantasy by completing autopsy cases. What did I learn from the fellowship? That pathologists are paramount to excellent patient care. Through pinpoint diagnoses and efficient laboratory and molecular testing, I witnessed firsthand how pathologists influence treatment plans and how vital pathology is to optimizing patient outcomes.

My experiences during the post-sophomore fellowship remind me of a trip I took to Spain. Before I began medical school, I visited the Sagrada Familia in Barcelona. Unfortunately, due to the untimely death of its architect, Antoni Gaudi, this great construction remains unfinished. As I scanned the building, I stood speechless and in awe.

> *"What did I learn from the fellowship? That pathologists are paramount to excellent patient care."*

The combination of stone, granite, wood, and concrete working in symphony with one another was strikingly beautiful. I continued to scan and noticed an area that was not finished. Simple steel beams stood firm in a scaffolding pattern. No gorgeous granite, no shiny stained glass, and no complex architecture to marvel at – just simple steel beams. However, what I failed to realize at that time (but genuinely appreciate now) is that those beams are what allow all the different materials to come together in perfect harmony. To me, those steel beams in the Sagrada Familia embody the role of pathologists in medicine. I believe

that pathologists are the hidden heroes of healthcare. These specialists work relentlessly behind the scenes and get neither the glory of clinicians nor the gratitude of patients – but, without pathologists, treatments would all be a guessing game. Those steel beams are symbolic because pathologists are the foundation that permits the rest of the hospital to synchronize and provide accurate, effective treatment plans.

Thanks to my post-sophomore fellowship, I gathered an amazing amount of information. I learned how to diagnose tubular adenomas, melanomas, and astrocytomas. I learned how to complete autopsies, interpret flow cytometry data, and perform bone marrow biopsies. I even learned how to properly use a microscope! Yet despite all these things that I have learned, the greatest lesson I took from the experience is that empathy and compassion can be found behind a microscope. This is the lesson that has convinced me to choose a career in pathology. Despite too often being far from the limelight, pathologists have a profound understanding of the ways their work directly impacts their patients. They understand the consequences of a diagnosis for their patients and they embrace the intense reality that millimeters make all the difference between treatable and untreatable – life and death. What amazes me the most is that pathologists see their patients through the microscope. Without ever even seeing their patients' faces, pathologists are still able to work with a patient-centered mindset. This mindset is what drives them to continually hone their craft – and it's what has inspired me on my path to path.

They Shoot Horses, Don't They?

Age-based stereotypes exist, even in scientific communities. But is age related to research productivity – and, if so, to what extent?

By Victoria F. Samanidou, Laboratory of Analytical Chemistry, Department of Chemistry, Aristotle University of Thessaloniki, Greece

The relationship between age and productivity is not a simple one to quantify. Older workers are assumed to be less effective and industrious than their younger colleagues when it comes to more physical tasks (1,2). But what about science in particular?

In scientific communities, opinions on the net effect of age on productivity are varied. Several factors influence the productivity rate of researchers or academics; experience, health status, position, rank, and many more. It also begs the questions: what exactly is "productivity" and how do we measure it? In academic communities, it is often measured by the number of publications, along with the number of self-excluded citations and the h-index; the former relating to quantity and the latter to the quality and impact of the work. Do older scientists publish less or more? It is difficult to make an estimation – the determinants of individual productivity are extremely complex and I doubt whether typical metrics are in any way useful. However, I can say that authorship is not always directly related to actual productivity.

Perhaps rather than trying to guess the productivity of individuals, it is more useful to reflect on the "typical" path of a scientist's career. In short, it can take a long time to get to the top. On the path to recognition, I have witnessed three typical turning points in the career of academics; the first occurs at around the age of 35-40 years, where researchers are expected to step up their productivity to reach a higher position. A second inflection point comes at the age of 50-55, when the rate of productivity can reach a plateau or decrease slightly (3).

"Perhaps rather than trying to guess the productivity of individuals, it is more useful to reflect on the 'typical' path of a scientist's career."

The third turning point, I believe, comes when researchers are approaching retirement age. As researchers move up the stratified hierarchy of science, recognition reaches a peak, leading to

"All scientific research relies on collaboration – and so researchers of all ages need to play a significant role in its dynamic."

collaboration with more productive groups, greater success in gaining access to funding and more likely publication in scientific journals with a higher impact – all boosting perceived productivity. However, there is another trend in this age bracket; older professors publish far fewer first-authored papers and instead move to the end of the list of co-authors, as they are more likely to be the leaders of their own groups.

No one can deny that with time, physical power decreases. In addition, technological developments and innovations are not always easily integrated by older scientists. On the other hand, a significant number of older scientists stay active in research, keep their productivity at a high level until their retirement and continue to inspire the young, still playing an effective role in the production of high impact papers. Indeed, if one is able to inspire 10 or more team members to be more efficient (while striving for high quality), the overall effect is an increase in productivity for the group, perhaps far outweighing the potential of a single individual.

So are older scientists more productive than their younger peers? I would argue that the most important aspect, whatever the age of the scientist, is the degree of satisfaction that they gain from collaboration with others – and, even more important, their passion for furthering research. And I don't believe either of those aspects have anything to do with how old you are. There are more than a few examples of scientists – young and old – who have simply lost interest; they require a change in attitude or should consider an alternative profession...

All scientific research relies on collaboration – and so researchers of all ages need to play a significant role in its dynamic. With understanding on both sides, it's a multi-way process; when we are surrounded by young people – eager students in academia or dynamic young scientists in research institutes or industry – it can be easier for us to maintain a "youthful" outlook; in turn, younger colleagues can benefit from the great experience, knowledge and tenacity of their superiors. To my mind, when it comes to age, it's less of a generation "gap" and more of a spectrum.

References

1. *Times Higher Education, "Are older academics past their productive peak?" (2016). Available at: http://bit.ly/1QZK9bt. Accessed July 7, 2017.*
2. *Taylor and Francis Online, "Explaining the increase in publication productivity among academic staff: a generational perspective", Available at: http://bit.ly/2tQ0EYv. Accessed July 7, 2017.*
3. *Y Gingras et al., "The Effects of Aging on Researchers' Publication and Citation Patterns", PLoS ONE, 3, [online only], (2008).*

Resigned to Resistance?

Technology-based solutions can speed microbiology diagnosis and improve outcomes – as well as tackling the ever-present AMR threat

By Steve Conly, Vice President and General Manager of Microbiology at Becton, Dickinson and Company, Franklin Lakes, USA

As every pathologist knows, the path from patient presentation to recovery should be a simple one: first, diagnosis; next, treatment; and, ultimately – hopefully – a resolution. But it's not always that easy, even when the first step is relatively straightforward. In

"Accurate and timely diagnosis drives the patient's treatment in a much more effective and efficient manner. But it's not always easy."

some situations, there simply isn't time to conclusively identify the patient's illness before treatment. That may mean that patients are given broad-spectrum (or even incorrect) treatments, which can slow down the recovery process or contribute to the growing threat of antimicrobial resistance (AMR). But if patients can't wait for therapy, how can we avoid such situations? By reducing the turnaround time from sample collection to final result – and here, technology-driven workflows, especially those incorporating automation and integrated informatics, can help.

Accurate and timely diagnosis drives the patient's treatment in a much more effective and efficient manner. But it's not always easy. Perhaps the best example is provided by the case of sepsis, where patients may display severe symptoms very quickly, so there may not be sufficient time to identify the exact causative pathogen and its potential resistance mechanisms. Therefore, clinicians administer broad-spectrum antibiotics as soon as possible, followed by a more targeted drug once diagnostic results are in.

By reducing turnaround time – while maintaining the high level of diagnostic accuracy we need to drive therapy decisions – we can start to move away from guess work in antibiotic use, which would not only be more responsible from an AMR point of view, but would also allow us to tailor treatments to a specific pathogen and any resistance genes it possesses.

What causes diagnostic delays? Well, a number of factors combine – including logistical challenges, and assay setup and execution – but it's the pre- and post-analytical phases that are in most need of optimization. Here, I believe that better process mapping and definition, combined with new and improved informatics can make a real difference. For example, the delay between obtaining a result and transmitting it to the appropriate clinician is a significant obstacle that can be surmounted with integrated informatics.

Most microbiology labs are in acute care hospitals or reference laboratories, which means that many of them operate 24/7 – infectious disease patients can't necessarily wait for a nine-to-five lab to open. But what good is a rapid result if it doesn't reach the clinician quickly enough to make a difference? It seems clear to me that informatics – such as automated result reporting or sentinel reports – will play a big role in speeding up that process and minimizing treatment delays.

"Automation and technology-based solutions can truly streamline the pathway from sample received to results."

Automation and technology-based solutions can truly streamline the pathway from sample received to results. To explore those options, though, laboratories need to commit to investing resources. The biggest challenge I see? The change management so often required to implement these end-to-end processes. As you implement innovations, technology is just one component of the total solution – you need to select an industry partner who not only has the best product for your needs, but also the right clinical expertise, the right training programs, the right change management programs… In short, all the support you need to integrate new technology into your laboratory workflow. And then, once the technology is installed, a good partner will continue working with you on continuous improvement. Transitioning to a new, more automated or technology-based workflow isn't just a single event; it's an ongoing process that involves a commitment on both sides.

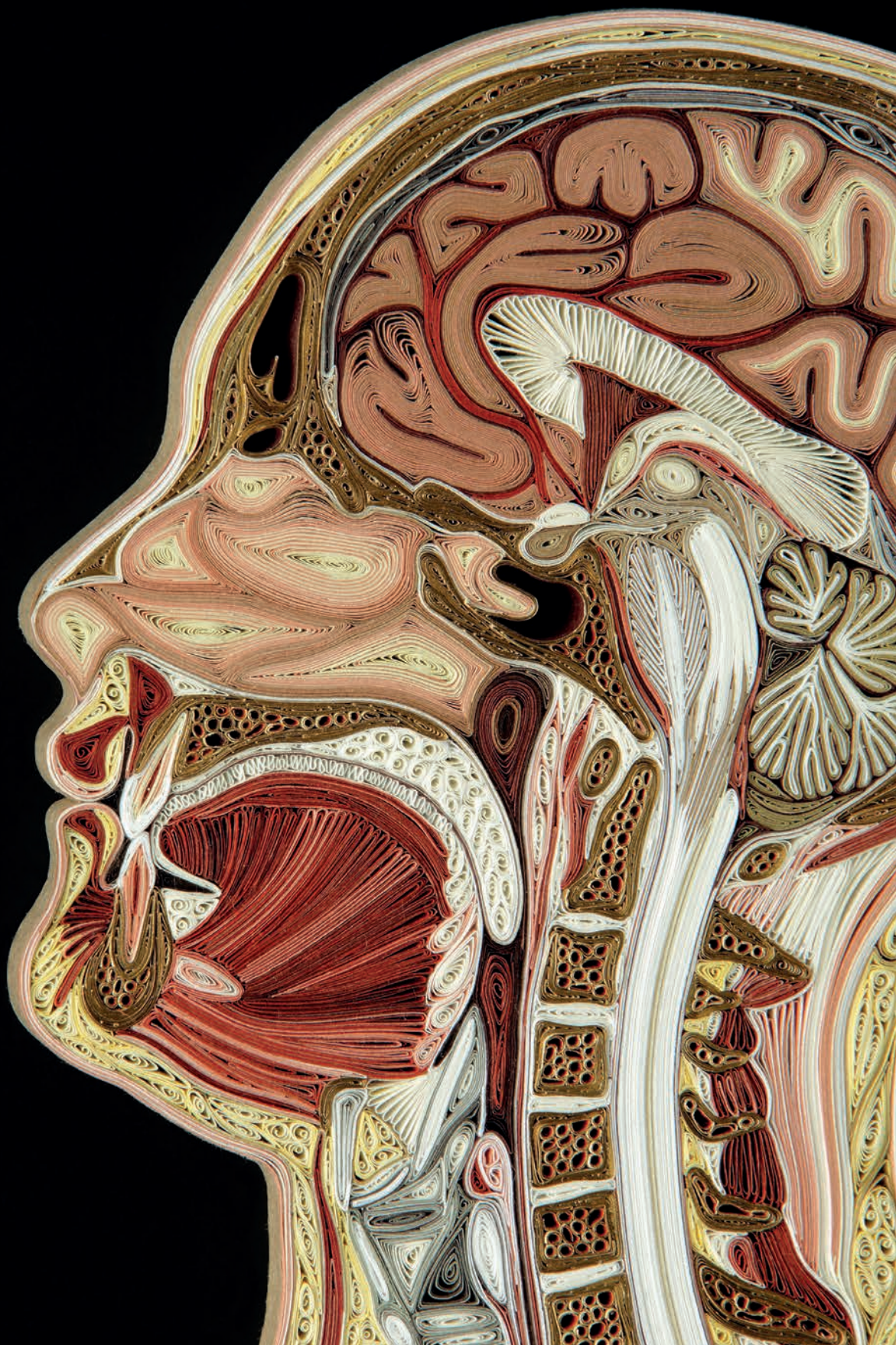
My colleagues and I have worked in partnership with laboratories around the world, transforming microbiology from a labor-intensive, error-prone manual process to an integrated, automated one. In doing so, we've been able to shorten the time to result by more than 24 hours in many cases – which, as noted earlier, drives faster and more targeted treatment, reduces length of stay, improves antimicrobial stewardship (through the optimized use of antibiotics), and lowers overall costs.

In my opinion, it is absolutely crucial that healthcare systems recognize the value of diagnostics; after all, they are the most effective tool to both reduce the cost of healthcare and improve patient outcomes. We must also recognize that these goals can be accomplished through the evolution of – and investment in – innovative technologies in microbiology, molecular automation, and informatics.

Gains can be made not only in the analytical phase of testing, but also in the pre- and post-analytical phases, where we can ensure that the correct test is applied to the correct sample and then returned to the correct physician as quickly as possible.

PORTRAITS OF PATHOLOGY

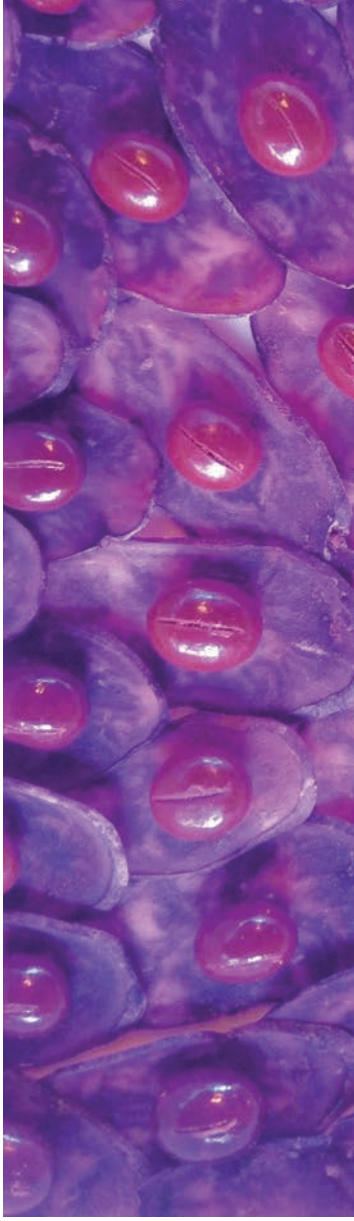
In a discipline as visually oriented as pathology, all practitioners are artists. For the third year running, you – our readers – prove that bold statement to be true with images that reflect unique insights into the delicate, beautiful structure and function of the human body.

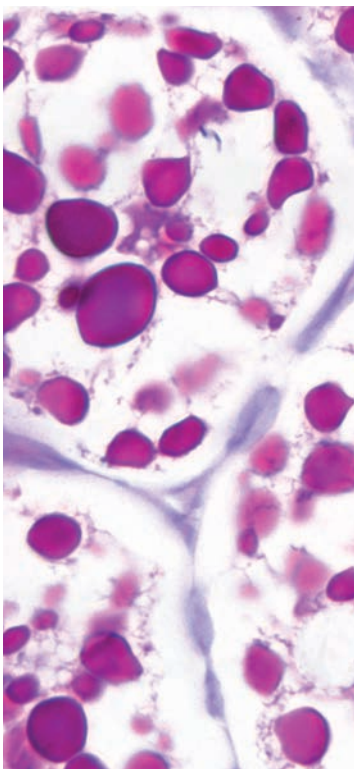


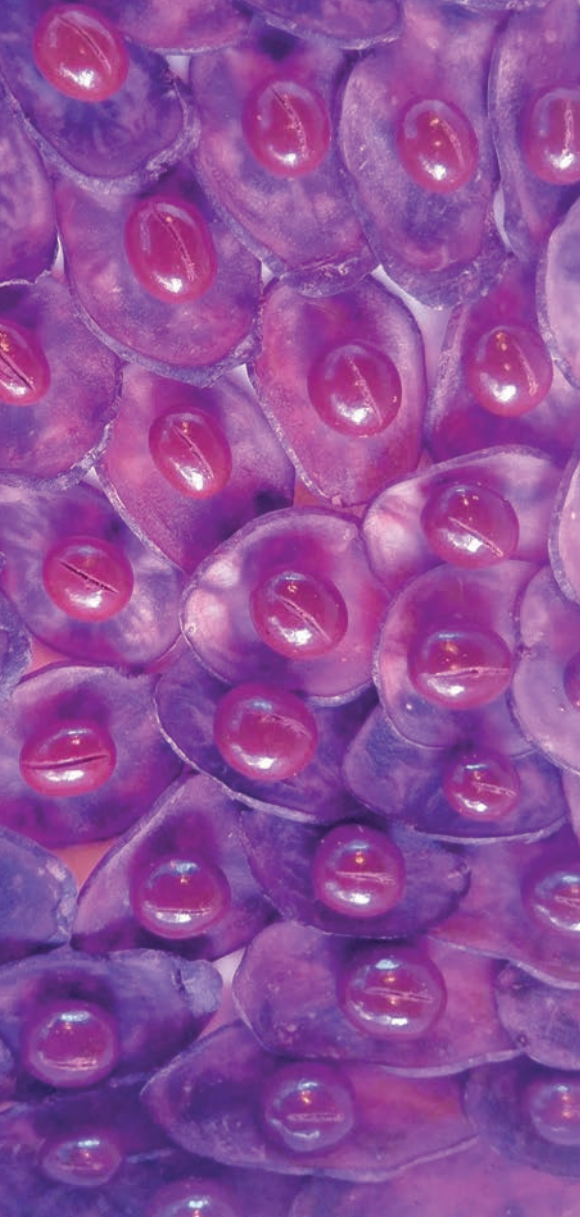
AI MEETS GEORGIOS PAPANICOLAOU

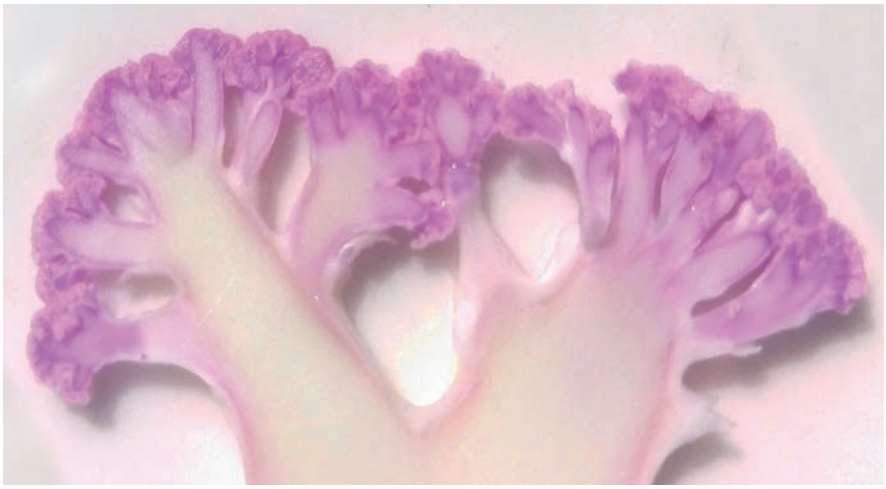
This watercolor was painted from a picture the artist made using an AI algorithm to combine a photo of a gynecological slide (superficial squamous cells) with a portrait of Georgios Papanicolaou.

Ali Al-Nasser, Dasman Diabetes Institute, Kuwait







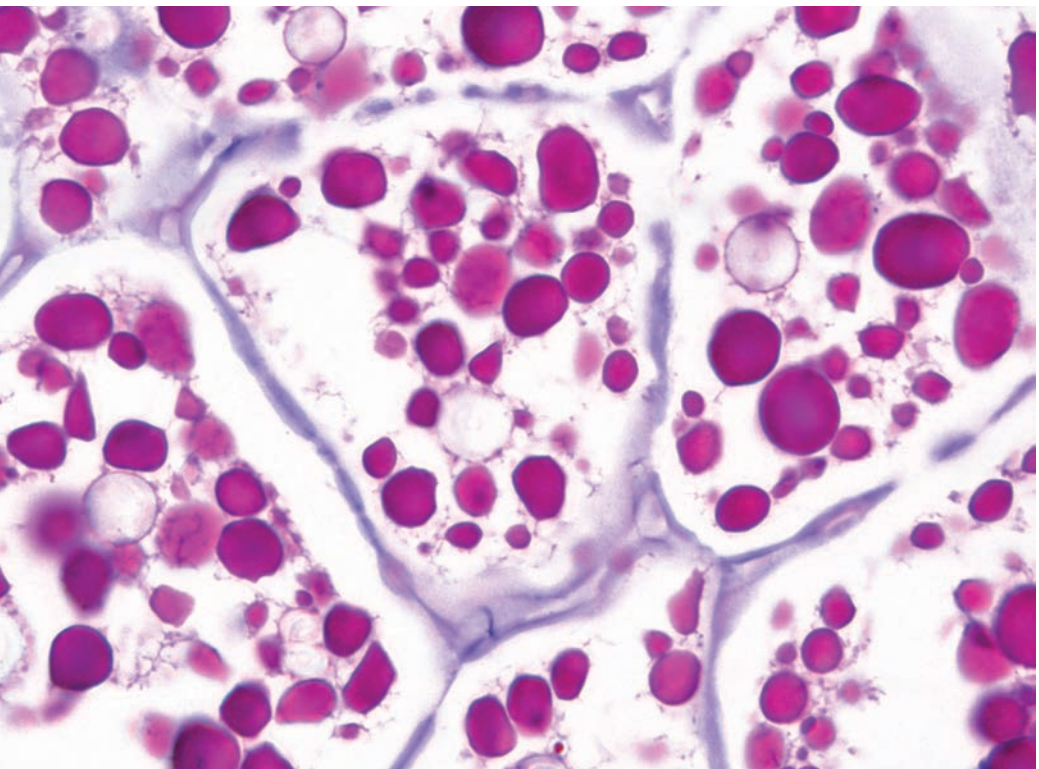


DON'T LICK THE SCIENCE: PATHOLOGY EDITION

At The Ohio State College of Medicine, Dr. Charles L. Hitchcock gave many pathology lectures using a time-honored pathology education tool: food analogies. Like many pathologists, he compared small cell carcinoma to oats and the nuclei of Brenner tumors to coffee beans, making it easier for students to identify micrographs during exams. He also used analogies that he may have invented himself, such as comparing Reinke crystals to Twizzlers and ovarian cysts to chocolate cream puffs. These culinary photographs are my tribute to Dr. Hitchcock, who taught so many classes so much.

Left: Brenner tumor (chocolate-covered espresso beans; thinly sectioned purple potato).
Top: adenomatous polyps (thinly sectioned purple cauliflower).

Cynthia Schwartz, The Ohio State University, USA



TOMORROW

PAS/d stain of vegetable material.

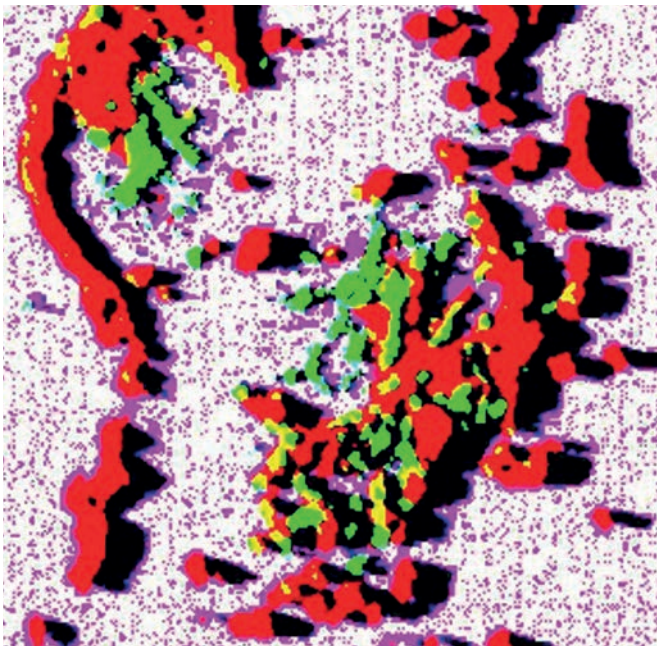
Christina A. Arnold, The Ohio State University, USA

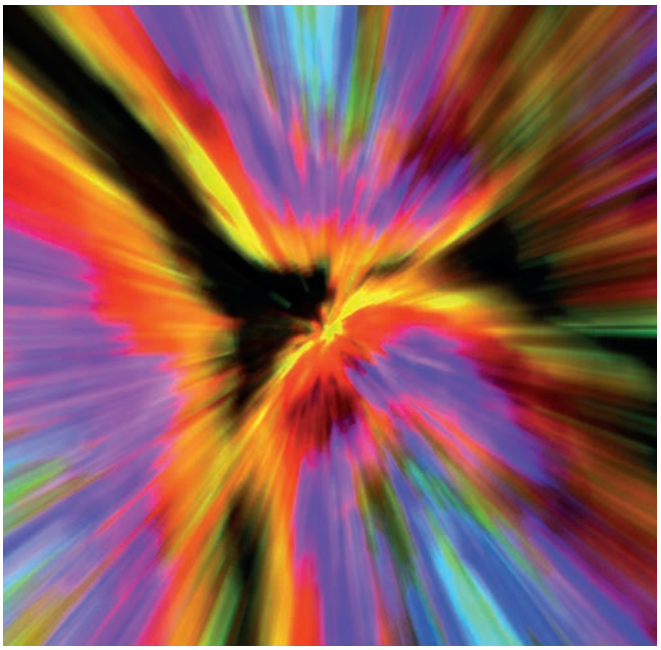
THE ART OF FLUORESCENCE DECONVOLUTION IMAGING: REDUX

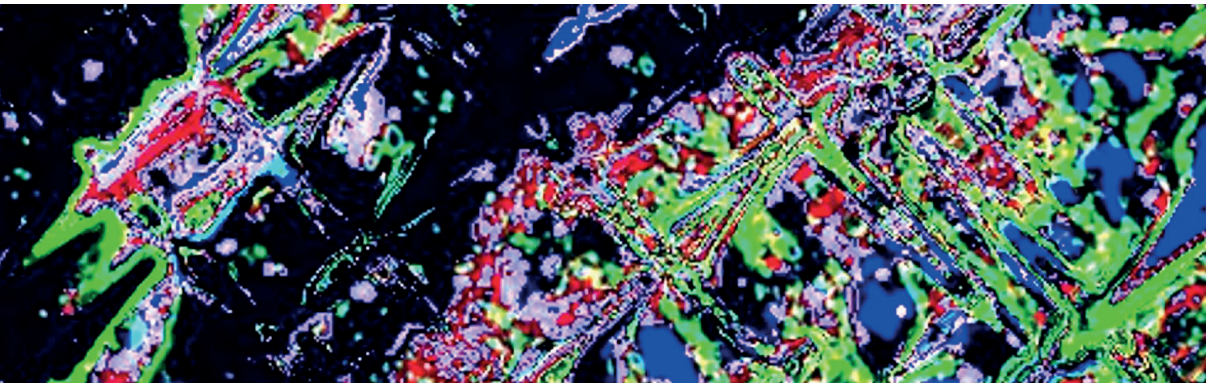
A series of artistic images created using fluorescence deconvolution microscopy.

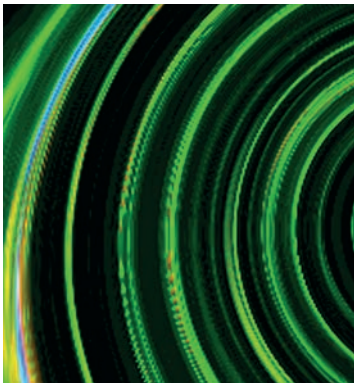
Clockwise from top left: transfected cancer cell; stained glass keratinocytes; twirling lung; epidermis map; kaleidoscope gut.

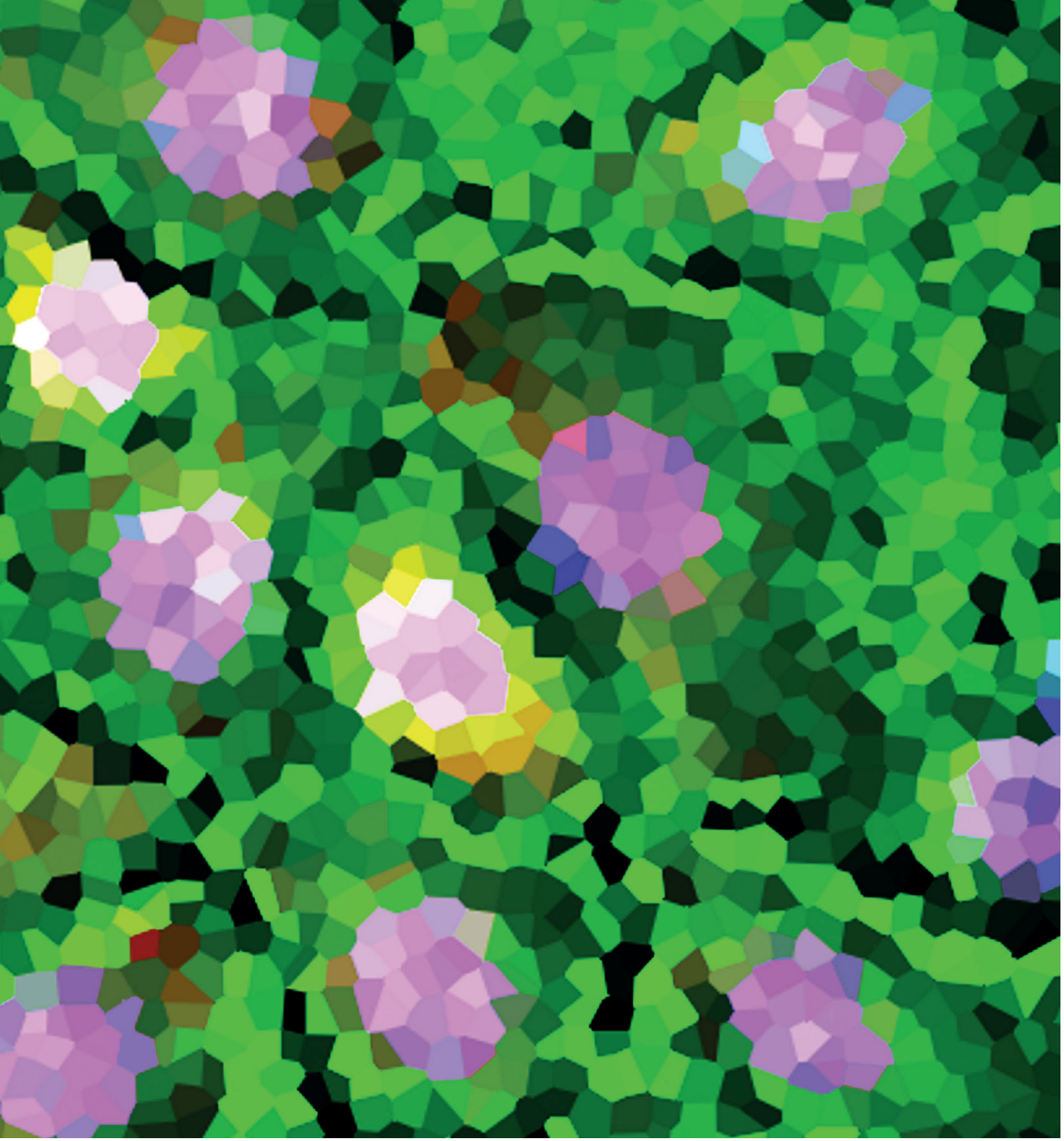
Brian J. Poindexter and Roger J. Bick, Multi-User Fluorescence Imaging and Microscopy Core Lab, UT McGovern Medical School, USA

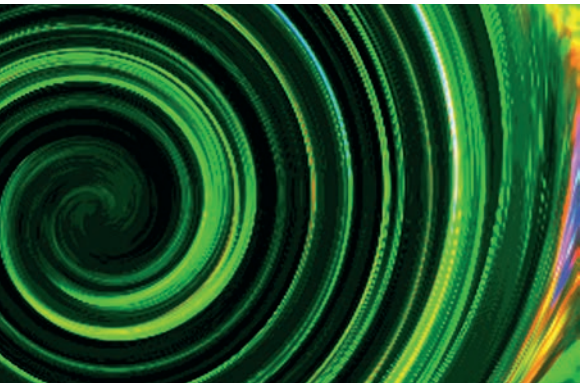


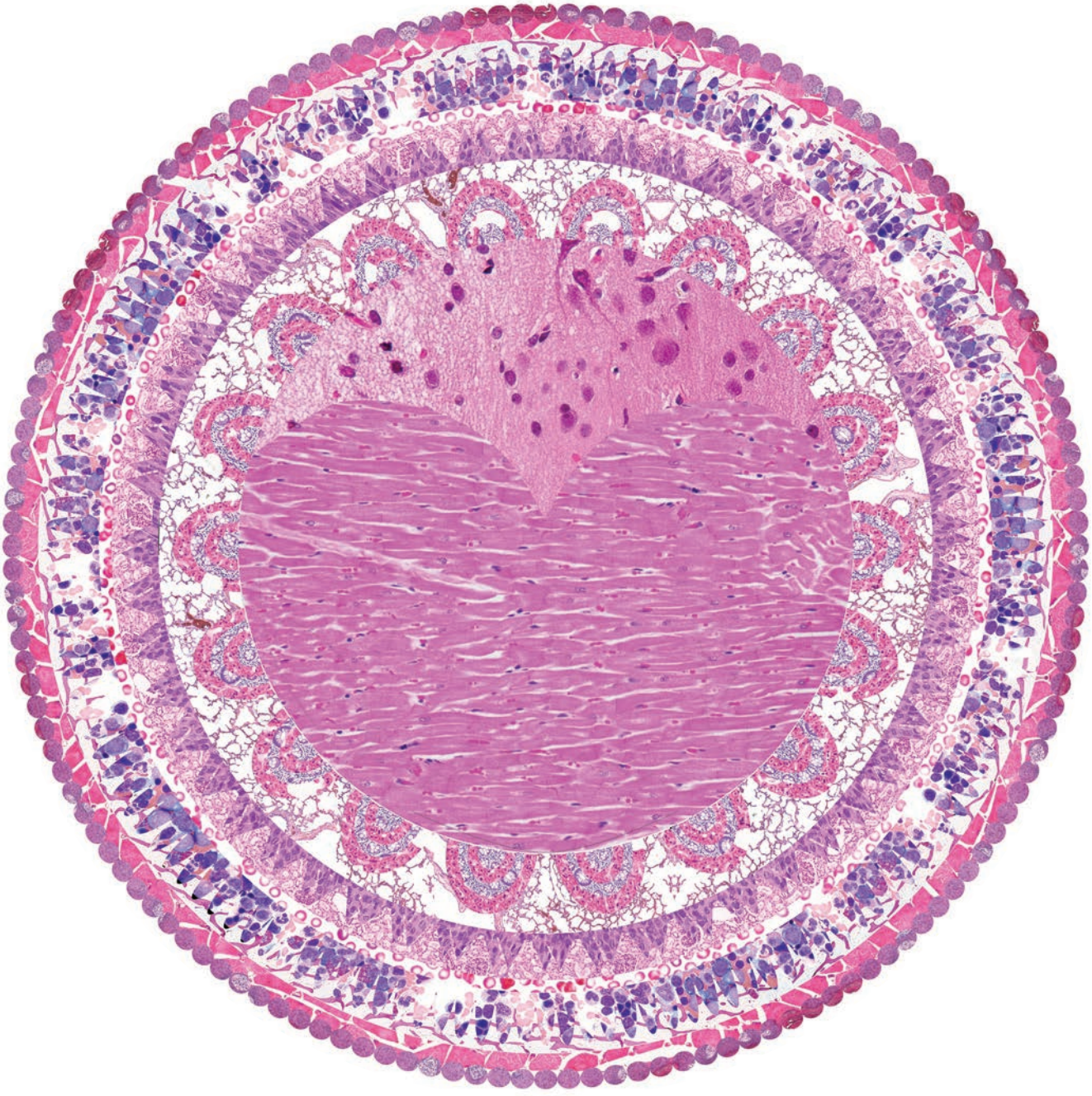








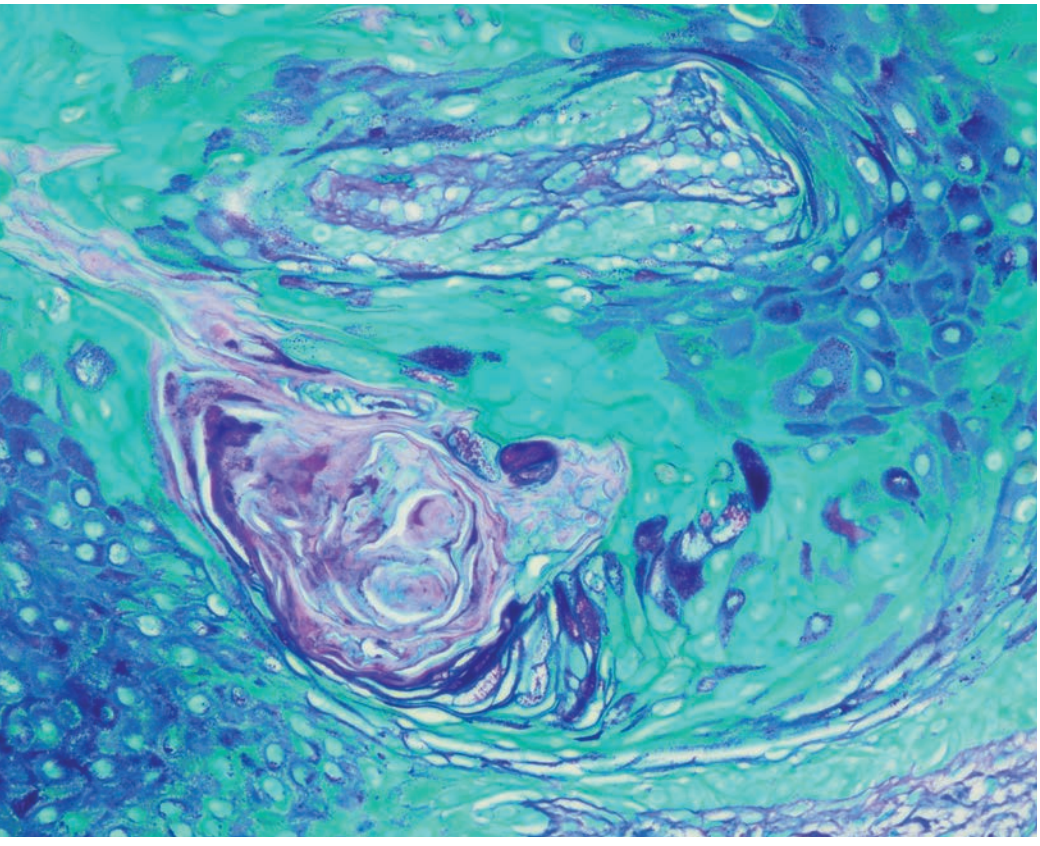


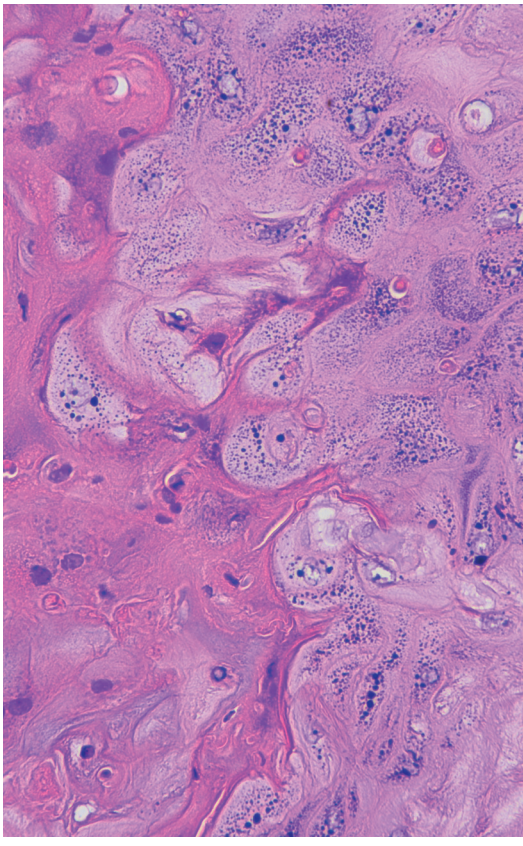


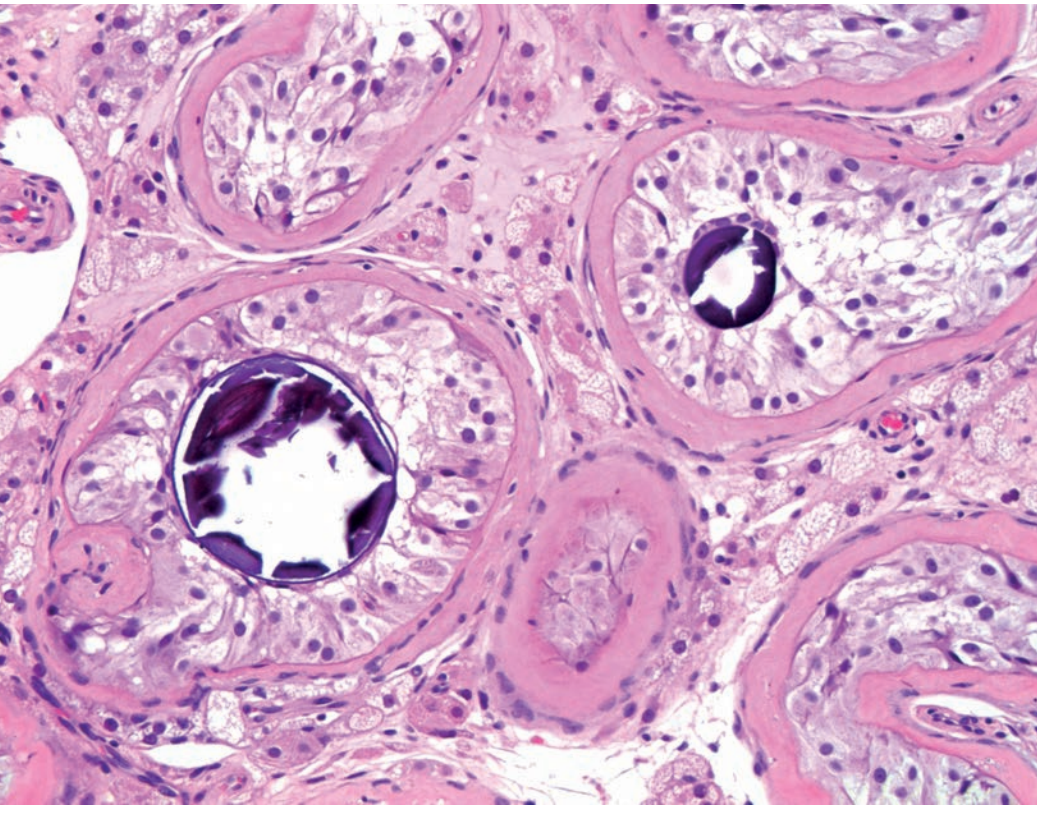
POLYPATHIA

From outside in: skin, muscle, bone, marrow, blood, kidney, bladder, lung, liver, colon, brain (top center), and heart (bottom center).

Aadil Ahmed, Loyola University Chicago, USA







WAVE KISS

Top left: 40X PAS stain of skin performed for a foreign body reaction.

ANGRY OCEAN

Above: 40X hematoxylin and eosin stain of a squamous cell carcinoma.

Mary E. Landau, MPathy Art, USA

STARS

Microliths in a cryptorchid testis.

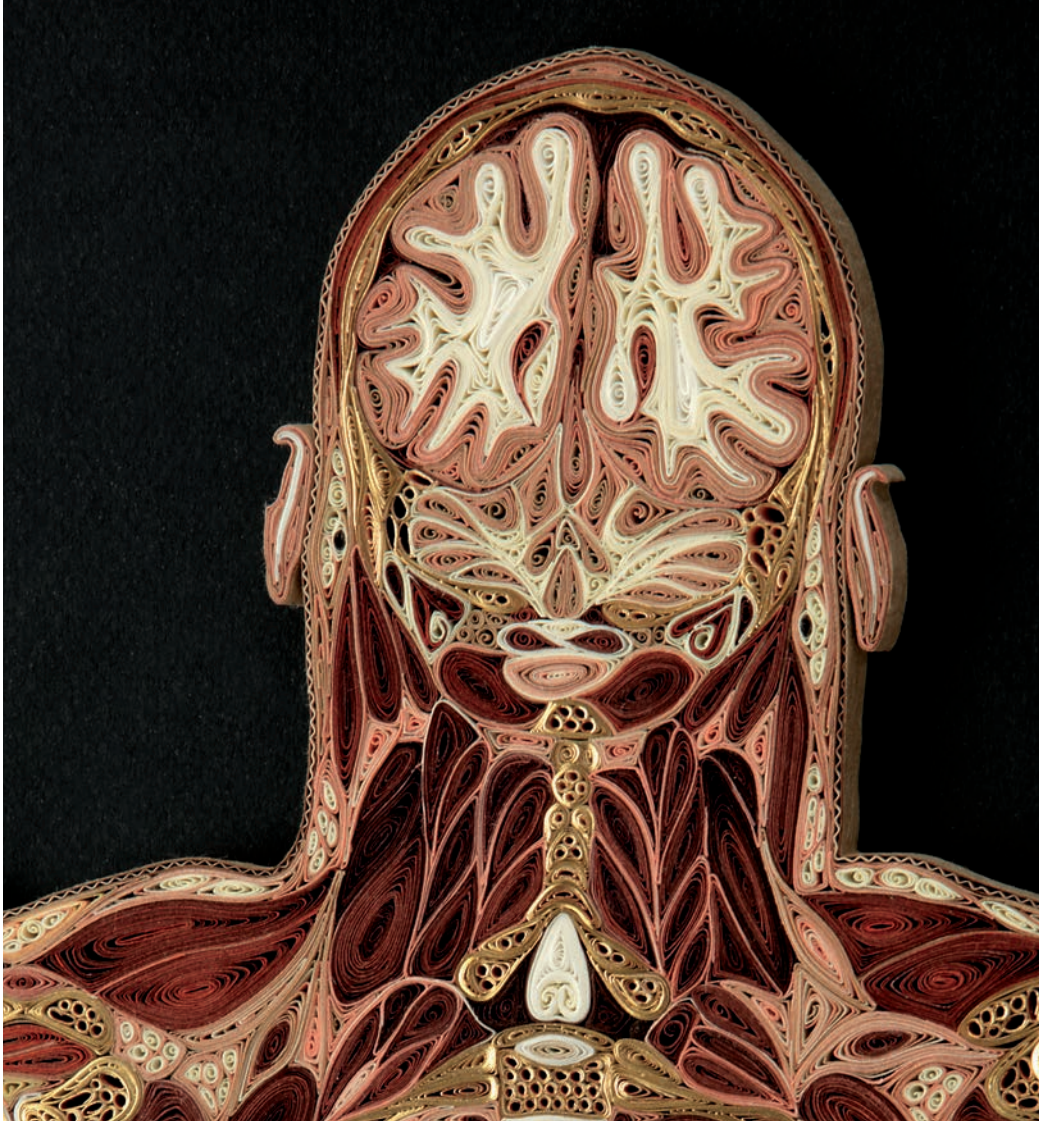
Debra Zynger, The Ohio State University, USA

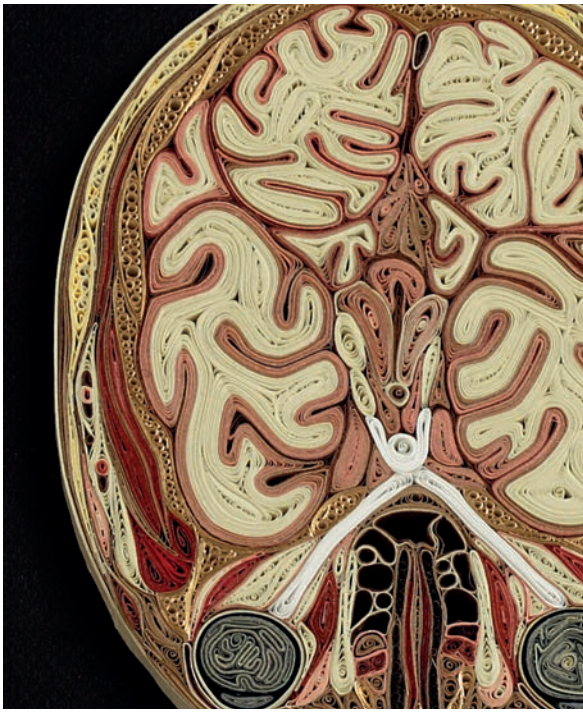
ANATOMICAL CROSS-SECTIONS IN PAPER

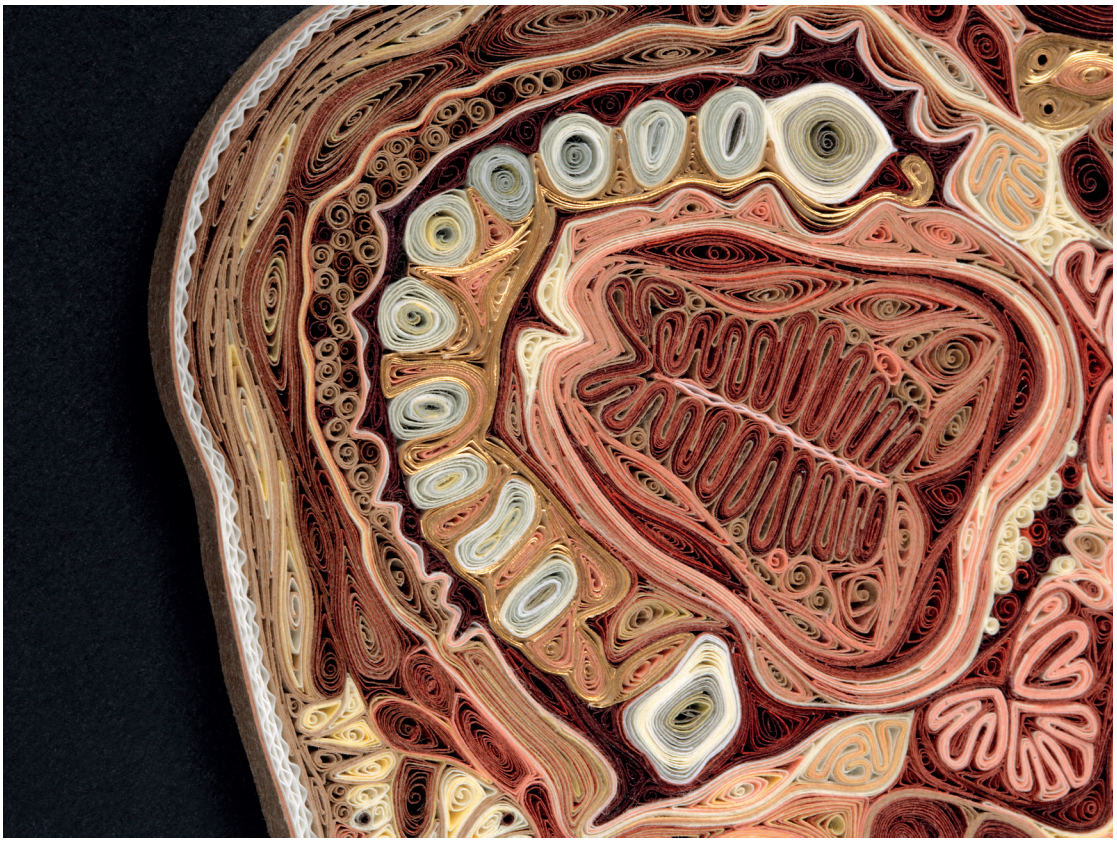
These pieces are made of Japanese mulberry paper and the gilded edges of old books using a technique called quilling or paper filigree. The artist says, "I find quilling exquisitely satisfying for rendering the densely squished and lovely internal landscape of the human body in cross section."

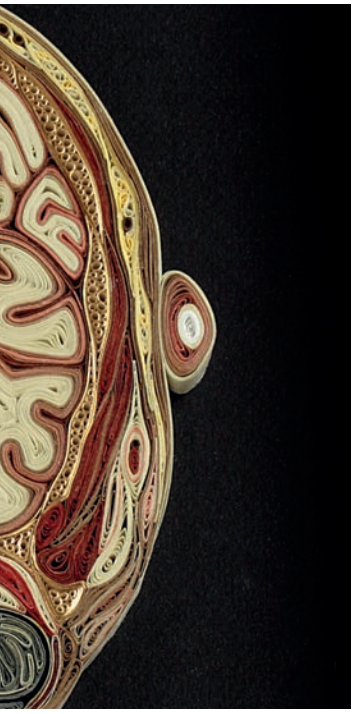
Clockwise from top left: Coronal Man; Transverse Head with Tongue; Female Torso; Head II; Angelico.

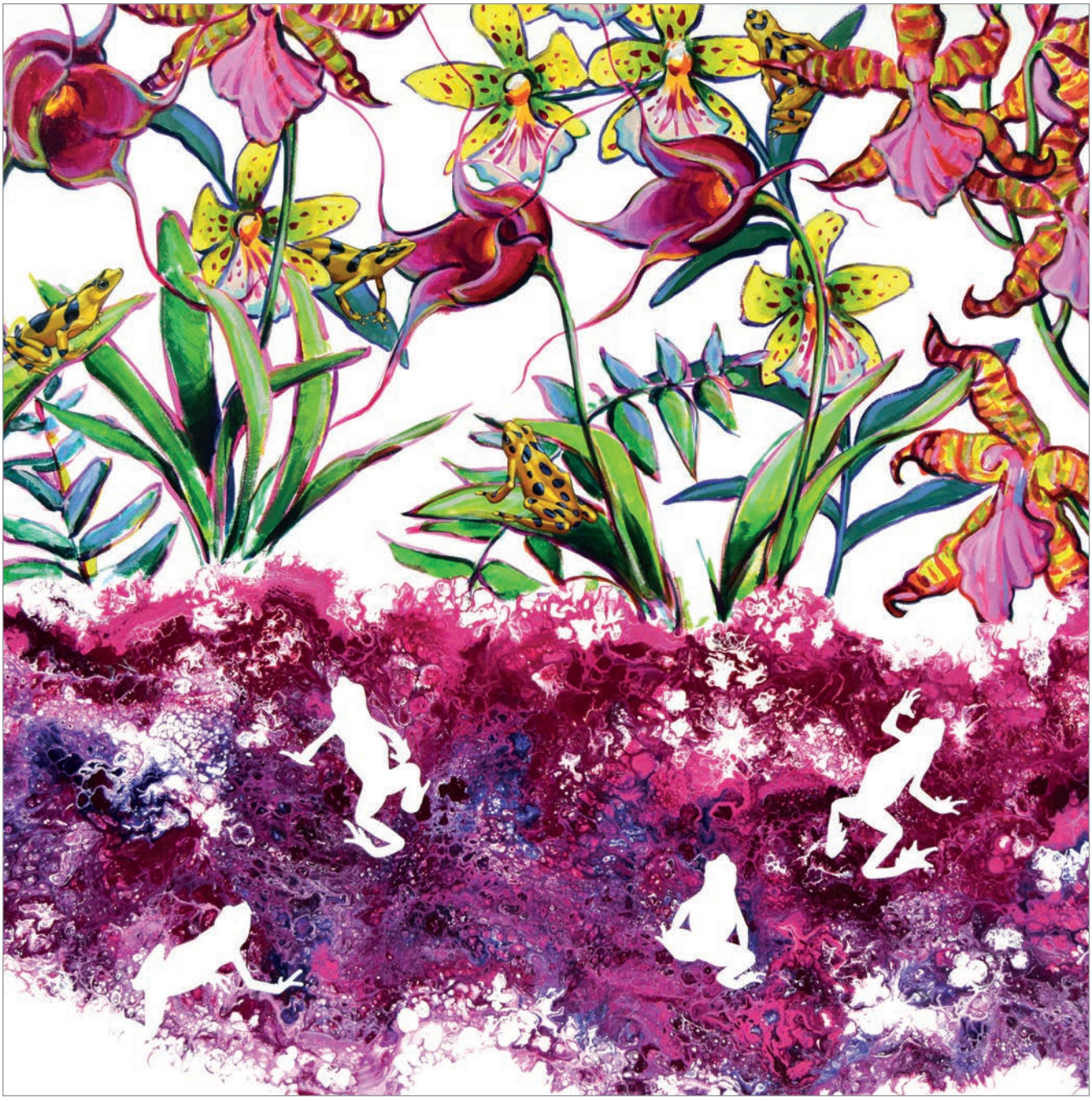
Lisa Nilsson, Artist, USA.
Photographed by John Polak.







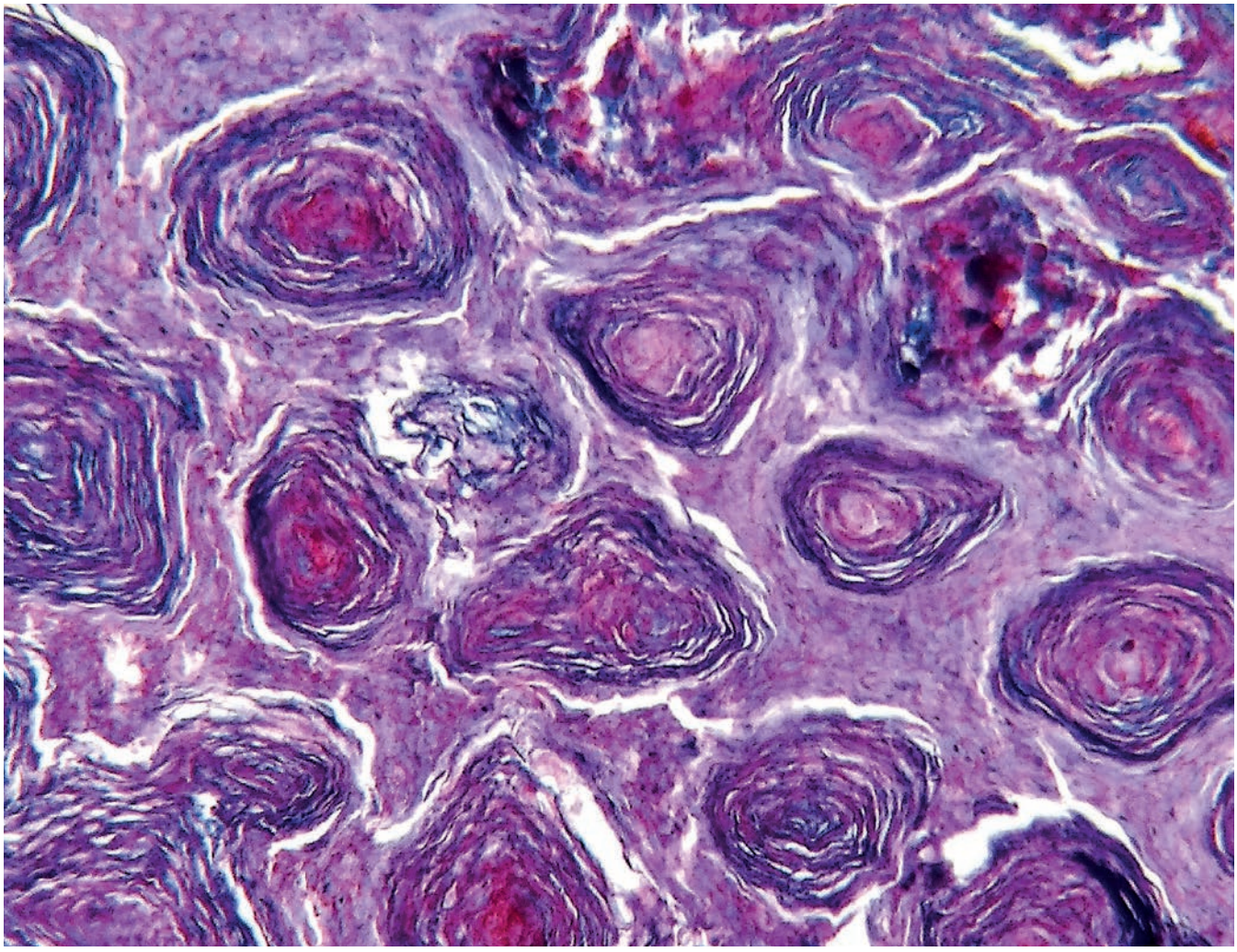




DISEASED

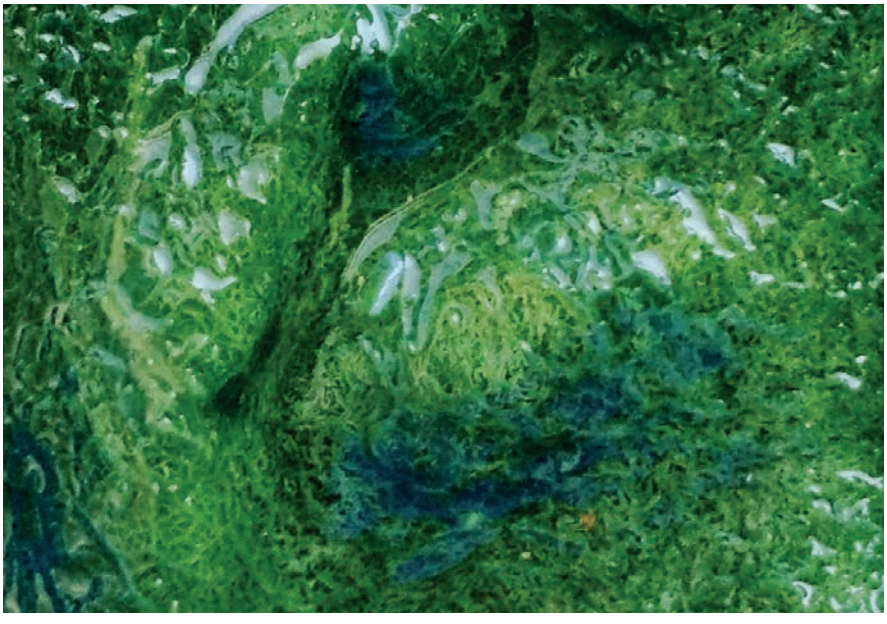
For six months of 2018, Pittsburgh-based artist Ashley Cecil served an artist-in-residence at the Richards-Zawacki Lab at the University of Pittsburgh – making artwork about the vulnerable state of amphibians. This particular piece focuses on the lab's extensive study of chytridiomycosis. Caused by a fungus, this fast-spreading disease is fatal to a staggering number of amphibian species worldwide, in some cases causing extinction. A histological section of an infected frog inspired this visual interpretation of the impact of the disease on one particularly striking species, the Panamanian golden frog.

Ashley Cecil, Artist and Illustrator, USA



KERATIN SKY

Nejib's stain of the corneum layer in a patient with congenital bullous ichthyosiform erythroderma.



GREEN

Gross pathology of the gallbladder, close-up.

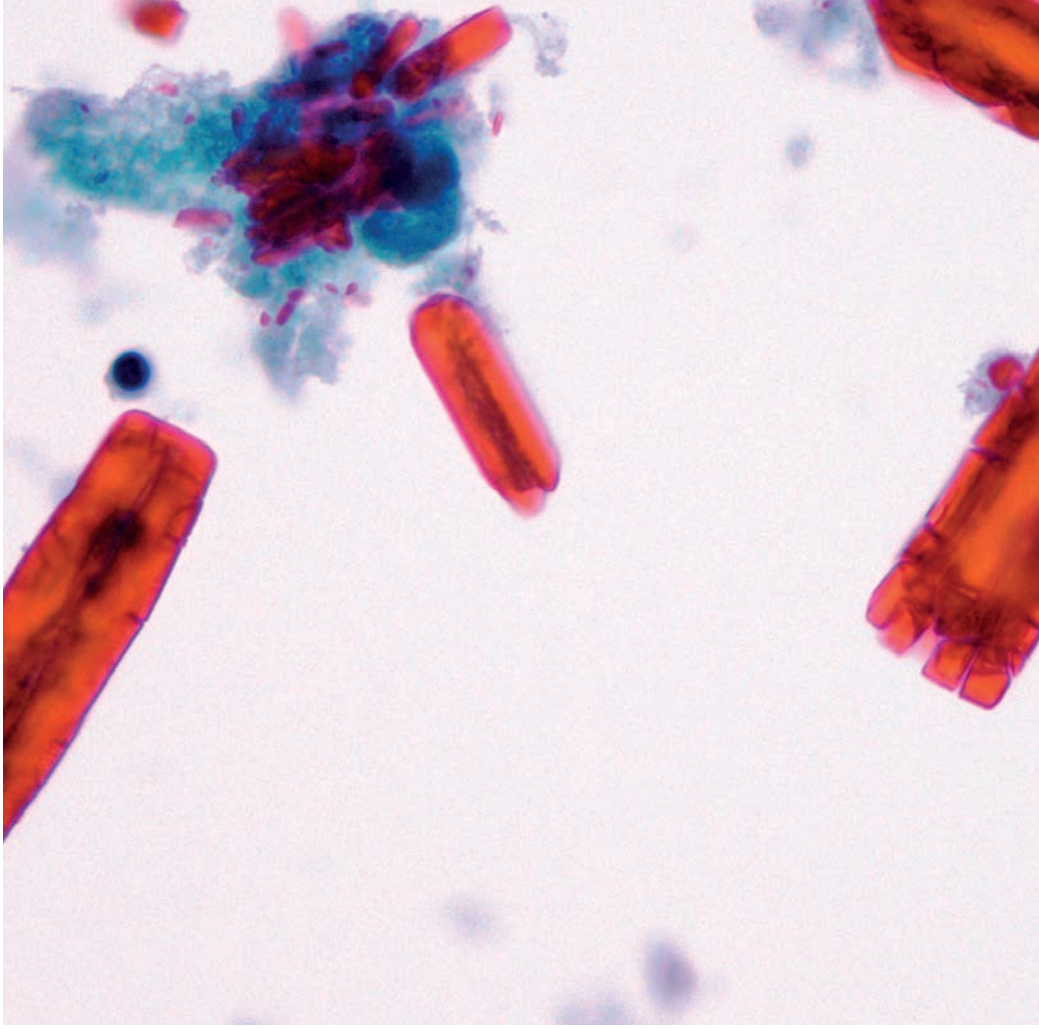
Luis Humberto Cruz Contreras, Hospital Materno Infantil Irapuato, Mexico

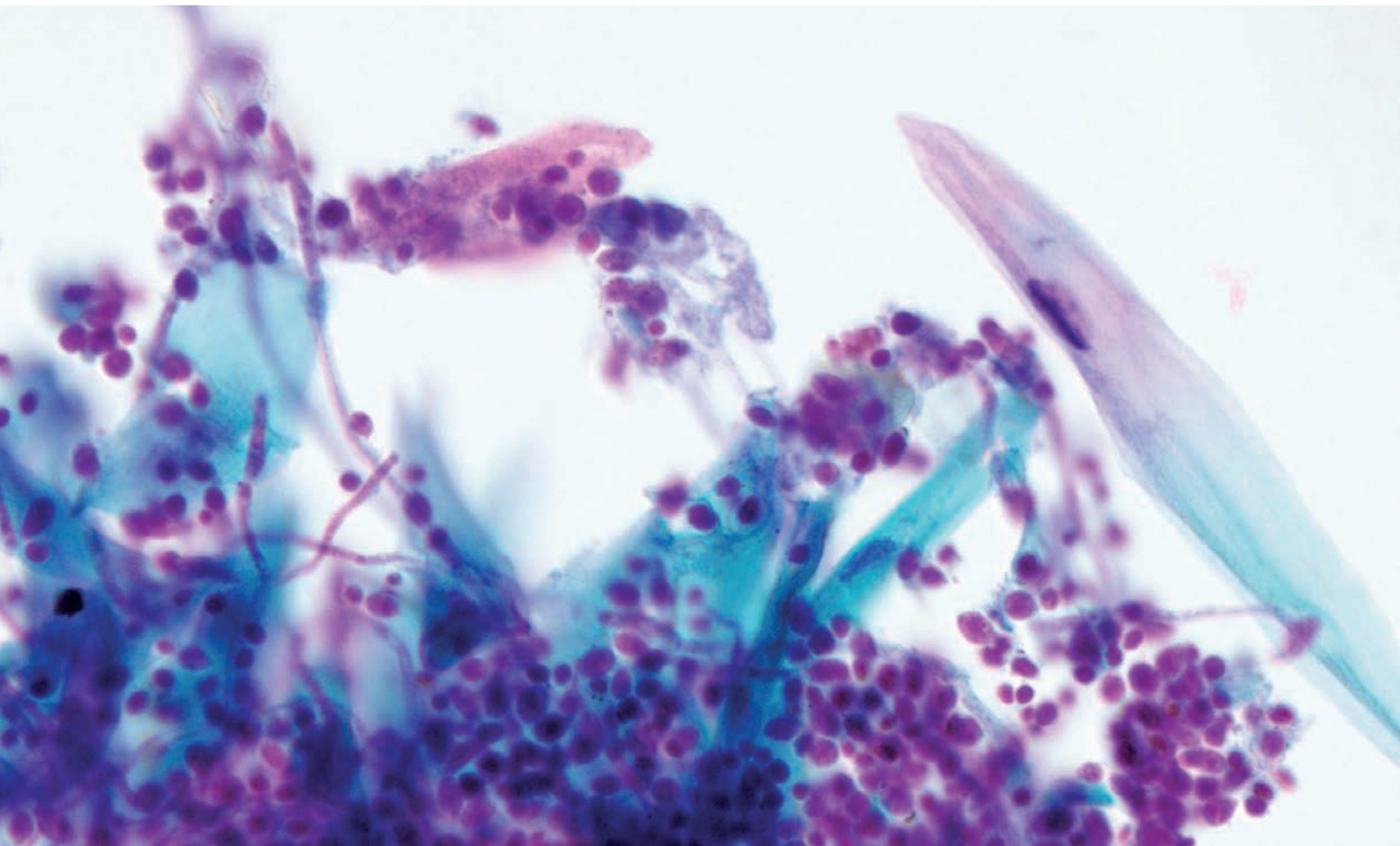
CRYSTALINE (RIGHT)

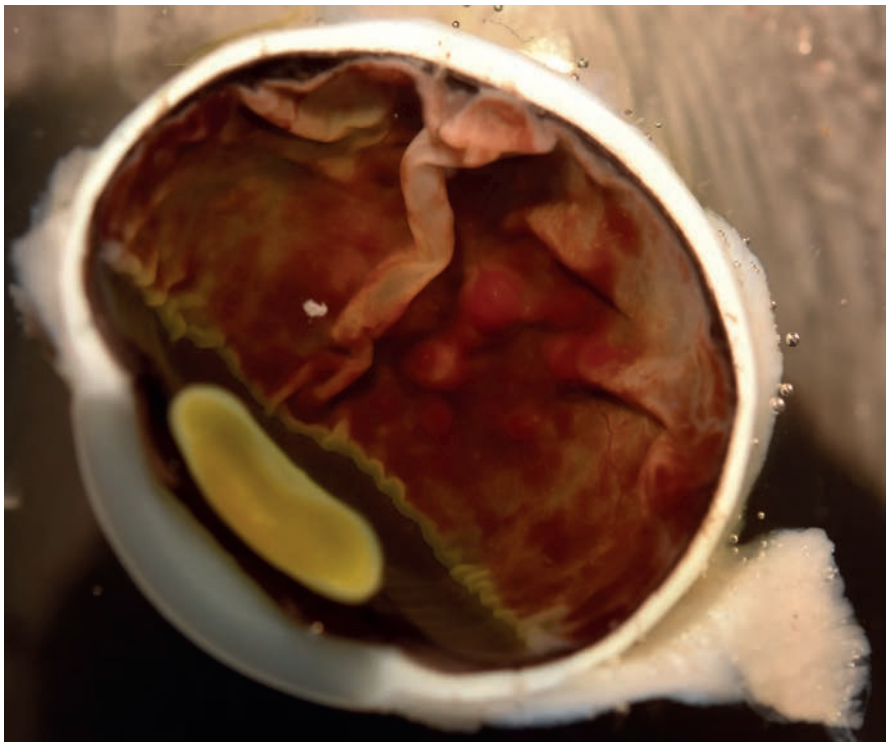
POLYCHROMASIA (BOTTOM)

These images showcase the beauty in even the simplest of microscopic images.

Katelyn Dannheim, Beth Israel Deaconess Medical Center, USA



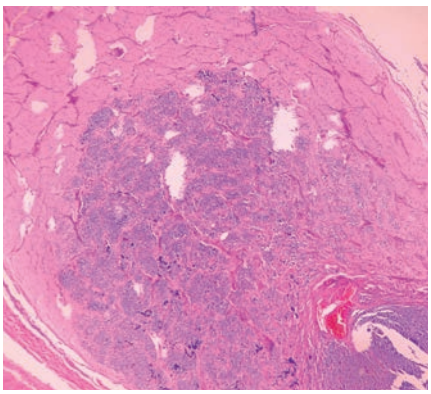


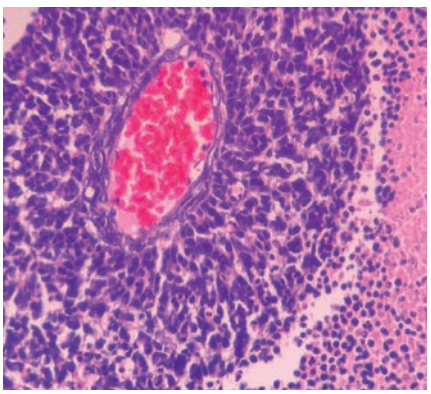


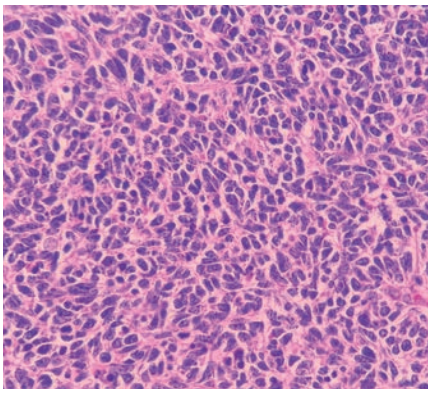
CS-EYE

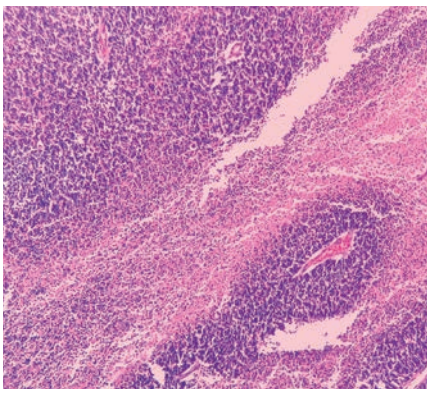
Image of an injured eye examined for a forensic investigation.

Narsing A. Rao, USC Roski Eye Institute, USA









RETINOBLASTOMA PATHOLOGY

These images show hematoxylin and eosin-stained sections of enucleated eyes from a four-year-old patient with retinoblastoma. Diffuse growth of primitive undifferentiated cells with scant cytoplasm and oval nuclei showing finely granular chromatin and absence of nucleoli can be seen, as well as invasion of the neoplasm into the optic nerve.

Alicia Nunez Abreu, Hospital HOMS, Dominican Republic

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In Practice

Technologies and techniques
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Workflow

Asking the Right Questions

To diagnose disease in a complex organ like the liver, you need all the relevant information – and possibly a little help

By William Aryitey

"I like to think of the liver as being a microcosm of the human body's pathology as a whole," says Robert M. Najarian, consultant in gastrointestinal and liver pathology at Beth Israel Deaconess Medical Center. The detoxifying organ doesn't directly recapitulate the body's physiological diversity; rather, it allows an immunological glimpse into the body's processes. "We see a whole spectrum of conditions, from infections to autoimmune diseases to a host of primary and metastatic neoplasms in the liver," Najarian says. "As a liver pathologist, you really do end up seeing everything – inflammatory, neoplastic, and other surprises." With the array of diseases expressed in the liver, the tools and techniques used for diagnosis are especially vital to differentiate between them – but, according to Najarian, one particular aspect stands above all others. "The most important tool we have is the availability of clinical history (something that, hopefully, is available at our fingertips), followed closely by a high-quality H&E-stained slide. This is the fundamental basis of what we do in liver pathology – and really all pathology – because they allow us to diagnose a pattern of injury first, then supplement what we see under the microscope with the clinical history to truly inform what's happening to the patient."

Modern, high-tech tools are great additions to a pathologist's roster from a technical perspective, but using them without a strong foundation from clinical history and H&E is like building a house on an unstable foundation. And in an era where efficiency and cost-saving measures are becoming increasingly predominant, those two pillars cost relatively little and contribute a lot.

"The most important tool we have is the availability of clinical history, followed closely by a high-quality H&E-stained slide."

A generalist specialist

Once you've firmly established the two main building blocks and you actually dive into the biopsy itself, what are the next steps? "A pathologist should ask themselves, 'What am I seeing in terms of the organization of the sample? Am I seeing reasonably normal liver architecture with intact portal triads and lobules?'" After determining the presence of abnormal inflammatory or neoplastic cells, Najarian says you should also keep an eye out for what isn't there. "Have intact native bile ducts been lost for some reason – possibly due to prolonged damage? Is there steatosis (irregular fat retention) where normal hepatocytes should be? Next, once abnormalities are identified, it's important to then ask yourself, 'Can I attribute these changes to a single pattern of liver injury, or is this perhaps illustrating features of multiple patterns and thus multiple causes of damage?' Once you've done that, as a pathologist, that's more than half the battle." From that point on, all the pathologist must do is narrow down the options and specify what diseases fit the patient's individual patterns or combinations – but this isn't a straightforward task.

Najarian emphasizes the need to question the possibilities and, in cases where you cannot make a conclusive diagnosis, seek the knowledge of an experienced expert. "The 'long story short' is to be aware of what you, as a well-educated pathologist, do and do not know – and to know when it's time to ask for consultative assistance," says Najarian. "You shouldn't allow your years of experience or your familiarity with a particular type of tissue to limit your willingness to call on others who might be able to give you a unique perspective or share their experience with you. Liver pathology can be quite complex." And with that complexity comes the potential for inaccuracy.

Two sides of an erroneous coin

"I think errors come in two different flavors. One is on the part of the

At a Glance

- *A patient's clinical history is essential for the diagnosis of liver pathologies*
- *Whenever there is any doubt, pathologists should not hesitate to consult subspecialty experts*
- *Most diagnostic "errors" stem from being either too specific or not specific enough*
- *The number of routine liver biopsies may decrease in the future, but the complexity of the remaining ones will likely increase*

pathologist who, feeling the need to be too specific with a histologic diagnosis, may attribute a pattern of injury to a specific disease when there isn't sufficient evidence to support it," says Najarian. The second aspect deals with the opposite end of the spectrum. "If you have an injury pattern that makes sense in the context of several different diseases, failing to mention the specific entities in what may be a broad differential diagnosis, and which one you might favor, is an issue that may mislead the liver specialist and affect what confirmatory laboratory tests they order."

The way to avoid these pitfalls is to have the plethora of information necessary for an accurate diagnosis. And what's the best way to provide that information? "I may sound a bit repetitive, but it starts with clinical history, combined with laboratory testing, and with imaging tests in certain situations. They make up the most important pieces of the puzzle," Najarian says. "The second most important piece is having more eyes in the game. It's vital to have more consultative opinions available to you, and to feel comfortable asking for those opinions." After all, two heads are better than one – and nowhere more so than in patient care.

Voracious variability

Despite taking precautions to avoid pitfalls, there's one tricky aspect of medicine that has the potential to affect all pathology tests: sampling variability. Its effect on blood tests is well-known (1) but, when dealing with tissue sampling, the solutions that work for blood don't necessarily apply. "By nature, most of what pathologists see in terms of liver samples are needle core biopsies taken via a percutaneous, transvenous, or even endoscopic route – the ideal sample of which is about 2.5 cm in length and 1–2 mm in thickness, depicting about 1/50,000 of the whole organ. That's going to bring about variability issues and raise questions as to whether or not

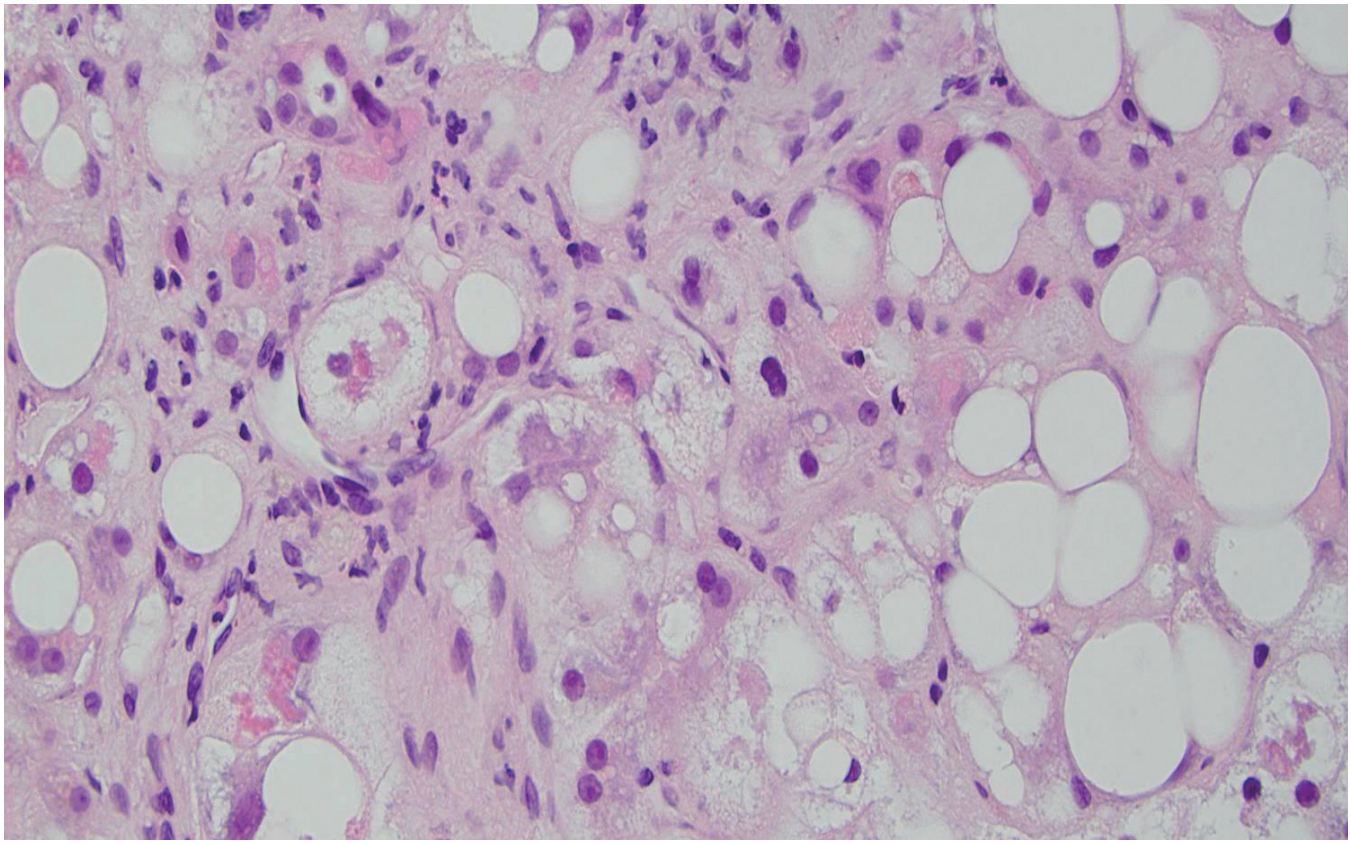
we're truly seeing a representation of the whole liver," warns Najarian. "With that in mind, I would encourage my fellow pathologists to first evaluate the adequacy of the samples they are assessing. Often, what we receive isn't sufficient in the first place, and we shouldn't be afraid of describing the limitations that might come with a diagnosis we render from an inadequate sample." He encourages pathologists to ask for more tissue or supplementary information if they need it – because having all of the information necessary for diagnostic accuracy is the key. "Consult your friendly expert liver pathologist often, if needed, in those circumstances where your own eyes may not be 100 percent certain," suggests Najarian. "H&E appearance is simple, but the differential diagnosis and the rendering of a specific diagnosis can be complex – so have no fear; consultants are here!"

Hepatic outlook

If these are the tools and techniques most essential in liver pathology right now, what does the future hold? Najarian believes that the field is going to become increasingly complex, so biopsy-based diagnosis isn't going to get any easier. "With the advent of new therapies to cure diseases such as chronic viral hepatitis C, I know that the number of routine liver biopsies most practices will see may decrease," he says. "But that doesn't necessarily mean that the amount of time we're going to spend on biopsies will decrease, because the biopsies we do see are going to reflect more complex and evolving disease processes (such as non-alcoholic fatty liver disease/steatohepatitis), multiple disease processes, injuries resulting from certain treatments – and, sometimes, all of those superimposed on top of each other." If this shift in complexity does occur, then the need for clarity becomes even more important – as does the need for the clinical history and collaborative aspects stressed by Najarian.

Reference

1. *J Nichols, "Variations on a drop", The Pathologist, 17, 44–45 (2016). Available at: https://bit.ly/2GNiRro.*



Steatohepatitis in a 74-year-old woman with amiodarone-induced liver injury. This high-power magnification H&E-stained image demonstrates prominent macrovesicular steatosis, ballooning degeneration of hepatocytes with intracytoplasmic hyaline, and lobular neutrophils – all histologic features more commonly associated with alcohol-induced steatohepatitis.

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NextGen

Research advances
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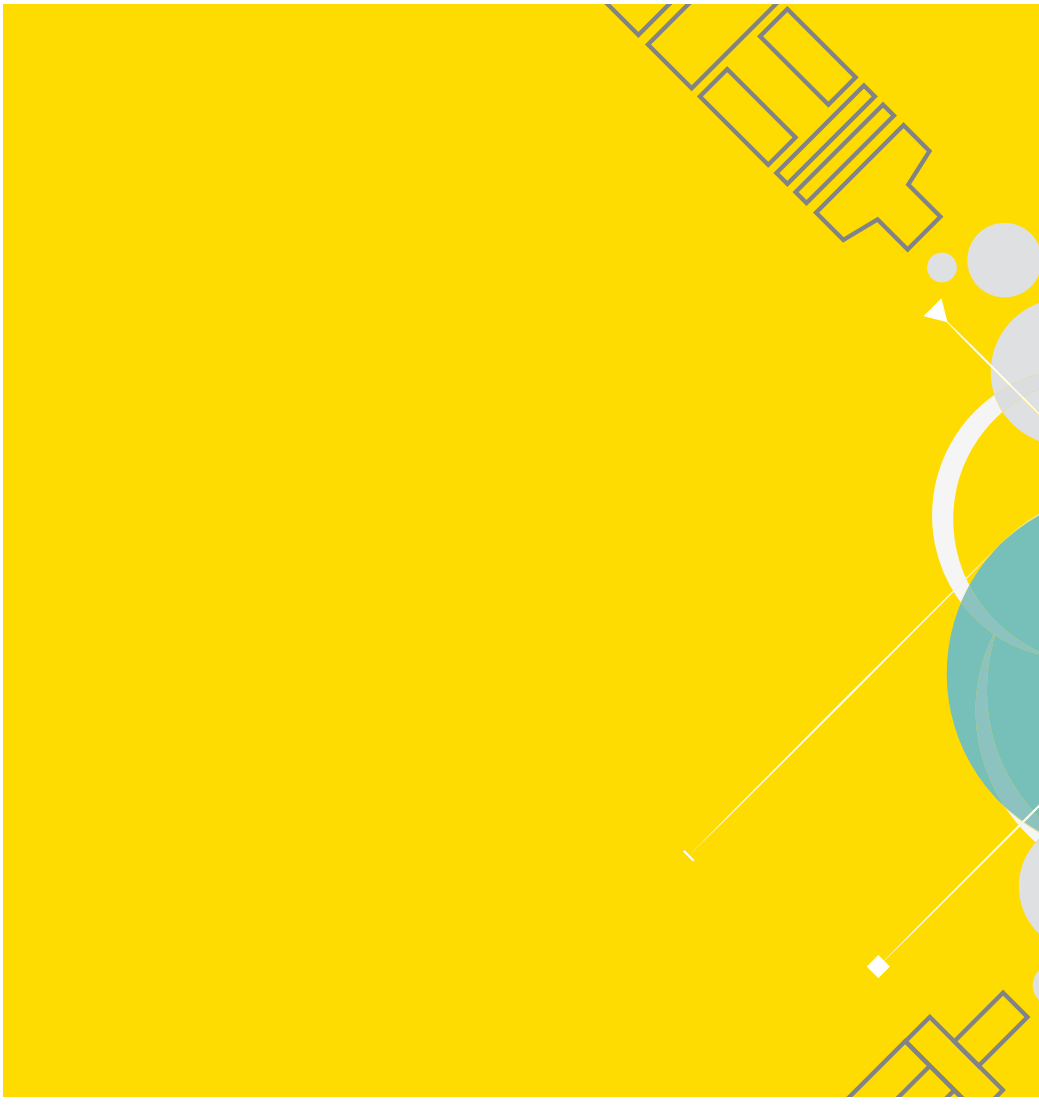
The Human Element

The challenges of using biomarkers to predict the health impact of e-cigarettes and heat-not-burn products.

Lion Shahab is a psychologist, neuroscientist and epidemiologist, with a focus on tobacco control: "My interest is in the use of biomarkers as a tool to motivate smoking cessation and investigate the effects of tobacco products and products such as e-cigarettes that are thought to mitigate harms.

"Around 2011, people started approaching our group at University College London about e-cigarettes, which were just taking off at the time," says Shahab. Based on his previous biomarker work, he secured funding from Cancer Research UK for a study examining biomarkers related to various negative health outcomes in users of e-cigarettes compared with smokers, and those using nicotine replacement therapy, such as gum and patches (1).



At a Glance

- *Biomarkers in the context of e-cigarettes and similar smoking alternatives have thus far not been well-studied*
- *Previous studies have focused on biomarkers with little link to long-term health or do not reflect the ways people actually use e-cigarettes*
- *Some components of e-cigarette fluids, like formaldehyde, have no useful exposure biomarkers at all*
- *To identify reliable biomarkers for monitoring ongoing health, the field needs long-term investigation of people who use smoking alternatives*

A lack of evidence

Shahab says that previous studies provided only limited evidence about the harms of e-cigarettes, with some focusing on biomarkers that have only a tenuous link with long-term health consequences. "For example, people have looked at changes in the inner lining of blood vessels, and claimed that e-cigarettes cause cardiovascular disease. The problem is, you see similar changes when you drink a cup of coffee," says Shahab. Then there were the usual problems of extrapolating results from in vitro or animal studies into humans – notably, nicotine itself is far more toxic to mice than humans.

It's also important to note that the risk of a product is not determined solely by its inherent properties, but also by how it is used. Water is safe to drink, but a teaspoon in your lungs could kill you, says Shahab. "There was a widely reported study showing that there is hidden formaldehyde in e-cigarettes – the flaw was that the machine used to

generate vapor from the product was at a setting that created "dry puffing" – something that consumers avoid at all costs due to the acrid taste," Shahab adds (2). Shahab also points to tobacco industry studies in the 1970s showing that adding perforations into the filter lowered toxin levels. In reality, no such benefit materialized, because human smokers covered up the perforations with their fingers and smoked more intensely, in order to get the same nicotine "hit."

As e-cigarettes have become more sophisticated, there is far more variety in how people use them in terms of temperature, choice of e-liquid, and so on, which makes it difficult to estimate how the aerosols will correlate with actual exposure, says Shahab. "For that reason, my preference is always to study humans."

The lesser evil

In the Cancer Research UK-funded study the team focused on a panel

"The risk of a product is not determined solely by its inherent properties, but also by how it is used."

"Compared to smokers, users of nicotine replacement therapy or e-cigarettes had greatly reduced levels of harmful biomarkers."

of exposure biomarkers reliably linked with long-term health outcomes, including tobacco-specific nitrosamines and other carbonyls, and a range of volatiles.

Bioanalysis was carried out at the Centers for Disease Control in the US, using LC and GC-MS/MS to measure nicotine exposure in saliva and urine, respectively. Carbonyls were measured using LC and atmospheric pressure ionization MS/MS, while volatiles were analyzed with UHPLC coupled with electrospray ionization MS/MS.

All the products performed equally well in terms of providing nicotine – but compared to smokers, users of nicotine replacement therapy or e-cigarettes had greatly reduced levels of harmful biomarkers. "There was a 95 percent reduction in some biomarkers for e-cigarette users versus smokers," says Shahab. "And that implies that they are likely to have better health outcomes in the long term." E-cigarettes are unlikely to be as safe as standard nicotine replacement – inhaling many e-liquid components (including nicotine) into the lungs causes irritation and inflammation – but the study suggests that they are much safer than smoking tobacco.

The unknown

Though Shahab is confident that vaping is less harmful than smoking, the risks are hard to quantify. One problem with tobacco research is that the health effects may take a long time to materialize. "If you look at the prevalence of smoking rates in the UK and US, you see a peak in smoking prevalence in the 1950s and 1960s, and then a peak in lung cancer deaths around 30 years later, so there's a huge time lag between exposure and associated health consequences," says Shahab. In addition, while some biomarkers, like NNAL (a nitrosamine metabolite) have been shown in long-term studies to have a close relationship with cancer, for others, the evidence is weaker. Other toxic compounds, like formaldehyde, have no good biomarkers to estimate exposure in humans.

"The other major problem is unknown unknowns", says Shahab. Research into vaping is informed by earlier research on tobacco cigarettes, but the chemistry is very different.

New technology, new risks?

Shahab's latest research is looking at long-term users of heat-not-burn products, like BAT's Glo and IQOS from Phillip Morris International. "Tobacco companies are keen to promote these products, which make use of their existing tobacco supply chains, and they claim that by avoiding combustion, they reduce harms," he says. "So far the research in this area has almost all been carried out by industry, so there is a need for independent verification."

Shahab stresses the need for long-term studies of heated tobacco products, taking into account

"While some biomarkers [...] have been shown in long-term studies to have a close relationship with cancer, for others, the evidence is weaker."

less than perfect use. "For example, when a stick is replaced some of the tobacco is often left stuck to the heating elements, and I suspect this could lead to the formation of carcinogens over time – but that's something that will only become apparent in long-term studies."

References

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Quantifying the Risks

Ed Stephens, a research fellow at St Andrew's University, UK, spent a decade studying health implications of heavy metals in tobacco. When e-cigarettes became popular, he quickly saw the importance of determining the chemical composition of the vapor – and giving users a straightforward estimate of the risks. In 2017, he published a paper estimating the relative cancer risk of people who vape compared with smokers or users of heat-not-burn products (1). We caught up with Stephens to find out more about the study, and his work in the field.

What are the challenges in vaping research?

First, there are no internationally accepted analytical protocols or reference standards in place so no two labs do things in quite the same way – it's effectively a free-for-all. The Tobacco Regulatory Science Program at the NIH is developing a standard device and liquid formulation to allow labs worldwide to standardize their analyses. Second, we know little about the speciation of metals in vapor such as their valence state and molecular species, and this can be a key factor in their toxicity.

What inspired your 2017 study?

I saw that there were many papers in the literature analyzing single components of vapor for toxicity, but very few taking a more comprehensive view. I decided to apply a toxicological risk method that has been previously used in tobacco research to aggregate the impact of the carcinogens reported in published studies to date. It involves a number of simplifications, but I was able to calculate a relative cancer risk of smoking tobacco or using various alternative nicotine delivery systems. As expected, smoking tobacco carried by far the highest risk, followed by heat-not-burn, then vaping, then nicotine inhalers.

What's next for your research?

I consider the initial estimates a starting point – I'm now working with toxicologists to address some of the simplifications in the model to create a more comprehensive assessment of disease risk, including health outcomes beyond cancer.

Reference

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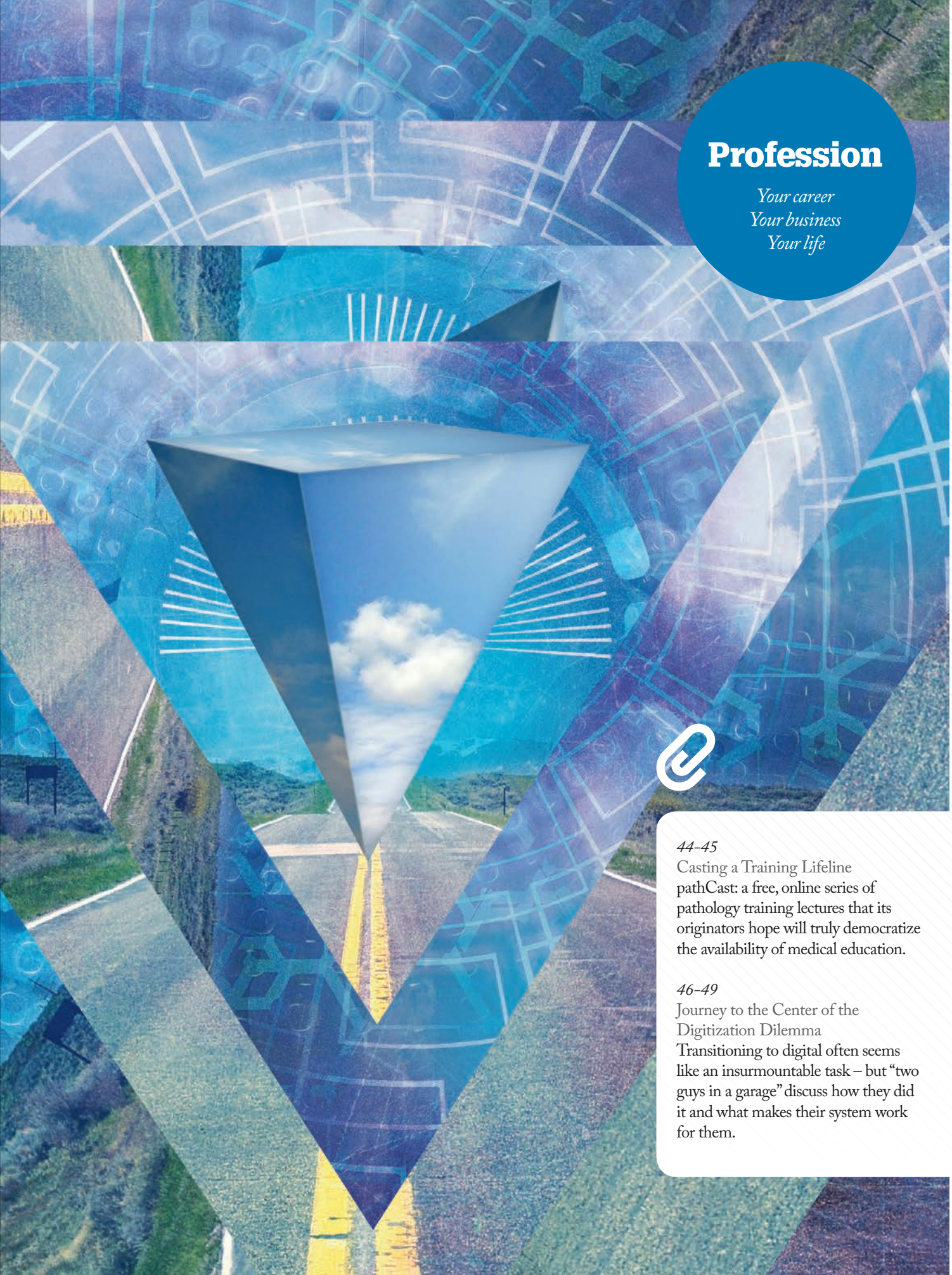

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Casting a Training Lifeline

A series of pathology lectures that can be viewed from anywhere, at any time, for free, could boost equality by providing medical education for all

By Rifat Mannan and Emilio Madrigal

Where did you receive your pathology education? Did you have access to state-of-the-art computers, simulated training, interactive quizzes, or the latest in multi-headed microscopes? Or did you work from textbooks, diagrams, or the basic information available on the Internet? Not every pathologists' medical training looks the same, and it's certainly true that not every student of pathology can access the same resources and assistance. It's those differences that we feel should be addressed – and that's what pathCast, a free pathology lecture series streamed live and available on demand, hopes to accomplish.

At a Glance

- *A significant resource and training gap exists between developed and developing countries*
- *The training gap also affects medical education – and pathology in particular – meaning that not every trainee in the field can access the same learning tools*
- *To tackle the disparity, we've developed pathCast – a free multicast lecture series that can be streamed live or viewed on demand at any time, from anywhere*
- *We hope this will help bridge the knowledge gap – and we invite all interested pathologists to consider participating*

Starting a multicast

In May 2016, we were about to start our fourth and final year as pathology residents at Mount Sinai in New York City. We were interested in enhancing the didactic sessions at our program with expert lecturers across different subspecialties, so we reached out to several pathologists both at our own institution and elsewhere – and they immediately expressed a strong willingness to participate! A challenge arose when many of the interested lecturers were not local to the New York area, because our program did not have an established policy for financing guest speakers. Unwilling to pass up the chance to learn from the many generous experts who had offered to share their time, we explored ways of circumventing the issue – including the possibility of "hosting" our guests as part of a webinar. We knew the necessary equipment was already available to us in the department, and the webinar format was already familiar to many of our speakers. And so we shared the approach with our residency program director, Mark Friedman, and he happily gave the nod. We quickly got started by organizing dates and times to host our remote guest speakers.

For our first webinar, we used WebEx, a tool our co-residents thoroughly enjoyed. Inspired by this initial success, we wondered if we could host another webinar – but this time, transmit a live, web-based broadcast to amplify the reach of the lecture beyond our conference room. Our first attempt involved trying out Twitter's Periscope, which was mostly successful, but limited by the fact that we relied on a smartphone for input – meaning that we had to use a small camera, a low-quality microphone, and no other tools. To transmit a speaker's actual presentation (either via computer slide show or whole slide images) and capture their voice with good sound quality, we created a YouTube channel to transmit and archive the lectures. And, of course, now that we had the speakers, the tools, and the channel, we needed the finishing touch: a name. We chose "pathCast" – a portmanteau of "pathology" and "broadcast."

A brief history of multicasting

"Multicasting" is the process of sending data across a computer network to several users at the same time. We've tried a few different platforms and online social networks, sometimes transmitting to as many as three at once: Facebook, Periscope, and YouTube. Most of the time, though, we only transmit to Facebook and YouTube, because that's where the bulk of our users reside.

Most of our lectures are planned exclusively for pathCast, but we have streamed sessions directly from conferences as well – two from the Lenox Hill Hospital Cytopathology Meeting in New York in 2017, and one from Johns Hopkins' 2017 continuing medical education event, "Current Topics in Gastrointestinal and Liver Pathology."

PathCast is our attempt at a truly open-access education platform in pathology; anyone from anywhere in the world with any kind of computer equipment can access the lectures – live or archived (on Facebook, YouTube, iTunes, or via our website, *pathologycast.com*) as they prefer, without requiring a prior invitation or registration. And, if they choose to participate live, viewers can interact with the speakers during the session via chat windows. All in all, it's a setup designed to offer truly accessible pathology training and education to any interested person.

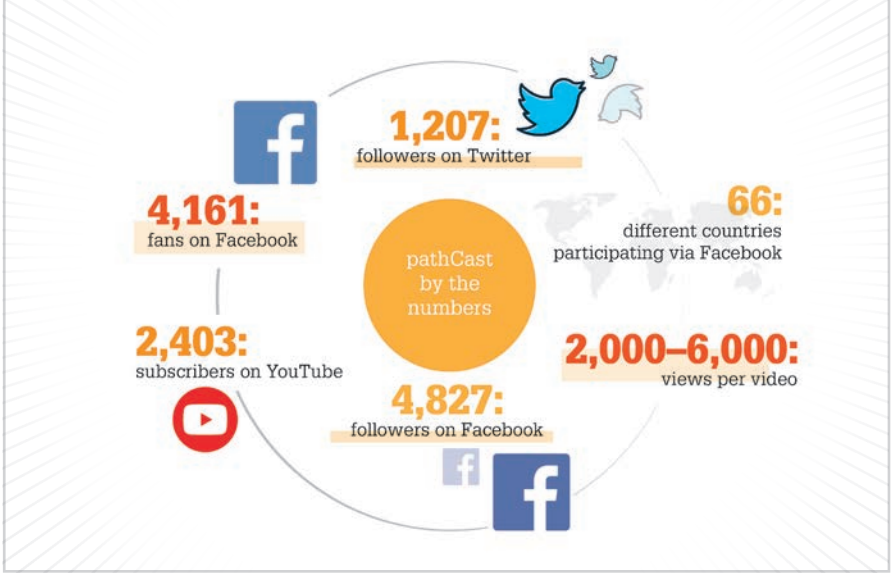
How it's made

Step 1: Invite a speaker

We personally contact our speaker(s) and invite them to give a pathCast lecture. Of course, we let them know in advance that we plan to broadcast the lecture live!

Step 2: Ensure that broadcasting equipment is set up

The basic arrangements include a computer with a reliable, high-speed Internet connection and a high-quality microphone



at the speaker's location. Depending on whether the lecturer is presenting a computer slide show, glass slides, or whole slide images, they will need to make sure that their software is up-to-date and their microscope-to-camera connection is properly set up.

Step 3: Go live!

We receive the guest speaker's computer screen and microphone input using video-conferencing software, which we then feed to locally installed open-source streaming and recording software. Once the audio and visual inputs are properly configured, a master stream key is generated that we then distribute to our Facebook and YouTube channels via a web-based multi-streaming service.

We also generate a promotional banner with a photograph of the guest lecturer, their name and affiliation, the title and date of the lecture, and information on how to access the pathCast. In the run-up to the event, we share the banner multiple times on our social networking websites to promote it.

Finally, when the live transmission takes place, we can learn from and enjoy it alongside (at least virtually) our colleagues from across the globe.

An unexpected impact

In the course of reviewing our Facebook analytics, we noticed that one of the cities that generated some of the greatest viewership was Korai, India. Though one of us is from India, we had never heard of this place – so, curious, we looked it up. It turns out that Korai (or Korei) is the name of a very small village in Odisha, one of India's eastern states. We were thrilled to find this. To us, Korai is an inspiration – and a vindication. It proves our belief that pathCast can (and will) indeed reach remote corners of the world. We are convinced that there are many other Korais across the world that our pathCast videos reach, and that's what encourages us to continue our efforts to promote pathology education and reach out to the farthest corners of the globe.

Recently, we had the opportunity to host a multilingual pathCast series focused on the Milan System for Reporting Salivary Gland Cytopathology, whose Atlas was recently released. Before the release, co-editors William Faquin (live from the Massachusetts General Hospital in Boston, USA) and Esther Diana Rossi (Catholic University of Sacred Heart in Rome, Italy) kicked off the series in English and Italian, respectively. That was soon followed by versions in French, Japanese, Mandarin, and Portuguese! We're proud to have provided the Milan System with an avenue to disseminate their classification system to a broad, international audience even before the official release of the Atlas.

One of our personal favorite pathCast seminars was our very first, which took place on May 11, 2016. Neil Theise, a renowned liver pathologist, was the speaker. Back then, he was also one of our faculty members (now a Professor of Pathology at New York University). He was very excited when we introduced him to the concept of pathCast. In fact, he rode his bike all the way from the Lower East Side to the West Side of Manhattan and was there at 7:30 in the morning, long before we were. He even brought doughnuts for breakfast!

Getting involved

Medical education, pathology or otherwise, should be accessible to everyone across the world, irrespective of geographic, language, or financial barriers. As medical professionals, we subscribe to the idea that accurate and correct patient care is paramount, but that is only possible when physicians – even in the remotest corners of the world – are aware of recent advances and best practice guidelines. By leveraging the Internet and social networking platforms, we can increase the accessibility of medical education. We hope our efforts will contribute to closing the knowledge gap and helping our colleagues better treat their patients – everywhere. To that end, we all have a responsibility to educate and pass on our understanding of pathology.

Our fundamental raison d'être is the idea that pathCast could become a pathology knowledge-sharing platform with perspectives from different parts of the world. Its overall goal is to bridge the knowledge gap between resource-rich and resource-poor regions. As such, we enthusiastically invite all pathologists to join us and help spread advances in pathology to every corner of the world. Anyone interested in delivering a pathCast is very welcome to contact us via our website or by direct message on Twitter (@pathologycast, @EMadrigalDO, or @mannanrifat03) or Facebook (@pathCast).

Let's work together to spread pathology education sans frontières!

Rifat Mannan is Assistant Professor of Pathology at University of Pennsylvania, Philadelphia, USA.
Emilio Madrigal is a Clinical Fellow at the Mass General Hospital, Boston, USA.

Journey to the Center of the Digitization Dilemma

Can two guys in a garage really shake-up current thinking on the transition to digital pathology?

Michael Schubert interviews Alec Hirst

In 2016, Alec Hirst and Chris Evagora, in partnership with their clinical leads Luis Beltran and Dorota Markiewicz, set up their company, Pathognomics. Their vision? To design and deliver a fully end-to-end digital histopathology laboratory to prove that whole digital pathology can work in a diagnostic environment – and that it can be implemented in a timely and cost-effective way. A lofty goal perhaps, given that Hirst and Evagora were working out of a garage rather than the shiny, fully outfitted building of an industry player…

Nevertheless, in under a year, they had built a wet laboratory, designed and implemented a diagnostic digital solution, successfully met Care Quality Commission (CQC) and National Health Service (NHS) Digital Information Governance (IG) Toolkit standards, and have been offered ISO15189:2012 accreditation. The laboratory has been operating diagnostically for six months and the team have completed 4,000 cases with two NHS trusts, as well as dentists and private healthcare providers. To learn more about their workflow and how others can learn from their approach to digital pathology, we sat down with Hirst.

At a Glance

- *Digital pathology is often approached as a minor adjustment to established practices, rather than as a substantive workflow change*
- *The major challenge in digital pathology at the moment is the storage and management of massive amounts of data*
- *To make a successful move to digital, it's important to have pathologist buy-in, LIMS integration, and scalable, future-proof technology*
- *It's not the solution to every problem, but digital pathology offers the chance to improve workflow efficiency with manageable cost and effort*

What's wrong with existing lab workflows?

The current approaches to laboratory practice are well-established, with some elements that have hardly changed at all over the last few decades. There is a drive to improve laboratory practice through automation tied to digital aspects, such as barcodes and macro-images, but these changes have been slow because, until recent years, laboratory quality assurance in the UK was captured under Clinical Pathology Accreditation. With the advent of international standards (ISO15189:2012), there has been improved assurance – but it has been more of a migration of established practices than a substantive change to laboratory assurance. As yet, no international standard has been developed to address the changes in digital aspects of pathology, particularly digital slide management. In addition, there is a lack of integration between regulating bodies – particularly with respect to data management and data security, which is assured under other legislation requiring skills outside of those needed in a traditional laboratory. This creates a need for more training, new staff members, or both, which can make it difficult to migrate a laboratory to a fully digital workflow.

To make such a migration work, we need to solve our key problem: data management. Digital pathology creates lots and lots of data. Where do you store it all? How do you retrieve it when you need it? Cloud-based solutions are both popular and important to delivering digital pathology, but the wrong type is expensive, and one cloud solution does not fit all. In trying to find the perfect solution, we have concluded that a lab should ideally use a mix of local hardware and cloud-based platforms to manage day-to-day operations, store digital slides, and backup information.

"Working with emerging technologies may mean that [...] trial and error can become your best friend."

Another significant hurdle is the human factor. People often find it difficult to accept change, especially a transition as major as moving from traditional to digital pathology – and even if everyone is on board, there's still a need for extensive training and education in the new workflow. To compound the difficulty, laboratory information management systems (LIMS) and image archiving and communication systems are not designed specifically for histopathology, meaning

that they can be difficult to use in a tissue laboratory, and may mismanage data in a way that complicates the workflow or introduces the potential for error. Finally, it can be extremely difficult to obtain the proper accreditations for a fully digital workflow. Working with emerging technologies may mean that there is very little literature to draw on – trial and error can become your best friend.

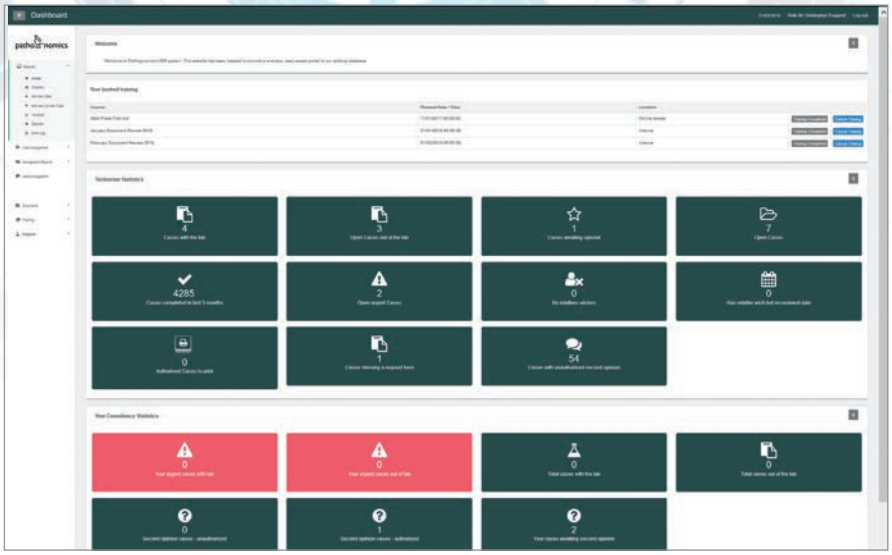
How have you tackled those challenges?

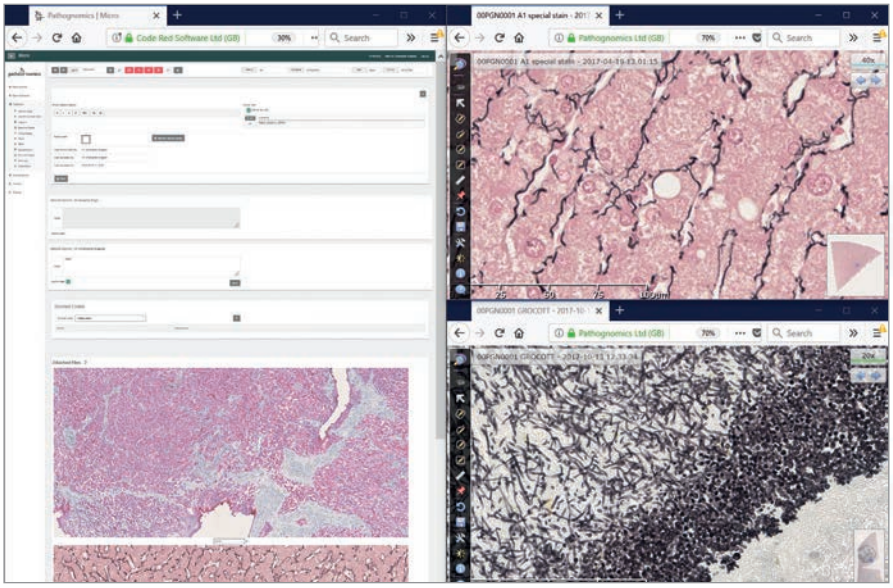
We have designed and built our own LIMS to knit together established laboratory practice with digital tools. It's designed specifically for histopathology and is a fully integrated digital platform validated and verified under our ISO15189:2012 schedule. In addition to diagnostic data, it manages staff training, ISO documents, reagent platforms, and finances, giving us a complete laboratory workflow that improves efficiency and significantly reduces our software overhead. In designing our LIMS, we have addressed all prerequisites for digital pathology under ISO15189:2012, IG Toolkit, General Data Protection Regulation (GDPR), and CQC:

- Quality control of images and patient reports,
- Responsive diagnostic environment,
- No local installation (minimizing user impact),
- Fast image transmission within IVD-CE controlled software technology, and
- Cost-effective image presentation and archiving in line with recommendations (currently 10 years for all images used for diagnoses).

Our goal was to present a seamless integrated digital product to the user – from laboratory management of training and education, ISO documents, and reagents to reporting and digital image management. And because the system worked so well for us, we now present it as a service to clients, removing the need for them to invest in technology and train their own workforce in the management and operation of digital histopathology solutions. Of course, larger laboratories may have the funding and resources available to handle their own transition – but for the many smaller labs and organizations who don't, outsourcing is an efficient way to make the move to digital without overcommitting.

We have no on-site pathologists at our laboratory; all diagnoses are undertaken remotely. As you can imagine, without a digital solution this would require an unmanageable logistical nightmare of couriering slides to many locations! Not only would it be massively inefficient, but it would carry what we consider an unacceptable risk of loss or damage, not to mention a significant time penalty. The success of our model relies on our integrated LIMS to manage, track, and host a platform for digital reporting – so





full integration between lab and LIMS is critical.

Our model is designed to be scalable, not just with workload, but also with emerging technologies. We are already in the advanced stages of integrating our LIMS with digital analysis tools. In a "big picture" sense, we have focused on capitalizing on the latest software and hardware to keep our costs to a minimum while future-proofing our technology. With the software we have implemented, we are well-positioned to benefit from future large-scale changes, which will be driven by data management, cloud-based platforms, and regulatory pressures on data and patient information.

Last, but not least, we have integrated our digital pathology workflow into our quality management system (including our surgical audits, digital validations, data management processes, and our obligations under IG Toolkit and the new GDPR), which ensures that our digital solution is quality-assured and accredited under ISO15189:2012. It was no small undertaking, but a valuable one – and one that we recommend to any laboratory moving to a digital setup.

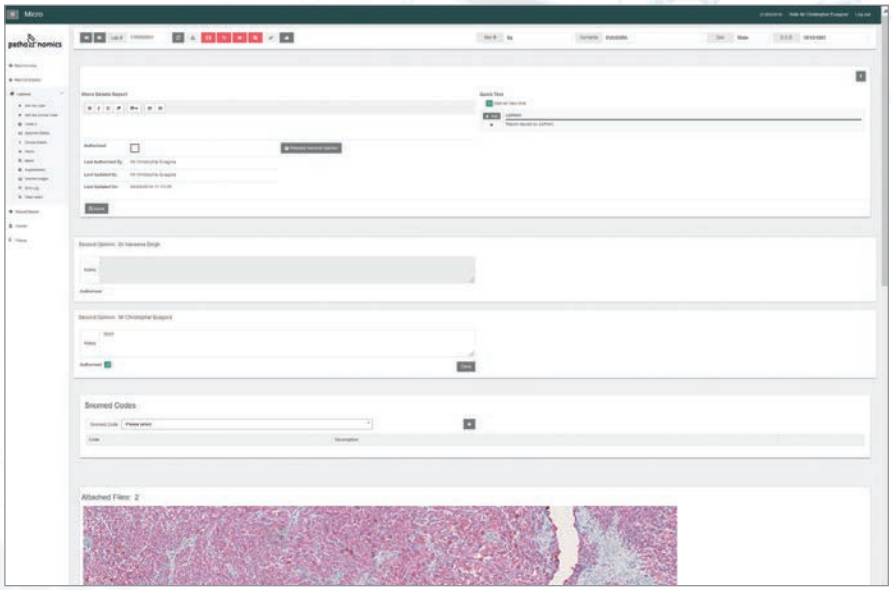
Even with our current setup, we are by no means finished. In my opinion, we've now mastered digital pathology – so our eyes are firmly fixed on the next step forward: AI and deep learning. That kind of technology is much closer than one might think. We are paving the way internally and have been in discussions with AI and augmented pathology companies from the start to assist in deep learning and the implementation of AI apps as a tool to help our pathologists in their daily work. Exciting times ahead!

"Digital pathology is a solution – but not the solution you may think it is."

What did you learn along the way?

Beware of two guys in a garage! As a startup and small enterprise, we are a driven team – but, all too often, driven by budget. With only finite resources to call upon, we are forced to be novel in our approach to issue resolution. The good news: we can share those new and exciting ideas for everyone's benefit. We are delivering a truly digital diagnostic laboratory that we hope is affordable and accessible to the NHS and to the wider community – just two guys in a garage!

By building our own platforms, we can be very accommodating to change. We have many routes for our clients and our team of pathologists to communicate



with us, and we take all of their feedback onboard, modifying our systems to accommodate their needs. Inevitably, we run into technical and data protection elements, but our size allows us to make adjustments quickly. Our pathologists find our LIMS a great place to work and have said they consider it the best platform they have ever used.

It's not all roses, though; we have also encountered some issues that I think are unique to micro-businesses like ours. The problem is a misalignment between the NHS drivers on engaging SMEs to supply services and innovations (something to which the NHS has expressed a commitment) and the benchmarks set by the NHS procurement processes. Pathognomics has failed two procurement opportunities at the pre-qualification questionnaire stage because benchmarks are too difficult for a micro-SME. It may not be intentional gatekeeping but, unfortunately, that is the outcome. But you can't expect innovation from SMEs to drive change, savings, and improvements, if the benchmarks for procurement lock them out in favor of more traditional business structures and sizes.

Taken as a whole, the most surprising thing to me is that our solutions don't already exist. In a way, though, our journey has given me insight into why: "digital pathology" doesn't just mean the slide itself; it means the whole laboratory workflow. There is still a misconception in the industry that going digital will fix all the problems pathology currently faces. Our view, and one that seems to be gaining ground, is that digital pathology is a solution – but not the solution you may think it is. It requires a rethink of the traditional model, an acceptance of where the benefits lie, and an understanding that things need to change – something that takes time and skills that the sector currently lacks.

What's your advice to others making the move?

Employ a project team comprised of all key stakeholders, from laboratory management and pathologists to IT and software experts. Moving to digital pathology is a complex change management project. We hear many stories where digital pathology is unsuccessfully implemented and, for the most part, it seems to be because of a lack of adequate project management. Expecting a laboratory manager or an enthusiastic pathologist to deliver a project of this magnitude will result in failure. They simply have too much work to do already – they don't have the additional capacity to manage a huge project on top of their everyday tasks! They do, of course, need to be consulted and engaged, but the project needs to be managed independently of the day-to-day operation of an existing laboratory.

I would encourage everyone in the pathology sector not to lose sight of where the benefits of digital pathology lie – and to be aware that it is not as costly as perceived! Some mistakenly believe that digital pathology will fix all of our issues – notably, the shortage of pathologists. In my opinion, digital pathology doesn't fix anything; rather, it is a tool that can be employed to increase the efficiency of the laboratory workflow. It helps, of course, that our pathologists can operate geographically independently of our laboratory; it means we always have someone available to ensure our turnaround times are met. In addition, we operate a model we call "fractional pathology," making efficient use of our team by only purchasing the specialist pathologist for the work on demand. Not only is this cost-effective for our clients, but it also gives access to all specialist pathology as needed to meet demand – a different approach to a traditional locum model. Finally, data storage is a bigger issue than I think is currently understood – but it still doesn't cost the thousands of pounds per terabyte offered by existing suppliers. It costs pounds and pennies, something we've proven in the course of our own work.

Digital pathology is not a panacea – but it's a far more feasible and efficient option than many labs believe, and I encourage all of them to consider jumping on the bandwagon!

Alec Hirst is Program Director at Pathognomics, Huntingdon, UK.

Research, Teaching, and Textbooks

Sitting Down With… Vinay Kumar, Alice Hogge and Arthur A. Baer
Distinguished Service Professor, Biological Sciences Division and The Pritzker School of Medicine, The University of Chicago, USA

How did you come to contribute so much to Robbins' pathology textbook – often considered "the bible of pathology?"

I came to the United States in July of 1972 and joined the pathology department at Boston University School of Medicine, having been recruited by Stanley Robbins himself. My primary motivation for the move from India was to pursue my research interests – a bid in which I was successful. In 1974, my colleagues and I published the very first paper describing the anti-leukemic role of a then-unfamiliar cell type – one we all now know as natural killer cells. Two years later, on the strength of that publication and my subsequent work, I obtained my first grant from the National Institutes of Health.

At the same time, my mentor had put me in charge of the pathology course at BU because of my interest in teaching. I worked hard on the course, and I guess he was sufficiently impressed by my dedication and excellence in teaching to offer me co-authorship of Basic Pathology (starting with the third edition, which was published in 1981). Soon thereafter, I was offered co-authorship of another textbook, Pathologic Basis of Disease, by Robbins and Ramzi Cotran. There, too, I worked on the third edition, which we brought to print in 1984. I continued to be the co-author of both books for the next several editions and, in 2000, became the senior author and editor of the seventh editions after Robbins retired and Cotran sadly passed away. It's a position I am proud to say I still hold, with Basic Pathology now in its tenth edition and Pathologic Basis of Disease in its ninth.

Would Robbins still recognize his original textbook?

Yes, he would! We have not deviated from the principles he laid down – namely, that pathology is the scientific basis of the practice of medicine, and that it is connected to clinical features. Back in 1950, Robbins was the first pathologist to write a textbook that contained more than simply morbid anatomy. He introduced the concepts of pathogenesis and clinical correlations. He also made our discipline more approachable than it had ever been by writing his book in a conversational style. Although the details have changed in the nearly seven decades since the book's initial publication, we have worked hard to keep its principles intact.

"Technology is a disruptive force that will change how we teach and assess."

Of course, it's not only the content that has undergone a transformation; it's also the way in which we deliver it. Digital options are becoming more and more popular, especially for interactive purposes. We consider electronic and print media complementary, so we use both.

We have also just completed a brand-new Robbins textbook – "Robbins Essentials" – that will be dramatically different. It will be media-heavy. The idea for this book arose in response to the way the teaching of pathology has changed from a standalone course to a part of an integrated, organ-based approach. Faculty felt that, with such a structure, students were losing touch with pathology – in part because there was no time to read books like Pathologic Basis of Disease. My colleagues and I decided to write a new book that contains what we consider core material. Each chapter is linked to several cases in which we focus on the application of science to practice of medicine. The cases are very interactive, with questions, text links, and clickable answers that sometimes contain illustrations (for instance, of the arachidonic pathway to convey how anti-inflammatory drugs act). Similarly, molecular mechanisms underlying cancer are presented in the context of a case. If there was a *TP53* mutation in the tumor, then there is a question on how p53 acts. We'll even have a quiz bank for students to test their knowledge!

You stepped down as chairman of your department to pursue medical education initiatives. What are they?

I am currently involved in setting up a global medical university with the goal of providing excellent education at low cost in the developing world. I also think there is a lot of progress to be made in the developed world!

Medical education has not moved with the times. Our methods have remained largely unchanged for over 100 years. Medical education remains knowledge-based, rather than competency–based; there is too much emphasis on learning facts and not enough on the ability to apply them. But nowadays, vast knowledge is readily accessible via a small, handheld device – so only the core content has to be learned (and taught). At the same time, highly sophisticated simulation platforms can be used to teach and assess competencies.

The bottom line is that technology is a disruptive force that will change how we teach and assess. I am not convinced, though, that artificial intelligence will replace doctors. If I could predict the future, I would not be spending time on this interview!

With all your accomplishments thus far, do you have any as-yet unfulfilled wishes?

I cannot play the piano (yet).

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