OCTOBER 2021 # 79

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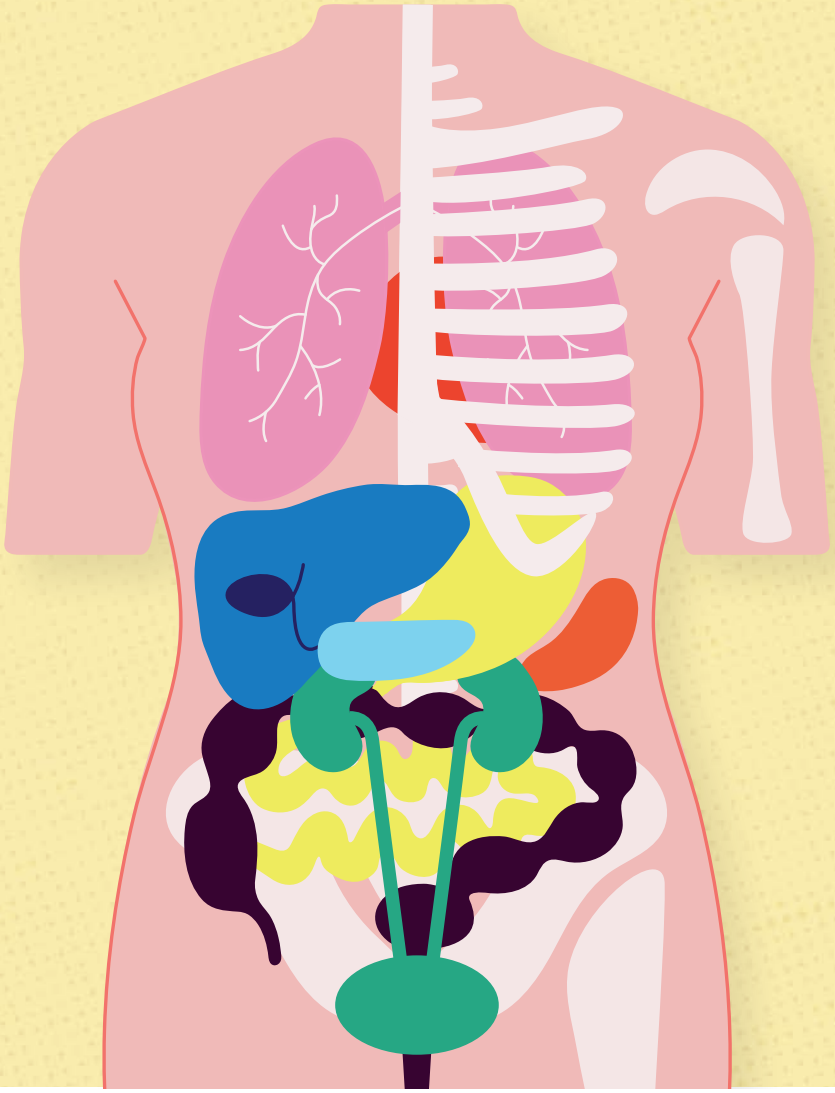
Anatomy of a Social Media Success

How the Institute of Human Anatomy became an Internet phenomenon



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Published in the USA, October, 2021
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Walk in the Park

When the pressure mounts and life is anything but easy, the answer is right in front of you

Here at The Pathologist, we're well into the busiest time of the year. There are articles to be written, meetings to be had, calls to be taken – and the pace always seems to double as we inch closer to winter. It's a phenomenon I recall from my days in the lab, although the emphasis has shifted; instead of desperately trying to design useful experiments and stockpile reagents so that the grant money is spent on time, we're now trying to publish all of the articles, address all of the hot topics, and wrap up all of our roundtables, events, and special features before the year is out.

Busy times like these highlight to me the value of balancing work and personal life – the importance of shutting down the computer at the end of the day or taking the dog for a walk. It can be difficult to switch off, especially during busy periods – but that's also when switching off is more necessary than ever. As workloads mount, stress levels rise, and the risk of burnout increases. Nowhere is this more evident than in the field of pathology and laboratory medicine, where staff shortages, snowballing demands, and a year and a half of pandemic crisis have taken – and continue to take – a toll.

Medscape's Pathologist Lifestyle, Happiness, and Burnout Report for 2021 shows a significant drop in pathologists' happiness levels over the course of the pandemic – from 82 to 56 percent (1). Forty percent of respondents said they were feeling burned out, depressed, or both – but, although nearly half felt that the issue had a "strong or severe impact" on their lives, few reported that they were seeking professional help to cope. Rather, common coping strategies included self-isolation, eating junk food, exercising, music, and sleep. Some of these are generally beneficial to health, others less so – but, in cases of burnout, people are often doing whatever they can, good or bad, to keep their heads above water.

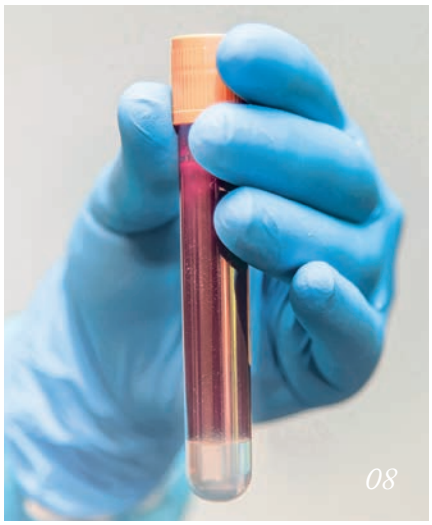
I'm lucky – I have a dog to drag me away from my screens when I'm spending too long at work. What about you? Let me know your best burnout busters (edit@thepathologist.com) – and let's get through the busy times together.

Michael Schubert
Editor

Reference

1. *KL Martin, ML Koval, "Medscape Pathologist Lifestyle, Happiness & Burnout Report 2021" (2021). Available at: https://wb.md/39NQgDb.*

Contents



On The Cover

A stylized representation of human anatomy

the Pathologist

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

General enquiries
www.texerepublishing.com | info@thepathologist.com
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Credit: McKinsey/Rawpixel.com

A (Bio)Sense of Hope

Biosensing technologies may improve point-of-care testing for neonatal sepsis

Sepsis is one of the leading causes of neonatal mortality across the world – resulting in around one million fatalities every year (1). Catching the infection early is crucial for effective management and improved outcomes – but many patients in developing countries lack speedy access to healthcare.

Point-of-care testing (POCT) should, in theory, enable healthcare professionals to rapidly detect and diagnose sepsis following inflammation. Current methods, however, rely on a single biomarker – a clear gap in the testing landscape. Now, a collaborative team of researchers has reviewed the latest diagnostic advancements in POCT for neonatal sepsis and the role biosensing may play in enabling rapid response.

Routine blood culture techniques can take two to five days to return results, during which time infections can worsen while infants are treated with unnecessary antibiotics – fueling the spread of antimicrobial resistance. PCR testing and mass spectrometry yield faster results, but sacrifice high specificity and cannot distinguish between viable and nonviable pathogens. The authors note that a combination of methods may alleviate each technique's weaknesses for diagnosing sepsis – but what about biosensors?

In the review, the authors discuss the potential of electrochemical sensors; the size, stability, and high binding affinity of aptamers (single-stranded nucleic acid probes); the high sensitivity and low limits of detection of sensors based on surface plasmon resonance; and the opportunity inherent in microfluidic devices and chip-based sensors that can detect bacterial and blood cells in patient samples.

What did they conclude? The team suggest that an integrated approach combining multiple techniques on a single platform may be best – hybrid biosensors that can rapidly detect multiple biomarkers or parameters from small samples. "Integrated POC-based diagnosis will help reduce detection time considerably and thus translate diagnosis from bench to the bedside," said lead author Anupam Jyoti (3). "An efficient POC sepsis diagnostic platform could expand health care access and impact populations worldwide."

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1. *World Health Organization (2017). Available at: https://bit.ly/3yWN1Uc.*
2. *A Jyoti et al., Clin Chim Acta, 521, 45 (2021). PMID: 34153274.*
3. *Shoolini Team (2021). Available at: https://bit.ly/3nvt6dd.*

TIMELINE

A Brief History of Breast Cancer

Reflecting on the key milestones toward improved patient outcomes

1882
William Halsted performs the first radical mastectomy

1959
Robert Egan publishes the results of his research into a method of screening mammography

1969
Dedicated mammography units become available for use worldwide

RESEARCH ROUNDUP

The latest research in pathology and laboratory medicine

Oncotarget: Acquired

Though human papillomavirus (HPV)-related oropharyngeal squamous cell carcinoma is on the rise, palliative treatment is still the norm. However, researchers have developed a new droplet digital PCR-based assay to detect HPV16 circulating tumor DNA and found that long-term changes to HPV16 ctDNA can predict treatment response earlier than standard imaging (1).

Reservoir Cells

TCF1+ tumor-specific CD8+ T cells have been found in lung tumors throughout their development (2). Though most intratumoral T cells change with tumor progression, many tumor-specific CD8+ T cells found in tumor-draining lymph nodes were stable over time, regardless of changes within the tumor microenvironment.

Photo Finish

Using photoimmobilized proteins, researchers have developed an automated microarray diagnostic system for detecting SARS-CoV-2 protein-specific antibodies (3). The test yielded superior sensitivity to conventional chromatography and demonstrated its usefulness for rapid serodiagnosis and immune status assessment of viral infectious diseases.

Safety Assurance

Use of organs donated by people with HIV to recipients with HIV is increasing – and a new study provides some reassurance when it comes to resistance risk (4). The researchers found that, though HIV drug resistance mutations are common, resistance that could affect integrase strand transfer inhibitor-based regimens is rare.

Face-to-Face

A new machine learning facial analysis tool may detect risk of genetic syndromes in children with an average accuracy of 88 percent (5). Accuracy was higher in white and Hispanic children than in Asian and African children; however, it remained at 82 percent or higher for all groups.

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3. *H Kashiwagi et al., B Chem Soc Jpn, [Online ahead of print] (2021).*
4. *WA Werbel et al., Clin Infect Dis, [Online ahead of print] (2021). PMID: 34453519.*
5. *AR Porras et al., Lancet Digit Health, [Online ahead of print] (2021). PMID: 34481768.*

CRISPR in the Maternity Clinic

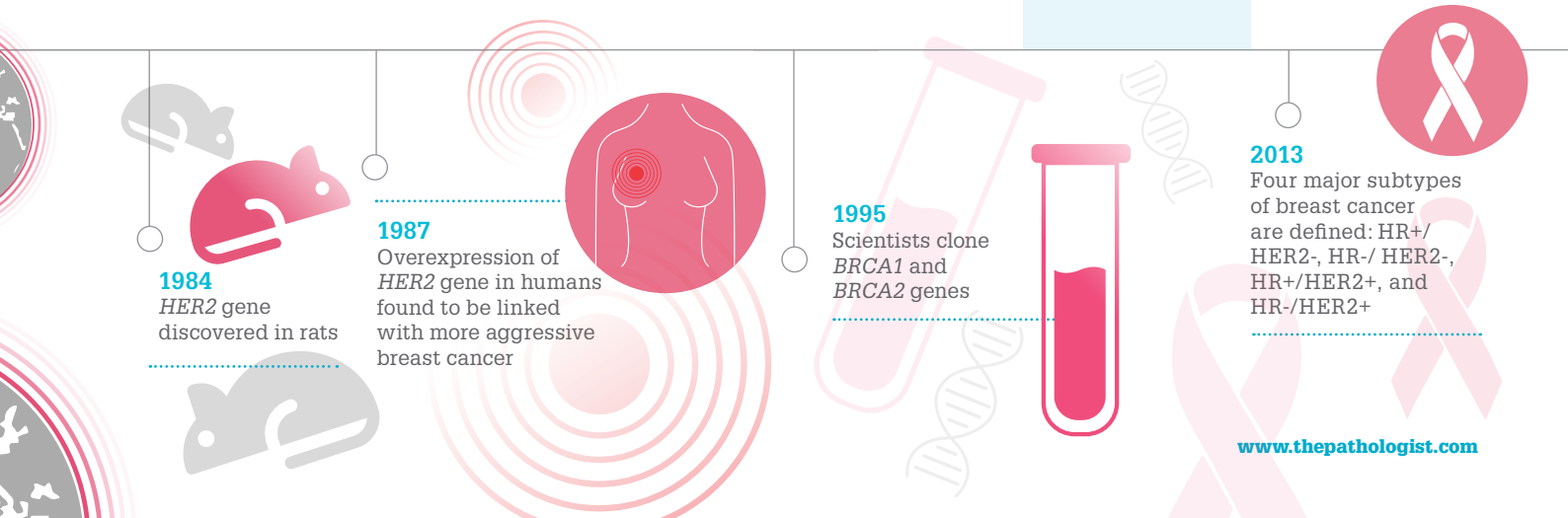
A CRISPR-based assay could improve pre-birth screening for group B *Streptococcus*

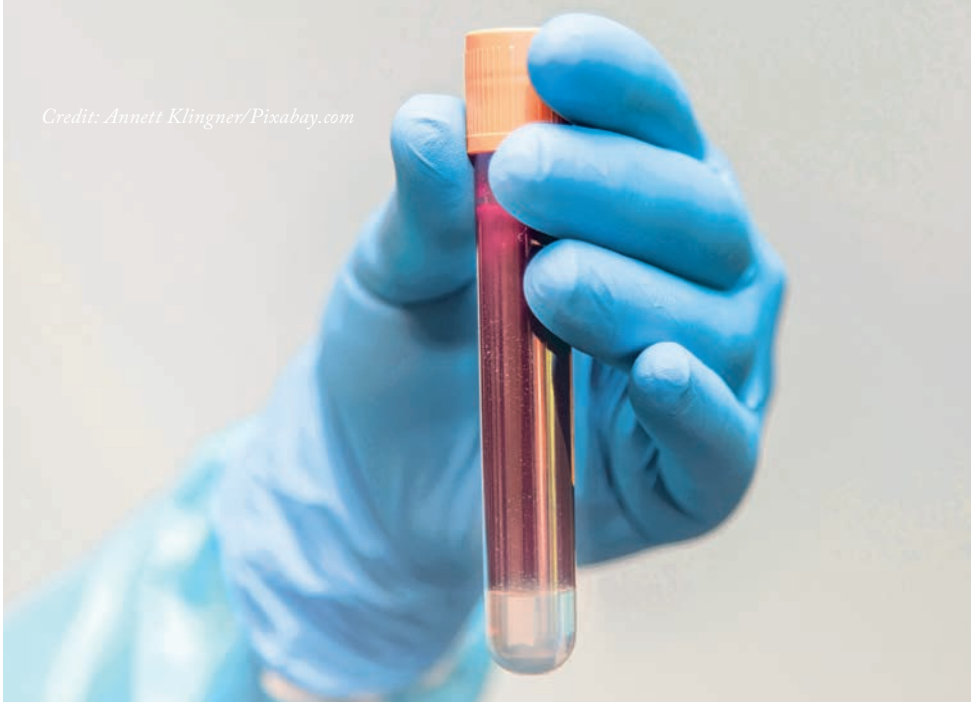
In the final weeks of pregnancy, most expecting mothers are screened for group B *Streptococcus* (GBS) colonization. Why? Because, when transmitted to a baby during birth, the common infection is one of the leading causes of neonatal illness and death – and easily prevented with the use of prophylactic antibiotics.

But screening may be unreliable because traditional culture-based methods take time, meaning that they must be performed several weeks before birth, when predictive values are lower. A new assay, CRISPR-GBS, uses CRISPR/Cas technology to offer a rapid point-of-care test for GBS that can help doctors determine which patients require prophylaxis (1). The test demonstrated high sensitivity (≥94 percent), short turnaround times (<1.5 hours), and the ability to identify even GBS cases deemed negative using culture-based methods, PCR testing, or both. Next stop? A larger, multi-center study that tests the assay's performance in a variety of clinical settings.

Reference

1. *L Jiang et al., Emerg Infect Dis, 27, 2379 (2021). PMID: 34424183.*




Credit: Annett Klingner/Pixabay.com

Blood-Based Biopsy

A new liquid biopsy approach makes cancer diagnosis in high-risk patients easier and more accurate

In patients with inherited conditions such as neurofibromatosis type 1 (NF1), tumors are a frequent occurrence. Although many of these tumors are benign, some can turn malignant – but there's no easy way to tell which tumors do this and when. To address this gap, Aadel Chaudhuri and colleagues at the National Cancer Institute and Washington University School of Medicine have developed a new blood test that could free NF1 and other cancer-predisposed patients from painful biopsies and extensive imaging procedures (1).

How will the new test affect diagnostic professionals? "In the future, we see our research improving clinicians' ability to detect and track cancer in high-risk patients predisposed to the disease, such as NF1 patients at risk for malignant peripheral nerve sheath tumors (MPNSTs). One could envision our test being run routinely in pathology labs to track high-risk individuals at each clinic visit, with pathology results integrated with the clinical picture and radiology results to inform decision-making and tumor board discussions."

But the development process was not entirely smooth sailing; Chaudhuri and his colleagues encountered several challenges. When they first realized that a standard targeted hybrid-capture approach wouldn't work well for NF1 MPNST due to the relatively low burden of single-nucleotide variant hotspots, they shifted to a low-pass whole genome sequencing approach to detect and track copy number aberrations such as aneuploidy – but even that approach was not sensitive enough.

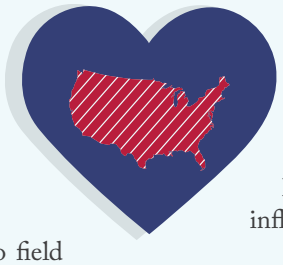
"We then observed that MPNST patients have shorter cell-free DNA fragment sizes than their plexiform neurofibroma precursor counterparts," Chaudhuri says. "Applying cell-free DNA selection for short fragment sizes and then performing genome-wide copy number analysis yielded the sensitive, specific approach we showcased in our paper for distinguishing MPNST patients from those harboring only the benign precursor lesion. We also showed that our test enables precise tracking of MPNST tumor burden, including the detection of minimal residual disease in plasma prior to radiographic recurrence." Taken together, the results suggest that plasma cell-free DNA analysis in NF1 patients has the potential to facilitate early detection of MPNST, which would enable earlier intervention and improve patient survival.

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

Diversity in DNA

Insight into coronary heart disease and epigenetic changes across genetic populations

Risk of coronary heart disease can vary between genetic populations – and now, evidence from the Strong Heart Study is providing insight into the association between epigenetic factors and heart disease across these groups (1). Researchers analyzed each participant's genome for blood DNA methylation and found 505 differentially methylated positions associated with coronary heart disease risk in American Indian adults.



"It can be challenging to do field research with remote population groups that don't have easy access to hospitals and clinics, so they are often left out of research projects like this," said senior author Shelley Cole (2). "The Strong Heart Study is providing extremely valuable insights for the participating tribes as well as for the broader global community about how environmental factors influence our health."

References

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2. *Texas Biomedical Research Institute (2021). Available at: https://bit.ly/3hugtv3.*

Admiring the Cellular Landscape

"Created for Cell Signaling Technology, Inc. and inspired by the stunning art of David Goodsell, this 3D rendering of a eukaryotic cell is modeled in Molecular Maya using X-ray, nuclear magnetic resonance, and cryo-electron microscopy datasets for all of its molecular actors. It is an attempt to recapitulate the myriad pathways involved in signal transduction, protein synthesis, endocytosis, vesicular transport, cell-cell adhesion, apoptosis, and other processes. Although dilute in its concentration relative to a real cell, this rendering is also an attempt to visualize the great complexity and beauty of the cell's molecular choreography."

Interested in seeing more? Interactive versions of parts of this landscape can be explored at: tp.txp.to/cst-land

By Evan Ingersoll, Scientific Animator, and Gaël McGill, Founder and CEO, Digizyme, Brookline, Massachusetts, USA

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

QUOTE of the month

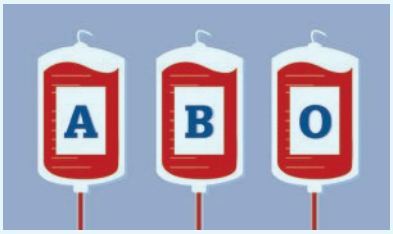
"Connecting students to information is key. Did you know there are four different programs of loan repayment for individuals who pursue and practice forensic pathology? Two of those pathways are also open to the rest of pathology. Debt should not deter people from their passions. Positive exposure experiences are only going to happen through the action of the pathology community. Talk with high school, college, and med students. Support pathology interest groups. Be a direct mentor to potential candidates. Role models matter, but they start with you."

Dan Milner (@damilnermd)
Read the original tweets here:
tp.txp.to/milner-tweet1
tp.txp.to/milner-tweet2

The O Advantage

Genetic blood group testing provides an indicator of people's cardiovascular disease risk

The *ABO* gene – consisting of three major alleles: A, B, and O – determines a person's blood group. Previous studies have focused on the link between blood groups and risk of disease; now, researchers at Uppsala University have revealed an association between ABO genotypes and cardiovascular disease risk (1). Instead of using traditional blood tests, they genetically analyzed patient samples to identify the variant inherited from each parent. Patients with two copies of A, B, or AB were found to have twice as high a risk as patients who had at least one O allele.



"This is not detected in a regular blood test, since both A and B mask the O gene. A person's genetic variants play a big role in the risk for cardiovascular diseases," said first author Julia Höglund (2). "If this was the standard method used with patients, it would significantly improve the ability to find high-risk patients."

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Journey into the Blue

The chemical, pathological, and emotional impact of the world's favorite color

Science journalist and molecular biomedicine specialist Kai Kupferschmidt has an unusual fascination: the color blue. For him, the color holds many mysteries – especially in living nature, where it is among the rarest of hues. To find out more, Kupferschmidt dove deep "into the blue," unearthing its most unusual presentations – including those in chemistry, biology, and beyond – and published them in the book Blue: In Search of Nature's Rarest Color.

What was the most interesting fact you encountered while researching the book?

There are so many! I think what most fascinates me are the connections that become apparent between things that seem so unrelated. One example: alchemists accidentally discovered a new blue pigment named "Prussian blue" in the early 18th century. It quickly spread around the world and was used in many masterpieces (for instance, Van Gogh's Starry Night, Hokusai's Great Wave Off Kanagawa, and Picasso's blue period). But scientists investigating the chemical structure of this pigment derived a new compound called prussic acid – hydrogen cyanide – the eventual basis of the Zyklon B used in German extermination camps.

At the same time, Prussian blue itself is today recognized as an essential medicine that can be used to treat radioactive cesium poisoning.

How do you want the reader to feel as they are reading Blue – or when they've read the final page?

I hope that they will take a sense of joy and wonder from it – and, more than anything, a sense of curiosity about the world. We all get so used to the beauty and improbability of all that is around us. Writing the book and understanding what is involved in all those blues we see certainly made me look at the world with different eyes. I really hope readers will have the same experience.

The sections – Stones, Seeing, Plants, Speaking, Animals – guide readers through Blue. But what were the main challenges in pulling together a book on a single color from so many different angles?

Blue is such a huge subject that I really had to let go of the desire to cover everything. And that was really hard in the beginning but, at some point, I learned to simply follow my curiosity. The book is just one path through a huge garden filled with stories and knowledge about blue. The simple, clear structure I adopted helped ensure that, even though I was wandering, I would never get entirely lost.

What story within Blue's pages will most fascinate a pathologist?

I've always been fascinated by the poison tetrodotoxin and knew all about the pufferfish and how it is prized as a delicacy in Japan. But there is another deadly animal called the blue-ringed octopus that uses the same toxin. To warn its enemies, it can make the blue rings on its skin pulsate. It's beautiful and terrifying; if I were a pathologist writing mystery novels, I would definitely include it in my next book.

On a chemical note, one of my favorite stories is about the blue of the cornflower. In 1913, Richard Willstätter isolated the molecule at the heart of it and called it "cyanidin." Two years later, he isolated the red of red roses and it turned out to be the same molecule. Today, we know that the cornflower does a lot of crazy chemistry to appear blue; it actually combines six molecules of cyanidin with six co-pigments and arranges the whole thing around metal ions like spokes on a wheel. And we really only got final confirmation of this with X-ray crystallography done in 2005!

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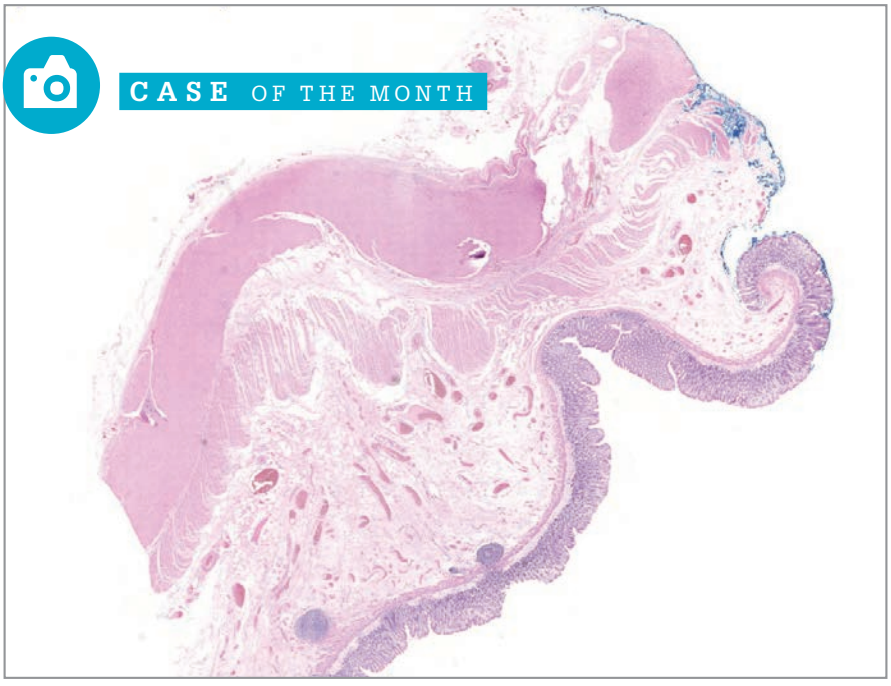

A 57-year-old man living in Brazil had a history of chronic intestinal obstipation for over five years. Following serologic and radiologic workup, he underwent resection of the sigmoid and rectum. A 20x225.5 cm segment of markedly dilate large bowel was submitted for histopathological evaluation.

Which of the following infectious agents is the most likely cause of these pathologic changes?

a) Hymenolepis nana
b) Schistosoma mansoni
c) Schistosoma haematobium
d) Strongyloides stercoralis
e) Trypanosoma cruzi

Answer to last issue's Case of the Month…
a) *Malignant PEComa*

Histologic sections demonstrate a mesenchymal neoplasm comprised of polygonal perivascular epithelioid cells with granular, eosinophilic-to-clear cytoplasm and large vesicular nuclei with macro-nucleoli. Background showed areas of hemorrhage, focal spindle cell morphology, rare cells with adipocyte morphology, many multinucleated giant cells with pleomorphic nuclei, scattered highly pleomorphic cells, and a focal area of coagulative necrosis. No mitotic figures were identified. The epithelioid cell component was approximately 90 percent of the tumor volume. Immunostains showed that the epithelioid cells were positive for MART-1 and HMB-45 and focally positive for actin. Desmin was positive in rare cells. The epithelioid cells were negative for pankeratin, AE1/AE3, Cam 5.2, cytokeratin 7, epithelial membrane antigen (EMA), CD10, RCC, CD117, S-100, PAX8, GATA3, and calretinin. Multinucleated cells were highlighted by CD68 and CD163 stains. FISH was negative for *TFE3* translocation.

The PEComa family includes angiomyolipoma (AML), lymphangiomyomatosis of the lung, the clear cell "sugar" tumors of lung and other organs, and a rare group of morphologically and immunophenotypically similar tumors occurring throughout the body in soft tissues, viscera, and bones. Most PEComas are benign and predominantly affect women. Folpe et al. described the criteria for classifying PEComas into benign, uncertain malignant potential (size >5 cm or nuclear pleomorphism/multinucleated giant cells only) and malignant (two or more of: size >5 cm, infiltrative, high nuclear grade and cellularity, mitotic rate ≥1/50 HPF, necrosis or vascular invasion).

Renal AMLs account for 1 percent of renal tumors and are commonly associated with tuberous sclerosis complex. Apart from the classic variant, other rare morphologic variants include epithelioid, atypical, oncocytic, clear cell, and cystic. This case demonstrates a morphologic and immunohistochemical neoplasm with melanocytic and myogenic phenotype and >2 criteria for malignant PEComa, supporting a final diagnosis of malignant PEComa.

Submitted by Swati Satturwar, Genitourinary Pathology Fellow, and Rajiv Dhir, Executive Vice-Chair, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, USA.

Further Reading at: tp.txp.to/com-34

To register your guess, please go to http://tp.txp.to/1021/case-of-the-month
We will reveal the answer in next month's issue!

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

There's more to resectable NSCLC than meets the eye

EGFR mutation testing can help identify the disease driver and guide adjuvant treatment decisions in certain patients with NSCLC[1,2,*,†]

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*Test for EGFR mutation on surgical tissue or biopsy in resectable stages IB-IIIA NSCLC.
†The NCCN Guidelines for NSCLC provide recommendations for certain individual biomarkers that should be tested and recommend testing techniques, but do not endorse any specific commercially available biomarker assays or commercial laboratories.

References: 1. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Non-Small Cell Lung Cancer V5.2021. © National Comprehensive Cancer Network, Inc. 2021. All rights reserved. Accessed June 17, 2021. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way. **2.** Galvez C et al. *Oncotarget.* 2020;11(21):1953-1960. **3.** Cheema PK et al. *Curr Oncol*. 2017;24(1):16-22. **4.** Aisner DL et al. *Am J Clin Pathol*. 2012;138(3):332-346.

Precision Medicine & Nurse Education

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In My View

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

We Need to Talk About Clinical Representation

Alzheimer's research should benefit all, regardless of ethnicity or race

By Renã Robinson Associate Professor of Chemistry, Dorothy J. Wingfield Phillips Chancellor's Faculty Fellow, Department of Chemistry, Vanderbilt University, and Department of Neurology, Vanderbilt University Medical Center; Leader of Outreach, Recruitment, and Engagement, Vanderbilt Memory and Alzheimer's Center; Training Faculty, Vanderbilt Brain Institute, Vanderbilt Institute of Chemical Biology, Vanderbilt University, Tennessee, USA; NOBCChE President-Elect

As of today, there is no cure for Alzheimer's disease (AD). Historically, Black people and other ethnic minorities have been underrepresented in clinical research. We have a duty to ensure that our greatest advances in scientific research are for the benefit of all. These statements, at least in my view, are simple facts. Therefore, excluding minority groups from Alzheimer's research is not only a disservice to them, but to the entire population, because it means we do not have a complete understanding of the disease. If we want to get serious about finding a cure for AD, we need to ensure we're including representative samples in our clinical studies.

Of course, this holds true across many different research areas, but our group's focus – and my expertise – is in AD. In recent months, we've focused a lot of effort on understanding the proteomic and lipidomic influences of AD across underrepresented groups – and it has become apparent that we have many challenges still to overcome in ensuring that clinical research is truly representative.

First, we need to ensure that everyone values true representation in their study populations. This may seem obvious to some, but the lack of diversity still seen in many cohorts would suggest that not all research communities agree. To start with, we should look at cohorts' diversity and ask whether they are inclusive. Some progress has been made with certain funding agencies, such as NIH, recognizing the importance of this work and trying to move toward equity in research – but there is still much more to be done to understand how systemic racism impacts our ability to perform outstanding clinical research.

I believe it is imperative that diversity, inclusion, and equity are built into the peer review process. We might have trainees from diverse backgrounds, but we need to ensure that work that is creating inclusive studies is valued and supported. We also need to recognize that there is some way to go to rectify issues of the past (for instance, current discrepancies with the level of funding and support available to researchers

"We might have trainees from diverse backgrounds, but we need to ensure that work that is creating inclusive studies is valued and supported."

interested in doing diversity and inclusion work). To support this effort, I believe there should be more accountability within these processes; we should be asking people to justify the lack of diversity in their cohorts and to contribute to making their studies more representative.

Second, even if you do want to have diverse cohorts, you need to identify enough biospecimens from minority groups. I'm involved in encouraging research participation among different population groups – African Americans in particular. We need to improve educational awareness and share with our communities the importance of research overall, but especially with respect to disparities faced by particular communities.

One way we are trying to do this is through sharing positive messaging around research participation within the African American community. Until now, we've focused mostly on negative messaging and the barriers to research and not on facilitating that research. To counteract this, we try to capture authentic (and positive) messages from people who have participated in studies, and highlight why they did so. We then include these stories in resources that are handed out at various centers recruiting participants for clinical research. We are also running a social media campaign and have created videos that can be used in outreach events, community settings, doctors' offices, and more. The idea behind all of this is to see whether this particular approach to storytelling is more effective than traditional (passive) approaches to recruiting people.

Clearly, much work still remains to ensure that the research community is undertaking truly inclusive studies and to fully understand the disparities present in AD. It's simply not possible to see the complete picture of this disease if we don't understand how it works – in everyone.

Success Through Centralization?

The path to realizing digital pathology's true value

By Geoffrey Metcalf, VP Clinical Diagnostics; Roberto Gianani, Medical Director and Chief Medical Officer, Flagship Biosciences; Meredith James, Chief Operating Officer, Flagship Biosciences, Broomfield, Colorado, USA

Digital pathology's benefits have been widely discussed – from alleviating staffing shortages to accelerating turnaround times; from increased consistency and accuracy to innovative teaching tools. But, in practice, those benefits have proven elusive. Why?

At its most intensive implementation, digital pathology has the potential to support primary clinical diagnosis. At a less intensive level, it can be used in targeted precision medicine applications, particularly in the area of immunohistochemistry (IHC) tissue diagnostics. In all cases, though, the burdens of digitizing often outweigh the benefits – mainly because responsibility for the system's performance rests with the local laboratory. Though many companies have created effective tools for managing slide images and streamlining workflow, they have done little to relieve the most time-intensive burden: the creation, validation, and maintenance of image analysis tools and diagnostic algorithms.

To comply with Clinical Laboratory Improvement Amendments (CLIA) regulations regarding laboratory-developed tests (LDTs), an artificial intelligence (AI) diagnostic algorithm must be thoroughly tested and maintained. Quality assurance procedures must be created and users provided with regular, comprehensive training. Digital pathology equipment must be purchased and the informatics expertise needed to integrate it into laboratory and hospital information systems must be established. The overhead necessary to support these activities is prohibitive for most laboratories in the current reimbursement environment. A potential solution: AI algorithms offered as LDTs on a national scale. To take advantage of this capability, clinical laboratories would send slides or digital images to a service provider and receive a clinically appropriate diagnostic result. This would leverage current digital pathology product strengths while mitigating the challenges associated with DIY solutions.

For instance, local laboratories have limited ability to design and execute a clinical study of sufficient power to verify and validate a lab-developed algorithm in line with CLIA requirements. Based on patient volumes at a typical hospital or regional laboratory, the investment of time and money needed would be prohibitively expensive. Leveraging national economies of scale, a central service provider could develop an algorithm and test it in a clinically robust study that could be published in leading peer-review journals available to the entire medical community. This approach would not only yield a clinically superior product, but also eliminate the "black box" nature of DIY algorithms. It would also eliminate the organizational and financial challenges associated with

DIY digital pathology solutions. Creating and maintaining image-based AI solutions is costly, time-intensive, and requires informatics expertise not every organization has. Testing them requires expertise in study design and access to clinical samples, which may be difficult or expensive to procure. And, as digital imaging equipment and staining technologies evolve, algorithms must be re-evaluated and updated to keep pace. Quality assurance procedures must be created and maintained and employee training programs implemented. All of this would need to be achieved within the current clinical diagnostic reimbursement environment. Without additional funding, it is not surprising that few laboratories can generate the financial ROI to justify a DIY digital pathology approach.

A centralized digital pathology service offered on a national scale would offer crucial additional benefits. For instance, purchasing efficiency is critical – so this approach enables the creation of a family of solutions local laboratories can procure efficiently. Most laboratories prefer to consolidate their purchases through as few vendors as possible; a centralized digital pathology provider could offer a "one-stop shop."

The provider would also be able to amass a powerful database that could be leveraged in support of clinical studies. A key characteristic of image analysis is that it generates large amounts of data. This data could support sophisticated clinical studies impossible to implement at the local level. Additionally, the data could be used in ways not otherwise possible, such as more robust evaluation of cut points and treatment decisions. For example, finding strong correlations between patient response to immunotherapy and currently available diagnostic data has been challenging. When studying such a complicated and dynamic clinical question, the larger the database the better. Imagine if a centralized provider – for instance, of PD-L1 AI solutions – stored the de-identified data from all of the samples it processed over time. Such a database would house an extensive range of clinical diagnostic data for tens of thousands of patients. When merged in a research setting with patient outcome data, it could yield true medical breakthroughs.

The final advantage to using a centralized send-out digital pathology solution is image storage and technical infrastructure. To achieve the degree of accuracy required for an AI solution to be practical across a wide range of samples, the image and resulting data files must be highly detailed, nuanced, and layered. This leads to not only large files that need to be carefully tracked, stored, and backed up for lengthy periods, but also millions of small files that must be effectively managed. This demands vast storage capacity and a highly redundant and available file system built around these specific needs. It also requires uniquely optimized, high-performance computational power to achieve the desired output in a viable amount of time. Any of these factors alone would be a major endeavor for a typical laboratory – but combining them into a cohesive, secure, compliant, and reliable ecosystem is an immense, complex undertaking. In my view, it is only by offering centralized solutions that we can get all labs on board with digital and computational pathology.

A local laboratory might be able to create an AI solution for a single indication, such as NSCLC, but this solution would not apply to other PD-L1 indications. It would probably not be wise for a laboratory to invest the time and money to develop a solution that is only applicable to a portion of its needs. Only a centralized service solution would deliver the economies of scale needed to support the creation of a family of PD-L1 solutions to meet the operational needs of local laboratories. And only a centralized service could promptly update its capabilities to keep up with the evolution of clinical care. Quickly adding new indications, stains, or digital scanners is only feasible for a large service solution provider.

In the immuno-oncology field, PD-L1 reactivity is only a portion of the clinical picture. Immunotherapy's effectiveness depends on both the PD-L1 reactivity of the tumor cells and the immune microenvironment. Current tests provide only a PD-L1 result because it is relevant in selecting FDA-approved therapies and it is the only reimbursable result. The fact that additional information about the tumor microenvironment (TME) is not typically available does not mean that it is not clinically relevant; it only means that the additional IHC stains required to identify macrophages and lymphocytes in the TME are not reimbursed.

What if the TME could be assessed without any additional time or cost on the part of the clinical laboratory? Though not commercially realistic using manual review techniques, an advanced AI algorithm could achieve this goal. AI is far superior to the human eye in detecting patterns that allow cells to be identified and classified across an entire tissue sample. What if a digital pathology solution could not only accurately detect PD-L1 reactivity, but also count and locate macrophages and lymphocytes and assess levels of tissue necrosis? Would an oncologist treating challenging patients benefit from this information? Although medical decisions must be based on clinically rigorous study data, the migration of ideas from research to FDA-cleared treatment typically takes decades. Oncologists perpetually find themselves in a grey area between cutting-edge research and fully validated, FDA-cleared treatments. The pathologist's goal is to provide treating physicians with the facts and tools they need to manage their patients. Artificial intelligence could be an important tool in fulfilling that mission – and only a centralized digital pathology provider would have the expertise, reach, and economies of scale to leverage that capability.

Kindling a Passion for Pathology

The importance of pathology education

By E. Blair Holladay

It's commonly estimated that only three percent of medical students go into pathology. There are many reasons why such a small number of students choose pathology – but one of the biggest influences on a medical student's choice of discipline is exposure.

And pathology isn't getting enough of it.

Medical students are simply not offered the same introduction or exposure to the laboratory sciences as they are to other disciplines. Medical schools' restructuring of curricula has come at the expense of pathology and laboratory sciences. As exposure to these disciplines decreases, it creates a ripple effect down the pipeline of medical students. The AAMC's 2020 Report on Residents shows that there are 2,265 active anatomical and clinical pathology residents (1). That doesn't seem like a small number, but compared with residents in surgery (over 9,000), family medicine (over 13,000), or internal medicine (over 27,000), it's almost unfathomably small – especially when you consider how much of a patient's medical journey pathologists are responsible for and how heavily pathology and laboratory medicine influence patient care.

The lack of inclusion of pathology in medical training goes beyond residency. Follow that path further and limited exposure to pathology studies in medical school curricula has an extensive detrimental effect on healthcare overall. We are currently facing a shortage of pathologists and the ever-present retirement cliff threatens our profession's sustainability. Without exposure to pathology and laboratory medicine, medical schools are effectively cutting off medical students' potential to discover what may be a prime path forward in their careers – and creating a dearth of pathologists. And without pathologists, healthcare systems would be in shambles, having lost the foundation upon which so much of patient care is built.

It's important to recognize that pathology education doesn't stop once medical students leave the confines of classrooms or residents end their training rounds. Not only do we, as pathologists and medical laboratory scientists, need to pursue our own continuing educational path, we also need to adopt the role of educator to those outside the laboratory. Extending our education to improve skills and services and to reinforce the integral role we play in patient care is a career-long journey.

Pathology needs to be included in medical school curricula – or even well before medical school – because, without it, the core of healthcare is missing from education. More importantly, for today's medical students and those to come, it needs to be reintroduced and better positioned within existing curricula. To ignite the fire of passion medical students seek when considering their careers, we must start by emphasizing the magnitude of pathology's impact on healthcare. The importance of the laboratory cannot be undermined – and it cannot be underscored enough.

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EGFR Exon 20 Insertion: A New Player in the NSCLC Landscape

The success of precision medicine relies on choosing the right targeted therapy for each patient. However, these therapeutic decisions depend on careful, effective molecular profiling. How to best address clinically relevant biomarker status? What technology should we use? Developments in lung cancer management may provide answers. Here, Luca Quagliata (Vice-President and Global Head of Medical Affairs, Clinical NGS and Oncology Division, Thermo Fisher Scientific) speaks to Parthiv Mahadevia (Senior Global Medical Affairs Leader, Janssen R&D).

LQ: What kind of unmet needs do you see in the non-small cell lung cancer (NSCLC) field?

PM: Many NSCLC patients have oncogenic driver mutations in the epidermal growth factor receptor (EGFR) gene, which cause EGFR to constantly mediate signals that drive malignant transformation. Most such mutations are deletions in exon 19 or L858R substitution mutations in exon 21 (see Figure 1). The next most common EGFR mutations are insertions in exon 20. This relatively understudied group is important because they are not only oncogenic but are also difficult to inhibit with currently available EGFR tyrosine kinase inhibitors (TKIs). There's no good standard of care in such cases; doctors default to older approaches, such as platinum chemotherapy. Consequently, these patients have a median overall *survival of ~16 months, compared with ~40 months for patients with exon*default to older approaches, such as platinum chemotherapy. Consequently, these patients have a median overall survival of ~16 months, compared with ~40 months for patients with exon 19 deletions or L858R substitutions. In brief, patients with exon 20 insertions aren't benefiting from personalized therapies – and that's a serious unmet need.

LQ: Janssen is addressing this unmet need with the breakthrough product, amivantamab (1). Amivantamab was approved in May 2021 by the US FDA for treatment of EGFR exon 20 insertion NSCLC that progressed on prior platinum-based chemotherapy. For this underserved group of patients in the NSCLC community, its approval could have a huge impact – no longer will they feel like EGFR outcasts!

And now, focusing on mutations, can you help us understand the difference between TKI resistance-associated EGFR mutations, such as T790M, and exon 20 insertions?

PM: The difference is that exon 20 insertions, like exon 19 deletions and L858R substitutions, are driver mutations. Resistance mutations, by contrast, occur later in tumor evolution, when the selective pressure of TKI therapy favors outgrowth of resistant clones – only tumor cells with resistance mutations can survive and proliferate in a TKI environment. So it's important to test for those types of genetic changes, including T790M, which is one of the most common resistance mutations to first- and second-generation TKIs. More recently, with osimertinib, a third-generation TKI, being used, new resistance patterns such as C797S and MET amplifications are common.

LQ: How should we test for these changes? What is your view on single-marker tests versus multiplex panels?PM: There are many mutations of interest – not just in EGFR but also in, for example, KRAS and ALK. Full genomic testing, as early as possible, is essential if we are to rationally choose optimal therapy. It makes sense, therefore, to opt for next-generation sequencing (NGS), which can detect all relevant genetic changes. Some use real-time PCR, but our analysis (2) showed that PCR detects only about 50 percent of the exon 20 insertion mutations found by NGS. We believe that is largely why exon 20 insertion mutations are currently underdiagnosed – people are using the wrong detection technology. In fact, even NGS tests can miss these mutations if the tests are improperly calibrated – you have to set them up carefully to ensure that they can detect all the different variant types. So, in addition to having the right technology, you need the right education regarding heterogeneity and presentation of exon 20 insertions. This is essential – misdiagnosis of patients can have far-reaching consequences. And remember that all patients on TKI therapy will eventually progress and require additional tests to assess resistance mutations. Biopsies from tumor tissue are best in these cases, because they permit higher sensitivity, but if that's not an option – for example, where the tumor mass is inaccessible – we can test circulating tumor DNA. But here again it is difficult to justify using any approach other than NGS.

> *"Targeting the exon 20 insertion mutations gives new hope to doctors and patients."*
> *– Parthiv Mahadevia*

LQ: So to avoid the issue of under-detecting exon 20 insertion mutations, it is critical to choose the right kind of test – and, in this context, NGS is clearly superior to PCR. Does NGS have any disadvantages?

PM: NGS turnaround times could be a drawback (although, for clarity, not all NGS

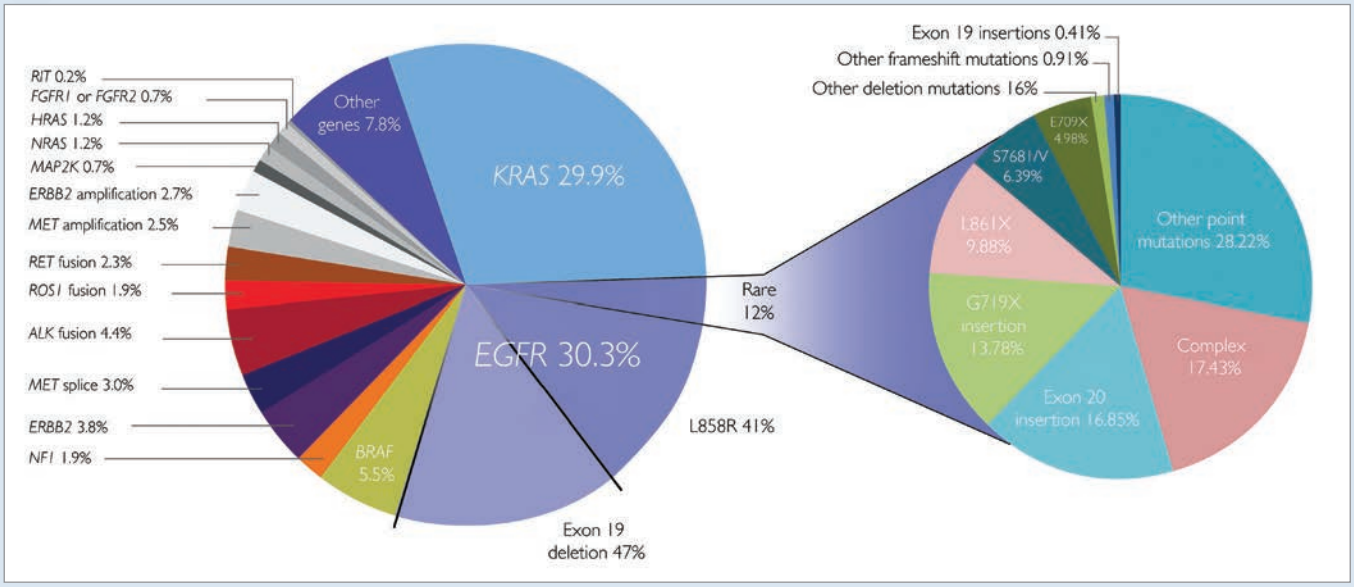

Figure 1. Mutational landscape of non-small cell lung cancer. Adapted from (3) and (4). © 2019 PT Harrison, S Vyse, and PH Huang under the terms of the Creative Commons Attribution 4.0 International Public License (3) and by permission from Springer Nature Customer Service Centre GmbH: Springer Nature, Nature Reviews Cancer, Co-occurring genomic alterations in non small-cell lung cancer biology and therapy, F Skoulidis and JV Heymach, © 2019 Springer Nature Ltd. (4).

tests have comparable turnaround times, so choosing wisely is again critical). Many NSCLC cases are diagnosed only after the cancer has metastasized; these highly symptomatic patients need to start therapy immediately, which means they need test results immediately. Unfortunately, many patients wait too long for their NGS results and must revert to the standard of care for people with unknown driver mutations – namely, platinum-based chemotherapy and immunotherapy. Consequently, when the NGS results finally come through, these patients must either finish the platinum course – which means delaying the EGFR therapy that will target their specific cancer – or switch to another therapy with different side effects. That's not the best way to manage patients; it's far better to have the NGS test results upfront.

LQ: What needs to be done to improve the situation?

PM: Education is needed to inform the NSCLC community about our new therapy (1) and how it addresses unmet needs. One barrier to amivantamab adoption is the idea that EGFR treatments have been around for years, so another EGFR therapy won't be any different. That's why we have to make clear that this new therapy targets a very specific group of patients who don't respond to standard EGFR therapies.

LQ: Yes, it is important for doctors to understand the different EGFR mutations and appreciate the importance of using the right test at the right time to ensure that patients with exon 20 insertions are never again left behind. But we should also remember that this drug is at the beginning of a journey; real-world clinical data will be of paramount importance, as there may be issues that aren't apparent in the context of a controlled clinical trial.

PM: The potential for better treatment is enormous. Not long ago, the idea of personalized medicine was just a dream. Today, we can define the genomic basis of a patient's progression and treat them accordingly. It's so impressive to see great responses to treatments that have been prescribed on the basis of genetic tests. And then, for those patients who progress, to see them switch to a different drug and respond to that treatment. By tracking each cancer's evolution and treating it with precision therapy, we are impacting many lives and helping patients to survive longer than ever before.

Thermo Fisher Scientific and Janssen Oncology have an agreement to validate the Oncomine Dx Target Test for multiple biomarkers as CDx claims in NSCLC and additional oncology indications. Earlier in 2021, Thermo Fisher Scientific filed for FDA approval of the test as CDx to identify NSCLC patients with EGFR exon20 insertions who are candidates for amivantamab.

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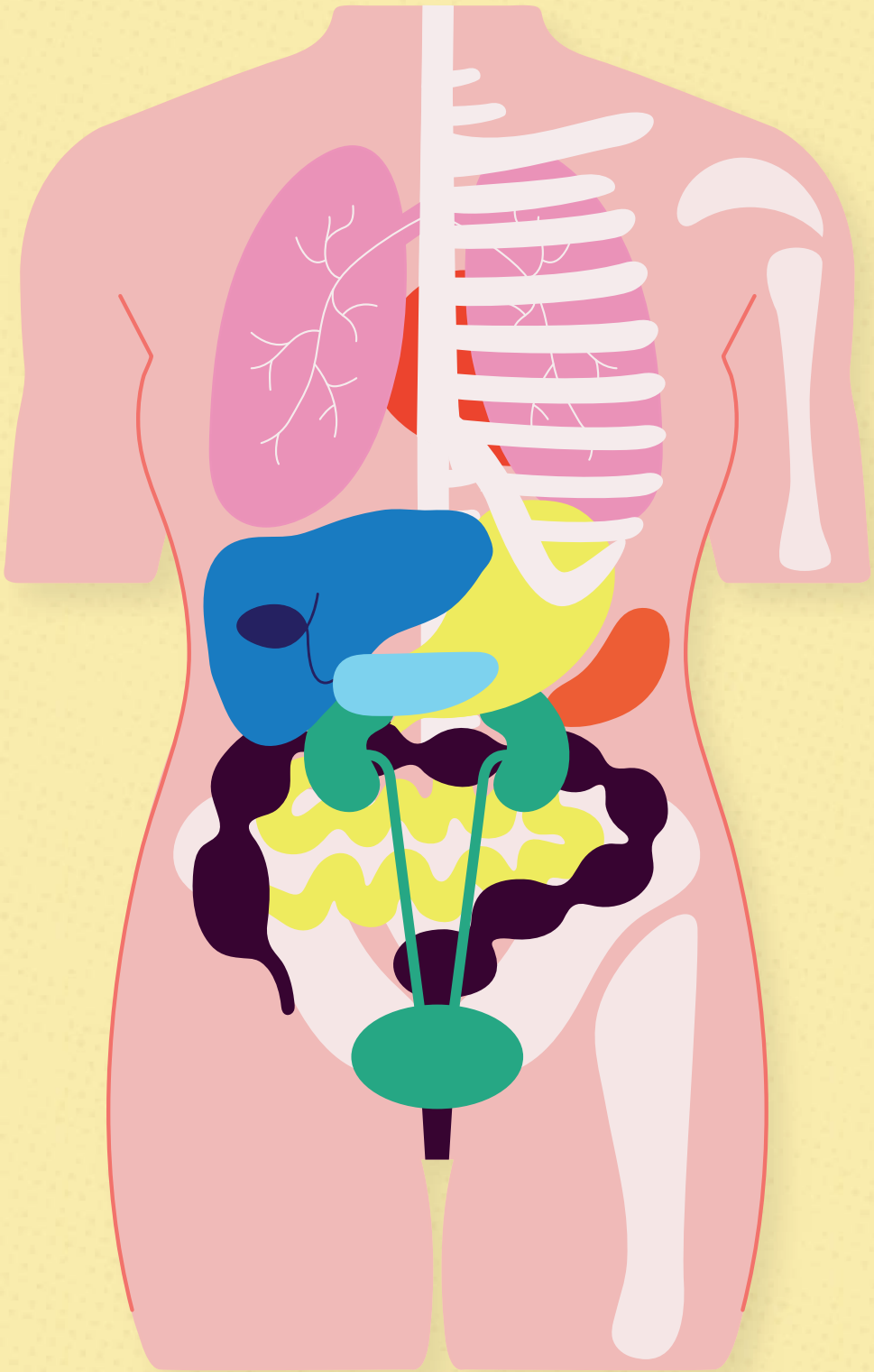
ANATOMY OF A SOCIAL MEDIA SUCCESS

Taking medical education to new heights with the Institute of Human Anatomy

An interview with Jeremy Jones, Jonathan Bennion, and Justin Cottle

Pathologists and laboratory medicine professionals have seen massive success on Twitter, with the #PathTwitter community emerging as a hub of social interaction and support. But what about social media channels outside the Twittersphere – photo- and video-based platforms that offer other communication styles for the public and healthcare professionals alike? We spoke to Jeremy Jones, Jonathan Bennion, and Justin Cottle of the Institute of Human Anatomy, who have skyrocketed the lab to social media stardom. Here, they talk about the benefits of taking medical education to Instagram, TikTok, and YouTube – and offer their tips on starting successful channels for medical teaching.



BUILDING THE BUSINESS WITH JEREMY JONES

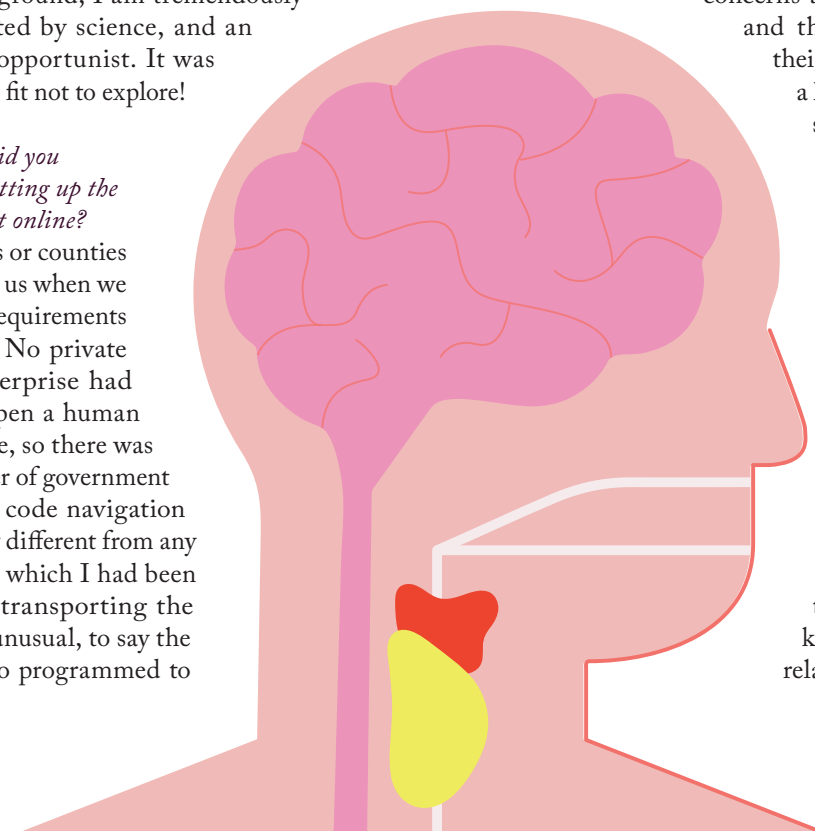
Can you give us a brief overview of the Institute of Human Anatomy?
Founded in 2012, the Institute of Human Anatomy is a unique facility specializing in the use of human cadavers as instruments for advanced anatomical education, medical device training, and prototype testing. We provide state-of-the-art education and experience for those engaged in or seeking a career that requires the study and understanding of human anatomy and physiology. Recently, we've taken a new approach to our mission of providing education to as many people as possible by distributing our content online.

What inspired you to establish the lab, particularly with a non-medical background?
My co-founding partner, Jonathan Bennion, identified the opportunity when a local massage therapy school where he was teaching anatomy lost its access to the university's cadaver lab. The students were incredibly disappointed that it would no longer be a part of their curriculum and it showed us that many practitioners in health-related professions could really benefit from the type of education we can provide about the human body. Although I have no medical background, I am tremendously curious, fascinated by science, and an entrepreneurial opportunist. It was simply too good a fit not to explore!

What challenges did you encounter when setting up the lab – and taking it online?
None of the cities or counties knew what to tell us when we asked about the requirements to open the lab. No private commercial enterprise had ever sought to open a human cadaver lab before, so there was an additional layer of government and commercial code navigation that was certainly different from any other business in which I had been involved. Also, transporting the bodies is a little unusual, to say the least. We're all so programmed to think of the deceased as being transported in either a hearse or an ambulance – it still feels a little awkward to use my pickup truck to bring our cadavers to the lab.

"MANY PRACTITIONERS IN HEALTH-RELATED PROFESSIONS COULD REALLY BENEFIT FROM THE TYPE OF EDUCATION WE CAN PROVIDE ABOUT THE HUMAN BODY."

Though we didn't start out with a specific social media strategy, we always planned to scale the business and use digital content to do so. However, we had concerns around the use of the cadavers and the respect for the donors and their families that made the process a little tricky. Even now, although social media has become a large part of what we do, we still need to develop and deliver our in-person workshops, training, and courses, and we take significant precautions regarding what we show and how we show it. We are currently working to leverage our social presence to expand into more e-commerce, art related projects and, most importantly, develop additional specialized digital courses for those looking for more specific knowledge around certain health-related disciplines.



JEREMY'S TOP TIPS

- Determine up front how social media will be leveraged. What platforms will you use, what content will get deployed on each, and for what ultimate purpose?
- Research what each platform requires to provide the best value to your audience and to your enterprise. Develop content that fits these parameters.
- Develop and keep a schedule/process and repurpose as much content as you can. Try to organize all content creation in the most efficient and beneficial manner possible.
- Research and find the right technical equipment and software needed to do the job.
- Engage with your audience as much as possible and don't be afraid to try new ideas.
- Analyze what does and doesn't work and continually optimize your workflow using that data.
- Enjoy the process and be authentic!

SOCIAL MEDIA SUCCESS WITH JONATHAN BENNION

What inspired you to take the Institute of Human Anatomy to social media?

It was always in the back of our minds to take the lab online, but there were ethical issues that we needed to consider first. We work hard to protect our donors and there's a fine line between providing education and going for shock value, which has never been our goal. We decided on a few ground rules:

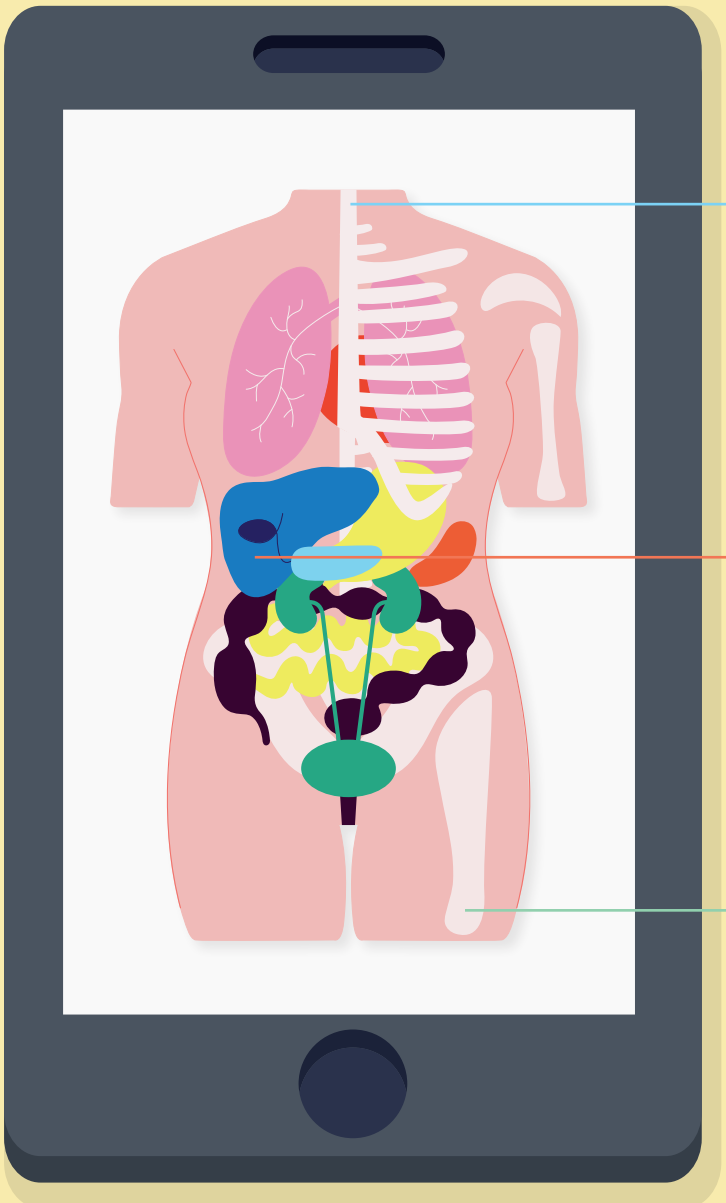
- We weren't going to show any identifying marks on bodies.
- We were going to protect identities.
- We were going to keep the organs safe and separated.

We planned out what we were okay with showing and what we wanted to restrict to in-person labs (or behind a firewall for online courses). We want to have fun in the lab – we don't want to treat it like a funeral home – but we also take it seriously, because those who donated their bodies to science have given students a wonderful anatomical gift from which to learn.

Meanwhile, we registered placeholder accounts for Instagram and YouTube and, in November 2019, Justin messaged me and Jeremy to say he had been researching TikTok and asked whether he should get on it. He uploaded a short video of the brain and, an hour later, he came back and said, "I think this video is going what you might call 'viral.'" It just kept growing and growing – so we started doing more and getting involved in other platforms. Justin really jumped into TikTok and I jumped into Instagram. They're two different animals with different demographics and, though we do keep gaining followers on our Instagram page, it didn't blow up as fast as TikTok, which now has over 7.9 million followers. We also have a YouTube channel on which we recently hit over 2 million subscribers. The best stories we hear are when people say our videos inspired them to go to medical school or pursue a degree in anatomy.

ANATOMY OF A SOCIAL MEDIA SUCCESS: IN NUMBERS

See the stats behind the Institute of Human Anatomy's social media success



TIKTOK

Follower count	**7.9** million
Average views	**400,000**
Top video view count	**26** million
Post frequency	Daily
Average video length	**25–35** seconds
Optimal video length	**22** seconds
Average watch time	**40%** of video length

YOUTUBE

Subscriber count	**2.1** million
Average views	**250,000**
Top video view count	**5,200,000**
Post frequency	Weekly
Average video length	**8** minutes
Optimal video length	**8–10** minutes
Average watch time	**20%** of video length

INSTAGRAM

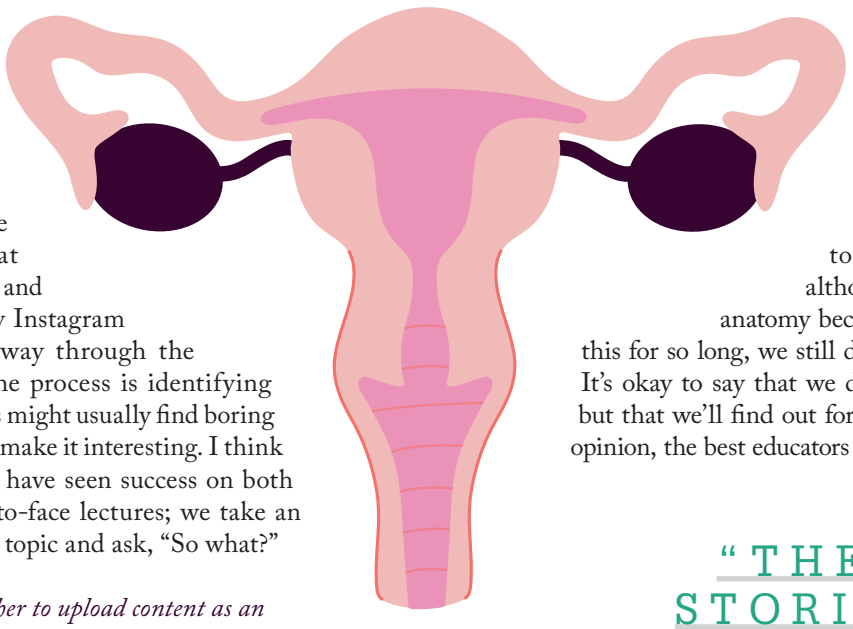
Follower count	**240,000**
Average views	**75,000**
Top video view count	**484,000**
Post frequency	Daily
Average video length	**25–35** seconds
Optimal video length	**25–35** seconds

Talk us through your process for creating videos…

From a content creation perspective, we've tried multiple different strategies – from running polls on Instagram ("Would you rather see this topic or that?") to taking inspiration from user comments. We keep a list of requests and, if a lot of people want the same topics, we bump them up to the top.

Listening to the audience helps a lot, but there have also been times when I made a video just because I thought it would be cool and it ended up being really successful. For example, just before Thanksgiving, I made a video about how much food people can stuff into their stomachs at Thanksgiving dinner – and it's our most popular video so far.

YouTube videos require by far the longest planning process. With Instagram, I just film a 30- to 60-second video, but YouTube requires us to dive into the nitty-gritty of anatomy and think about how we can make it fun. For Instagram, I remember what previous students have found interesting that could make a fun video – and I usually batch-film my Instagram videos and make my way through the list. The fun part of the process is identifying something that students might usually find boring and thinking of ways to make it interesting. I think that's why Justin and I have seen success on both social media and face-to-face lectures; we take an anatomical structure or topic and ask, "So what?"



How do you decide whether to upload content as an Instagram story, post, or reel?

Instagram has so many options. It can be fun to experiment, but it is a guessing game because, with social media, there's a level of control that you just don't have and you have to step back and accept that. From a creative perspective, it can be frustrating when Instagram changes its algorithm to prioritize different types of content, so I try to do a little bit of everything. Sometimes I create reels; other times, if I can't fit the content into 30 seconds (the maximum for a reel), I turn the content into posts (which can be 60 seconds long). I also need to start asking basic call-to-action questions at the end of my videos – something like, "What do you guys think? Let me know in the comments!" It really blows up the comments more than the videos in which I don't invite audience participation.

I also post quizzes on Instagram stories, which followers have really seemed to love. All it takes is snapping a photo of a cadaver and asking what the structure is. We get messages every day about the quizzes, so they are definitely here to stay.

What are the key things to keep in mind when creating medical education content for Instagram and YouTube?

Logistically, we have to make sure we're protecting the privacy of the cadavers and using them appropriately. Justin and I also feel that it's a moral obligation to make sure what we're saying is accurate. There's a lot of stuff out there that people can make inaccurate claims about; anatomy isn't too bad because it's pretty much a point-and-shoot topic, but when we talk about things like supplementation and whether it works on the body, we have to be careful, because people are so interested in applying anatomy to the health and wellness of their bodies.

It's also important to make it clear that, although we're experts in anatomy because we've been doing this for so long, we still don't know everything. It's okay to say that we don't know something but that we'll find out for the audience – in my opinion, the best educators are the ones who don't

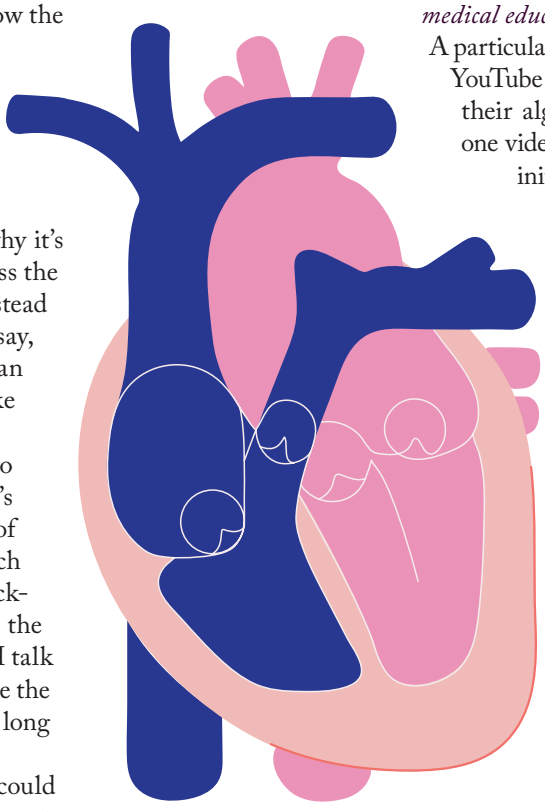
"THE BEST STORIES WE HEAR ARE WHEN PEOPLE SAY OUR VIDEOS INSPIRED THEM TO GO TO MEDICAL SCHOOL OR PURSUE A DEGREE IN ANATOMY."

make something up on the spot because, if they're wrong, they lose all credibility.

Furthermore, medical content can be dry, so you need a presenter who is engaged and enthusiastic. We have audience members from many different backgrounds and professions, so we have to think about how a video might change for massage therapists compared with pathologists or nurse practitioners or non-medical professionals. The factual part of the video doesn't change, but the *why* does – why does that profession care about this content? We have to be quite general because our audience is so vast and we want to reach and engage everybody, no matter their background; however, if you're targeting a particular audience, think about why that group cares about the topic.

What about presenting to the audience – is there anything you have to think about?

First and foremost, you have to show the audience that you're excited about what you're teaching. If you're not engaged, your audience won't be either. In some videos, I'll explicitly say, "This is why this is so cool." Have a smile on your face, tell people why it's important to their lives, and address the audience directly. For example, instead of saying, "This is the stomach," say, "Did you know your stomach can hold this amount of food?" Make it personal.



For YouTube, the main thing to bear in mind is how to keep people's attention. From an editing point of view, we change the angles as much as possible, even if it's just a quick-cut zooming in or out. This keeps the audience engaged and stimulated. I talk with my hands a lot, too, and change the tone of my voice, especially if it's a long "talking head" video.

We steer clear of clickbait. We could do it if we wanted to; we could create content for the sole purpose of shock and awe, but we want to stick to education. It's important to us that we have catchy titles to pique people's interest but, if they click on the video and it has nothing to do with the title, they're going to lose trust in our channel and we'll lose our credibility.

JONATHAN'S TOP TIPS

- Stick with the grind and be consistent
- Be flexible with the ups and downs; one month, you could do really well and have a video go viral, but the next month could be slow.
- For medical professionals who are trying to teach, you have to tell your audience why your subject matter is important to them.

What challenges have you faced in creating online medical education content?

A particular problem we've encountered is having our YouTube demonetized. When you upload a video, their algorithm makes sure it's appropriate. In one video, I popped an abscess; it was monetized initially but, two days later, they demonetized it. Some things are okay and some aren't – but they don't tell you why.

The other isn't really a challenge, but I think every creator needs to prepare for it. You can have a perfect video or post and you will still get people who don't like it or respond negatively to it. We don't receive a lot of negative feedback, but there have been a couple of emails from people saying, "How dare you use human bodies to teach like this!" What they don't see is that Justin and I are in the lab every day caring for the bodies – we're like stewards for them, making sure all the tissues are separate from one body to another so they go back into the same body, back to the donor program, and cremated to either be returned to the family or taken to the local cemetery, depending on the wishes of the person when they were alive.

How do you expect people to learn about the human body? This is how medical education happens and it's why these people donated their bodies. In 2021, medical education is both the same and different to the past – the basic principles of learning

are still there, but having the opportunity to deliver it both in person and online is the best of both worlds. There's no true replacement for learning in person (despite some really cool 3D apps), because your real patients aren't going to be virtual, but there is still tremendous value in online learning – especially because cadaver labs are decreasing in number and students are finding them more difficult to access.

What's next for the IoHA's video content strategy?
Increasing the volume of content we produce would be nice, up to two or three YouTube videos per week. Our efficiency keeps increasing and the only way to get better is to just do it, learn from your mistakes, identify what's not efficient in your workflow, and tweak it.

People want to make a living as content creators, but we struggle with how much effort and resource we can put into answering hundreds of questions "for free" and still get our other work done. The more followers you get, the harder it becomes to answer them all, so we've thought about doing "talking head" Q&A videos on YouTube to hit two birds with one stone – the audience gets free content and, as a channel creator, you can monetize it.

TIKTOK 101 WITH JUSTIN COTTLE

What inspired you to take the lab to TikTok?
Jonathan, Jeremy, and I have been talking about creating online content since 2013; the problem was that we were all too busy. In March 2019, the massage school I was working at went under and I was left with a lot of spare time, so I thought I should start thinking about how to bring the lab online. I started taking online digital marketing courses for Facebook, Instagram, and Twitter, and then I heard of this thing called "TikTok." I downloaded it and saw that it was nothing but dancing teenagers, so I didn't know whether it was going to be the best fit for us, but I kept it on my radar while focusing on YouTube.

By August 2019, I had become obsessed with it and its young user base because it presented the perfect opportunity to inspire them early. TikTok is a very difficult company to reach, but I eventually contacted its parent company's PR team with a video explaining what I wanted to do on the platform. Originally, I wanted to check whether it would be okay if I showed cadavers on the platform – I didn't want people to be scrolling through like: dance video, dance video, food video, human heart, dance video. So we developed the idea, went through best practices, and got full approval from the team. After that, it took a few months for me to figure out how to do it right – I needed to have a hook to get the attention of younger individuals while they were scrolling.

In my very first video, I decided to focus on the brain, because it doesn't fully mature until you're 25. I thought, "If my target audience is under 25, I'm going to call them out." I also made sure my language was clear and let them know it was a real human brain. After publishing it, I put down my phone to make dinner. When I came back after an hour, the video had 50,000 views! By the next morning, it was over 1,000,000 views. It was immediately rewarding to see that because I had spent so long planning it. I decided very early on that I was going to show people something that is extraordinarily simple, but that they've never seen before.

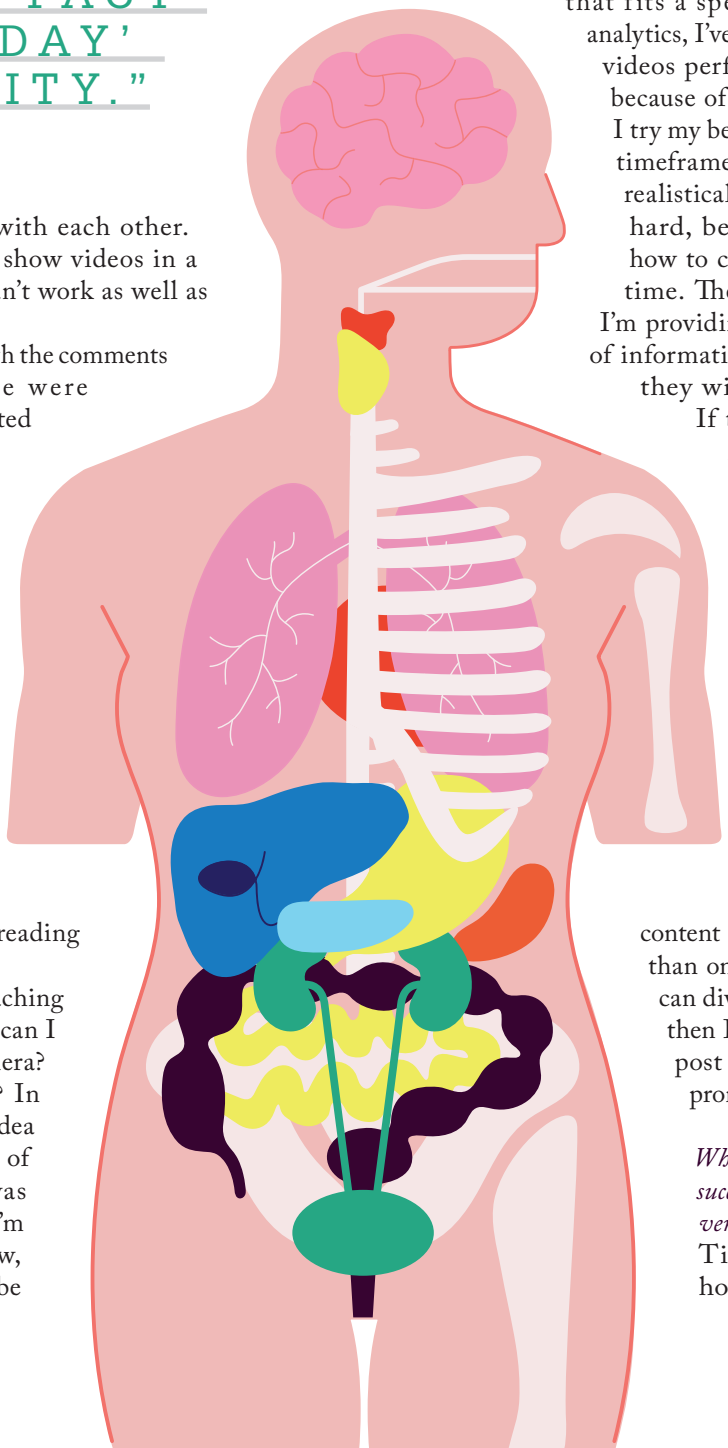
Talk us through your content creation process…
At first, I wrote down every anatomical single structure that came to mind and asked myself, "Can I create a video around that?" For the first four months, I worked my way through the list, but then I had the idea of making our TikTok account into an atlas of the body. From there, I started making videos that could build a body from the ground up. The idea was that people could come to the page and get a good idea of how the body works

"WHEN CREATING MEDICAL CONTENT ON TIKTOK, TRY TO HAVE A 'FACT OF THE DAY' MENTALITY."

and how tissues interact with each other. However, TikTok doesn't show videos in a sequential format, so it didn't work as well as I had hoped.

Once I began engaging with the comments and seeing what people were interested in, it really started to take off – and I realized that video selection should be based on audience comments, rather than on what I wanted to do. For example, if I talk about the detailed science of anatomy, I can guarantee only about five percent of users will be interested or even understand, so I've moved to far simpler videos based on user interests. I spend around an hour every day reading everyone's comments.

I also have to consider teaching in a lab versus on camera – can I replicate what I do on camera? Will users see it properly? In the initial stages, I had no idea what I was doing in terms of editing or lighting – I was doing it all on an iPhone 6. I'm much more comfortable now, because I edit all our YouTube videos, but I still practice and try out different angles on the cadaver to see what works before we hit "record." Now, I film everything in 4K, edit in Adobe software, and make sure everything is as inclusive as possible for people with disabilities.



How do you adapt your content for different platforms?

The hardest part is creating engaging content that fits a specific platform. From our analytics, I've found that 20- to 23-second videos perform best, which I think is because of the modern attention span. I try my best to keep videos within that timeframe and ask myself what I can realistically say in 20 seconds – that's hard, because I have to figure out how to convey value in such a short time. The idea with TikTok is that I'm providing quick, digestible chunks of information that, if users really like, they will binge from our profile. If they don't do that, then at least they've learned one new thing.

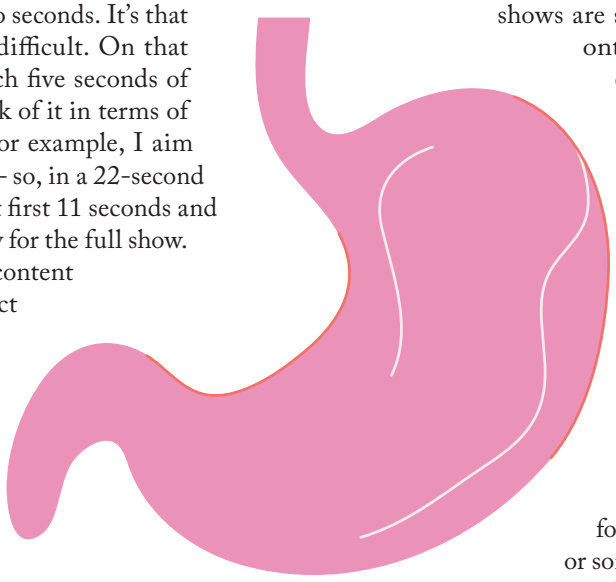
On YouTube, I try to replicate what I do when I'm teaching my students – whether that's in the classroom or in the lab. YouTube is our most variable platform; one of our most successful videos is two minutes long, but I recently posted a 28 minute-long video that is performing extremely well. The content needs to be fleshed out more than on other platforms because we can dive deeper into concepts – and then I can take quick snippets and post them on TikTok or create promo videos.

What goes into making a successful video for TikTok versus YouTube?

TikTok can be hit or miss; however, I've found that the

overarching theme for success is to hook viewers and show something visually and auditorily stunning within the first two seconds. It's that short, which is why it's so difficult. On that note, even if they only watch five seconds of your video, you should think of it in terms of "watch time" percentage. For example, I aim for a 50 percent watch time – so, in a 22-second video, I need to have a great first 11 seconds and hope that makes viewers stay for the full show.

When creating medical content on TikTok, try to have a "fact of the day" mentality; if you can teach just one interesting thing, you will see success. But that's not all – now that more people are doing it, you need to get creative, especially if you're trying to teach them nitty-gritty details. YouTube is very similar because, when you look at your analytics, you see that it's all about watch time. If I want a YouTube video to perform well, it has to have a good thumbnail and a good title, which influences clickthrough rate. The holy grail of watch time on YouTube is around 40 percent of the video, so that's what I aim for.



After that, my main goal is to teach people something. The most valuable, intensive content is usually towards the end of the video because, if viewers have made it that far, they're in it to win it. Most of those people aren't going to watch 70 percent of my video and then bail – they're going to watch the whole thing. It's hard though; personally, I've never experienced anything more difficult than trying to be creative and engaging while also conveying value. But it's amazing to see that it's actually paying off.

What are the educational benefits of short-form video for medical teaching?

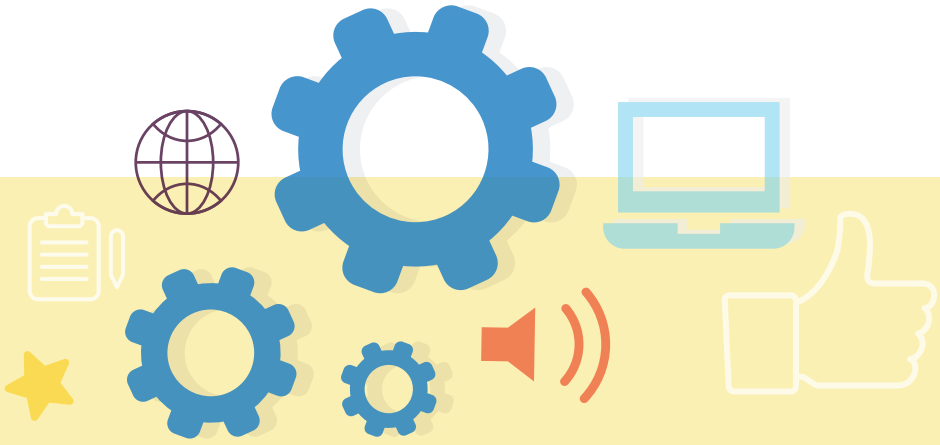
Anatomy is boring – and I say that as someone who loves anatomy. The human body itself is amazing, but anatomy is actually boring; it's just structures connecting to other structures. What people like is physiology – that's where things get exciting, because you're showing them how it works. In that regard, you have to teach people something that's exciting to deliver – attention spans are getting shorter and the way people consume content has changed. We want to teach viewers something quick and interesting about the body because that's how our brains work. But everyone is interested in their bodies – there's a reason why medical shows are so popular – and if you're able to latch onto that (even for 15 seconds), there's enormous power in it.

How did you overcome the "dancing videos" stereotype when you first started out on TikTok?

Honestly? I just didn't care. I haven't actively tried to break stereotypes – I just try to be me and teach people. It sounds cliché, but I want to change the world with teaching, because it bugs me that people know more about cars and computers than about their own bodies.

Authenticity is part of the winning formula. As long as you have a story to share or something of value to teach, people will be attracted to it. Many users are already getting sick of the generic content and are saying how much they love "anatomy TikTok!" The bingeability of the platform is incredible. Users can easily spend 20 minutes continuously scrolling and, though there is a lot of competition, they will still see your content and the growth is more organic than on platforms like YouTube. Then again, "success" is different for everyone – you need to dial down your expectations and

"EVERYONE IS INTERESTED IN THEIR BODIES – AND IF YOU'RE ABLE TO LATCH ONTO THAT (EVEN FOR 15 SECONDS), THERE'S ENORMOUS POWER IN IT."



JUSTIN'S TOP TIPS

- *Spend time on TikTok.* You can start extracting information as to what makes TikTok videos interesting and successful. I always look at the "share" icon – how many times was that video shared? That's a better indicator of a video's success than likes or views, because it shows that people are enjoying the video and want other people to see it, too. TikTok is the perfect social platform to teach people, as long as you have something interesting to say quickly. And the fact is that kids love it. It's amazing how integrated social media has become – it's a fantastic method to teach and bring value, and TikTok is no different.
- *Be strategic.* Know what you want to talk about and try to find a niche. Don't lock yourself into a corner where the only thing you can talk about is a small part of your field – have a wider plan of the topics you want to talk about. At the same time, don't try to do everything under the sun. If it's medical, you could start off with describing certain conditions or surgical techniques, then maybe show them a day in the life of a pathologist. People love that type of content, especially on TikTok. Micro-vlogs (showing people what you get up to during a day in your life) are always successful on social media. Laboratory medicine (or anything medical) is unique and relates to that "Grey's Anatomy" type of attachment.
- *Practice with the camera.* It doesn't matter if you place a teddy bear in front of the camera to practice with – just make eye contact with the bear and never leave. I know from teaching my students that it is one of the most valuable things you can do. Learn how to speak to a camera and not look away – no matter what else is happening, you have to lock onto the lens. I think that really helps the viewer to feel connected to you, especially if you're doing "talking head" content.
- *Practice public speaking.* If your face isn't in the shot, you need to practice speaking well to keep viewers engaged and listening. Make sure your voice isn't monotonous – go up and down and have proper inflection.

Passion can get you a long way, but it's these little things that set good creators apart. After that, just make sure you bring value to every single video – if you're there for education, then educate.

think about the impact you're making on those who do see your content instead. If you have that mindset, you're more likely to be successful. In the end, I believe it boils down to:

- Discipline
- Perseverance
- Doing what you know
- Looking at your analytics
- Reading and engaging with comments
- Bringing value to users

What else do you keep in mind when creating medical education videos for social media?

I try to make topics relevant to viewers in some way. For other specialties, I know that's not always possible, especially if you're talking about certain conditions or procedures – but, in that case, it needs to be something that people will find interesting or that you can make interesting. We all know that someone who speaks passionately about even the most boring subject will hook you. But it takes practice to speak (well) to the camera so, if you're just starting out, choose topics you're pretty sure people are going to be interested in until you build enough of an audience that you can start experimenting with other topics. Don't go too nuanced in the beginning – people won't know you, so they won't trust you. Instead, they want something of value that's relatable and outright interesting. That's what I would focus on in the beginning – keep it simple and slowly build to the more obscure topics.

Once you get into the detailed side, make sure you're doing Google keyword analysis – looking up the density of keywords and what people are searching. There's a YouTube plugin that can analyze keyword frequency and, if people are searching for it on YouTube, I guarantee that they'll be interested in it on TikTok, too.

On that note, you also have to be okay with the fact that people aren't going to watch your entire video. The people who make it to the end, no matter how short or long it is, are your diehards. Those are the people who would go down with you on the ship. But it's probably only a handful of people – the rest of them switched off a long time ago. Be okay with that.

Are there any other unique challenges to making content for YouTube?

You have to be careful with what you're saying and showing on YouTube, and the biggest challenge is that it gives no feedback about what the exact problem is. One infuriating issue is that educators teaching medical content have to use medical terminology, which can be a barrier to entry for creators.

Sometimes you have to play the game. I've uploaded a video sometimes 10 or 15 times just to figure out what they want. Anyone who wants to do really cool, unique content needs to be aware that, if you say or show the wrong thing in a 30-minute video, you may not be able to get it published and it can wreak havoc on your algorithm.

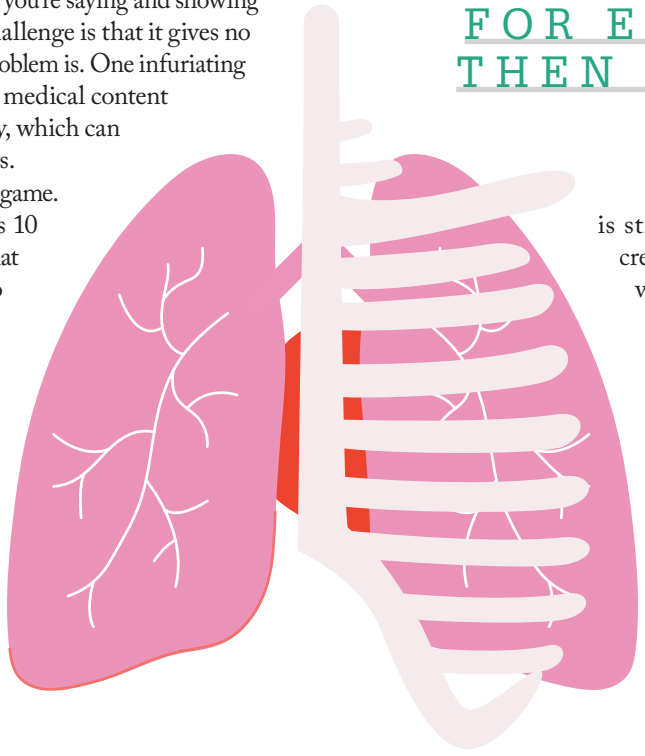
Once, I was able to get some feedback from YouTube. We uploaded a video in which Jonathan cut into an abscess and it got flagged, so we gave them examples of much worse videos approved by their algorithm. They finally got back to me and said it was the blood (though it was only a small amount). It made me aware that blood, even the smallest amount, is not okay on YouTube. So, as a pathologist, how do you get around that?

There's so much more we want to show that YouTube won't allow. For example, they won't allow us to put a scalpel to the tissue. I get where they're coming from, but there's no case-by-case basis. Other creators have reached out to us and asked how we're monetized, and I look at their channel and see they're taking a scalpel right to the tissues! That's why they're not monetized, and it's a serious challenge. YouTube is fine with any piece of surgical equipment as long as you're not cutting or showing blood.

What's next for IoHA's content strategy?

The problem is that we have too many ideas. Our grand goal is still the website atlas – we want to create an engaging, searchable database with cool cadaver videos. In terms of our social channels, our main focus right now is YouTube because we're hitting our stride with it and really starting to figure it out. TikTok is always going to be important, but it's getting a little harder to find the absurd levels of creativity required to stand out.

"MAKE SURE YOU BRING VALUE TO EVERY SINGLE VIDEO – IF YOU'RE THERE FOR EDUCATION, THEN EDUCATE."



I want to do more neuro topics and structures because I want to start getting into thornier subject matter. I'd like to start talking about mental health; that's where I believe value can be put out there. You have to carefully consider how you're going to talk about delicate subjects, but they're so much more valuable to viewers than simple videos ("Look! It's a kidney"). We have to at least try to generate more intensive conversations – and, if people don't like it, we can always go back to our roots!

Jeremy Jones is Co-Founder and Executive Director at the Institute of Human Anatomy, Salt Lake City, Utah, USA.

Jonathan Bennion is Co-Founder, Director of Education, Lead Dissector, Anatomist, and MPA-C at the Institute of Human Anatomy, Salt Lake City, Utah, USA.

Justin Cottle is Marketing Director, Dissector, and Instructor at the Institute of Human Anatomy, Salt Lake City, Utah, USA.

In Practice

Technologies and techniques
Quality and compliance
Workflow

One Step Beyond

Leveraging artificial intelligence for tumor detection and prognostication

By Nicolas Orsi, Elizabeth Walsh, and Katie Allen

It can be disheartening to hear pathologist colleagues say, "With artificial intelligence, I'll be out of a job in 10 years." It is reminiscent of 1999, when doomsayers expected Y2K to unleash technology Armageddon. The reality, of course, is more nuanced, but there is no denying that AI-related innovations will have a transformative effect on our discipline. Though many of its perceived benefits focus on improving diagnostic services, there is also scope to harness these innovations to bridge the gap between pathology and oncology.

When digital pathology and whole slide image (WSI) analysis transitioned from the research space into the clinical environment, they received a lukewarm welcome. Reluctance to engage with this technology is traceable to a lack of familiarity or training; belief that digital diagnosis is inefficient; higher levels of confidence in light microscopy; and individuals' thresholds for embracing new technology (1–3). However, as scanners, algorithms, and perspectives have matured, WSI-based diagnosis has proven comparable to that with light microscopy (4–6) and numerous large centers across the globe now run partially or fully digitized pathology workflows (3,7).

This forward motion is key to the current state of affairs in histopathology. Globally, the discipline is under growing pressure – our increasing, aging population will yield a 60 percent increase in diagnostic demand by 2029. The increasing complexity of patient-tailored investigations will further exacerbate this burden (8), and the diagnostic backlog in the wake of the COVID-19 pandemic will have a compounding effect. Ironically, this rise in service demand is expected to be paralleled by a 30 percent fall in active pathologists relative to 2010 staffing levels (9). This dismal scenario is exemplified by figures from the Royal College of Pathologists' workforce census that reveal that only three percent of departments are adequately staffed to meet diagnostic demand – a situation echoed in the US by analogous workforce shortages (10–12) that will only be worsened by an incipient retirement crisis and a shortfall in trainee recruitment (10). The impact of the status quo is not insignificant on National Health Service coffers, addressing the shortfall by using locum doctors and outsourcing services costs an estimated £27 million per year in the UK alone.

AI steps in

AI in digital pathology offers a range of potential diagnostic solutions with clear merits – yet it has received a cold shoulder in some quarters, something

"Once a scarce commodity, digital pathology is now reaching remote corners of the globe."

of a disappointment for the "third revolution in pathology" (13). Despite early teething problems, many AI-based solutions have shown potential clinical utility, albeit in an academic setting. One key benefit is that AI could shorten pathologists' reporting time; algorithms capable of tumor detection, cell counting, and mitosis detection are now increasingly available (8). Others highlight areas of interest for review within WSIs (1), reducing the time needed for a pathologist to scan a case at low power. This is particularly useful in biopsies and resection specimens that are known to be time consuming to report (for example, nodal [micro] metastases) or where multifocality is important (for example, breast and prostate specimens) (1, 14).

Busy clinical pathology departments, such as those dealing with high-volume primary care skin excisions, could also make use of simple algorithms (for example, cancer present or absent) to screen and prioritize malignant cases for review (7). They could also standardize diagnostic performance to offset inter- and intra-pathologist diagnostic discordance (15) – in essence, providing a second opinion. The possibility of bypassing ancillary testing and its allied delays is also welcome, highlighted by algorithms that resolve immunohistochemically stained HER2-equivocal cases without the need for fluorescence in situ hybridization (16). Notionally, the aim is to adopt such solutions clinically to accelerate case turnaround, minimize ancillary testing analytical time, improve diagnostic accuracy, and reduce costs. However, the disappointing reality is that none of these technologies have transitioned into routine reporting practice; their use remains largely confined to the academic setting.

Offering prognostically meaningful information that could guide patient management would be a further boon. And within the research environment, we now have tools at our disposal that increasingly attempt to link tumor morphology to the underlying biology and subsequent clinical outcome. However, this is much more than a simple exercise in satisfying academic curiosity; algorithms have been developed to appreciate the spatial distribution of tumor-infiltrating lymphocytes (9) and to capture tumor-associated stromal features (17) or microvascular proliferation (18) – all of which have demonstrated prognostic significance. Indeed, we feel the greatest promise can be drawn from these tantalizing early results suggesting that AI may be able to identify prognostic features that elude visual inspection.

Reaching far and wide

Other deep learning-based (and thus inherently less defined) methods in the research environment have delivered prognostic information that outperforms existing molecular and morphological prognostic markers in colorectal cancer (19) and refines prognosis in hepatocellular carcinoma (20). Similar approaches have extended this reach across multiple cancer types within and across pathologic stages (21). However, many have also attempted to improve the robustness of their algorithms using circuitous, often non-validated strategies, such as combining histology data with ancillary test results and clinico-demographic metadata. However, emphasis is increasingly on developing clinically ready solutions that can achieve regulatory body compliance. One promising platform uses a combination of statistical physics, computer vision, and tumor biology to harmonize diagnosis (including grading and molecular subtyping) and prognosis in breast cancer (22–24). Perhaps most importantly, it overcomes many of the thorny issues surrounding dependency on large training data sets, working with pre-annotated WSIs, generalizability across histological backgrounds, and scanning platform agnosia. Accordingly, it offers a clinically more attractive and accessible "white box" solution for both pathologists and oncologists.

The implications of consolidating the relationship between pathology and oncology are manifold. Getting a better handle on prognosis and molecular profiles offers a unique opportunity to reduce diagnostic costs and turnaround times, as well as inform the selection of optimal therapeutic modalities. Importantly, prognostic AI algorithms would give pathologists the opportunity to lead more strongly and holistically on both specimen evaluation and therapeutic management based on predicted outcomes. A single operator controlling all these facets of specimen reporting should also mitigate diagnostic or treatment delays and improve patient management across the cancer care pathway. This tailored approach could also minimize the risk and sequelae of under- or over-treating patients, predict chemotherapy and immunotherapy response, improve clinical outcomes, offer personalized prognostication, and contribute to pathology's role in making precision oncology a reality.

Although it may be difficult to appreciate the scale of the benefits ensuing from explainable, automated diagnostic

Credit: 4D Path.

solutions, they would undoubtedly have a global reach. Because most of these technologies can be readily deployed in cloud-based environments, enhanced pathology services could be accessed from developing economies or those where diagnostic histopathology services may be inaccessible or unaffordable. In these environments, the threshold for acceptance may be lower. Indeed, although we have a legal, regulatory, and ethical duty to provide robust, reliable, and fully clinically validated diagnostic and prognostic solutions, the use of AI in digital pathology does not have to be perfect to be useful. Consider that Rwanda has six pathologists for its 12 million inhabitants, whereas Burundi has only two to serve a similar population – a stark contrast to the United States' 60+ pathologists per million people. Once a scarce commodity, digital pathology is now reaching remote corners of the globe. Digital histopathology "packages" – from tissue processors to slide scanners – have even been deployed in remote sub-Saharan areas where they support a three-day diagnostic turnaround service (25). As such, it is pathologists and not digital pathology services that are lacking. If such countries had access to AI, the potential benefits would be immeasurable – from timely diagnosis to management and prognostication.

Staying on the bench

Frustratingly, many of the promising new AI advances discussed above have yet to translate into clinically meaningful solutions, largely due to real-world generalizability and large-scale validation problems that continue to dog widely used deep learning-based approaches (8). A noteworthy stumbling block is that any AI algorithmic solution that is not fixed (that is, prone to further learning-related instability and vulnerable to diagnostic drift) is unlikely to achieve regulatory clearance.

Despite independent, robust review, some of the residual unease among pathologists in embracing AI may lie with the naïve clinico-legal framework of its implementation. Given the adjunctive nature of AI-based technologies, diagnostic responsibility will still lie with the reporting clinician. One of the principal concerns surrounds areas

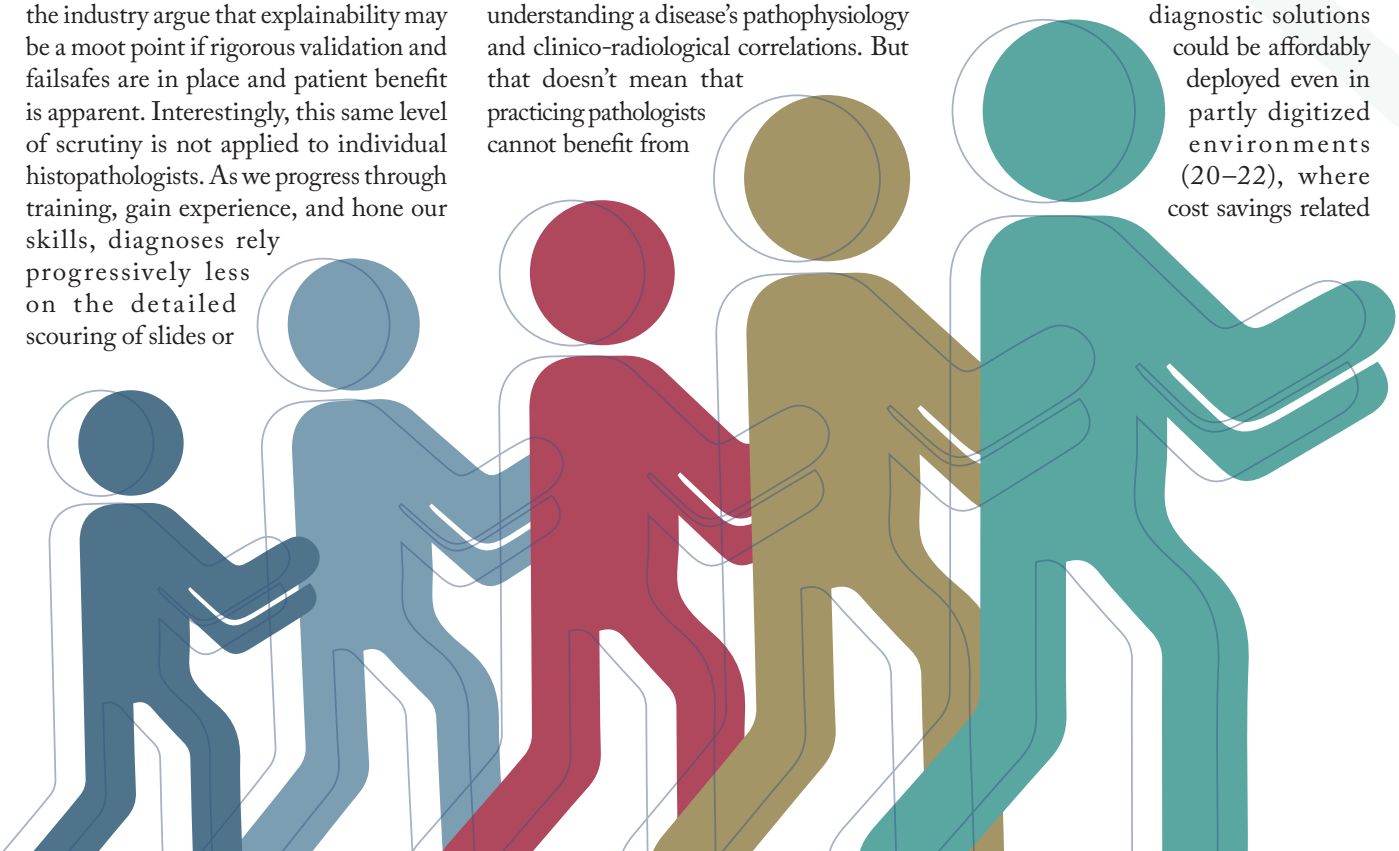
of pathologist diagnostic error in the face of a discordant opinion relative to the supporting AI. One path out of the woods could be to limit early-stage AI technologies to the diagnostic (and not prognostic) interpretation of "lower risk" cases, such as basal cell carcinomas, in which diagnostic inaccuracy would be unlikely to cause significant harm, or to simple dichotomous diagnoses, such as the identification of metastases in lymph nodes. These reports could further include disclaimers acknowledging the potential limitations of partly AI-reported cases. Finally, the answer could also come from AI-based solutions themselves – a measure of diagnostic discordance with or without AI support would inform the associated level of diagnostic bias, confidence, and safety, thus gaining clinical credibility.

It remains difficult to escape the mysticism of the "black box" phenomenon; few algorithms to date offer an intelligible rationale to underpin their inner workings, which can impact their clinical acceptability. However, many in the industry argue that explainability may be a moot point if rigorous validation and failsafes are in place and patient benefit is apparent. Interestingly, this same level of scrutiny is not applied to individual histopathologists. As we progress through training, gain experience, and hone our skills, diagnoses rely progressively less on the detailed scouring of slides or WSIs. Instead, we begin to undertake overall assessments that conform to a mental diagnostic blueprint and enable us to home in on important key features – a process notoriously challenging to impart to others. This doubtlessly contributes to the verbosity of free text reports that can leave other specialty colleagues bemused by our elaborate morphological descriptions, some of which may seemingly have no bearing on the bottom-line diagnosis, but which may carry an as-yet ill-defined diagnostic or prognostic relevance for AI to identify.

Looking to the future

AI is stirring a sea-change that we can no longer ignore – so how can we reach the nonbelievers? A key issue is the idea of being replaced. Why would anyone endorse a technology that might one day put them out of a job? To relieve these concerns, we must not lose perspective. Though AI and digital pathology can transform our specialty, machines cannot simply replace a histopathologist's multifaceted role – from intelligent specimen cutting to understanding a disease's pathophysiology and clinico-radiological correlations. But that doesn't mean that practicing pathologists cannot benefit from AI, particularly in environments where subspecialty expertise may be lacking. This fact is echoed by ongoing discussions we have had with patient groups internationally. Although patients acknowledge the value of AI, particularly in circumstances where it outperforms histopathologists, they still believe that it should be in the hands of a clinician – a striking endorsement for a profession that is conspicuous by its lack of patient interaction. Thus, with the comforting knowledge that AI can be used as an adjunct to enhance diagnostic performance, increase efficiency, reduce cost, and consolidate pathology-oncology cohesion, we may be able to change more minds. After all, as we embarked on our clinical careers, we committed to a path of lifelong learning, acutely aware of the shelf life of "current" medical knowledge. This is widely accepted across all branches of medicine and has underpinned the acceptance of new surgical approaches and therapeutic strategies – so pathology should be no stranger to this notion.

The path to bring AI from our imagination to the laboratory has clear milestones. AI diagnostic solutions could be affordably deployed even in partly digitized environments (20–22), where cost savings related



to reduced dependency on ancillary tests could be diverted to budgets supporting the adoption of new technology. More specifically, a viable end-to-end diagnostic platform should be fully automated, improve diagnostic accuracy by providing a second opinion and a diagnostic confidence score, offer a range of safety features and, above all, be explainable in terms of the underlying tumor morphology and biology. Developing a computationally light device that integrates seamlessly into existing clinical workflows and healthcare systems' IT infrastructure and produces pre-annotated, interactive synoptic reports pertaining to the original WSI could offer appropriate quality control while both reducing pathologists' workload and increasing their throughput.

Although AI may appear to be a panacea for histopathology, pathologists' current distrust is entirely natural. The addition of AI solutions to our diagnostic toolbox should be embraced and encouraged, but a significant burden of proof remains for real-life clinical utility. If, as a profession, we can actively engage with and maintain the open mindset with which we adopted immunohistochemistry and genomics during previous revolutions, we are well on our way to harnessing the potential of this next wave of disruptive technologies. We have a responsibility to not only embrace, but also drive, shape, and take ownership of AI to oversee its safe introduction into diagnostic practice. The impact of our flexibility and ambition will naturally cascade down the cancer care pathway to our oncology colleagues and, most importantly, to our patients. If AI's inherent potential can overcome our initial skepticism and resistance to change, its transition and successful deployment in clinical histopathology will be with us before we know it.

Nicolas Orsi is Chief Pathologist at 4D Path, Newton, Massachusetts, US, and Clinician Scientist in Histopathology, University of Leeds, Leeds, UK.
Elizabeth Walsh is a Specialty Registrar in Histopathology, University of Leeds, Leeds, UK.
Katie Allen is a Specialty Registrar in Histopathology, University of Leeds, Leeds, UK.

See references online at: tp.txp.to/one-step-beyond

The 1-2-3s of IBD

Inflammatory bowel disease: does histopathology make any difference?

By Roger M. Feakins

Idiopathic inflammatory bowel disease (IBD) is a common, disabling chronic condition that affects about 7,000,000 people worldwide – and that number is only increasing (1). Classified into ulcerative colitis (UC) and Crohn's disease, IBD presents with symptoms including rectal bleeding, abdominal pain, and diarrhea and has many long-term complications, including intestinal strictures and colorectal cancer.

Fortunately, medical therapy for IBD improves continually. However, confident diagnosis and classification of IBD – and exclusion of its mimics – is not always easy. The diagnostic process is multidisciplinary and there is no single specific test. Clinical assessment, imaging, blood tests, and endoscopy all play an important role – but robust histopathology support is essential.

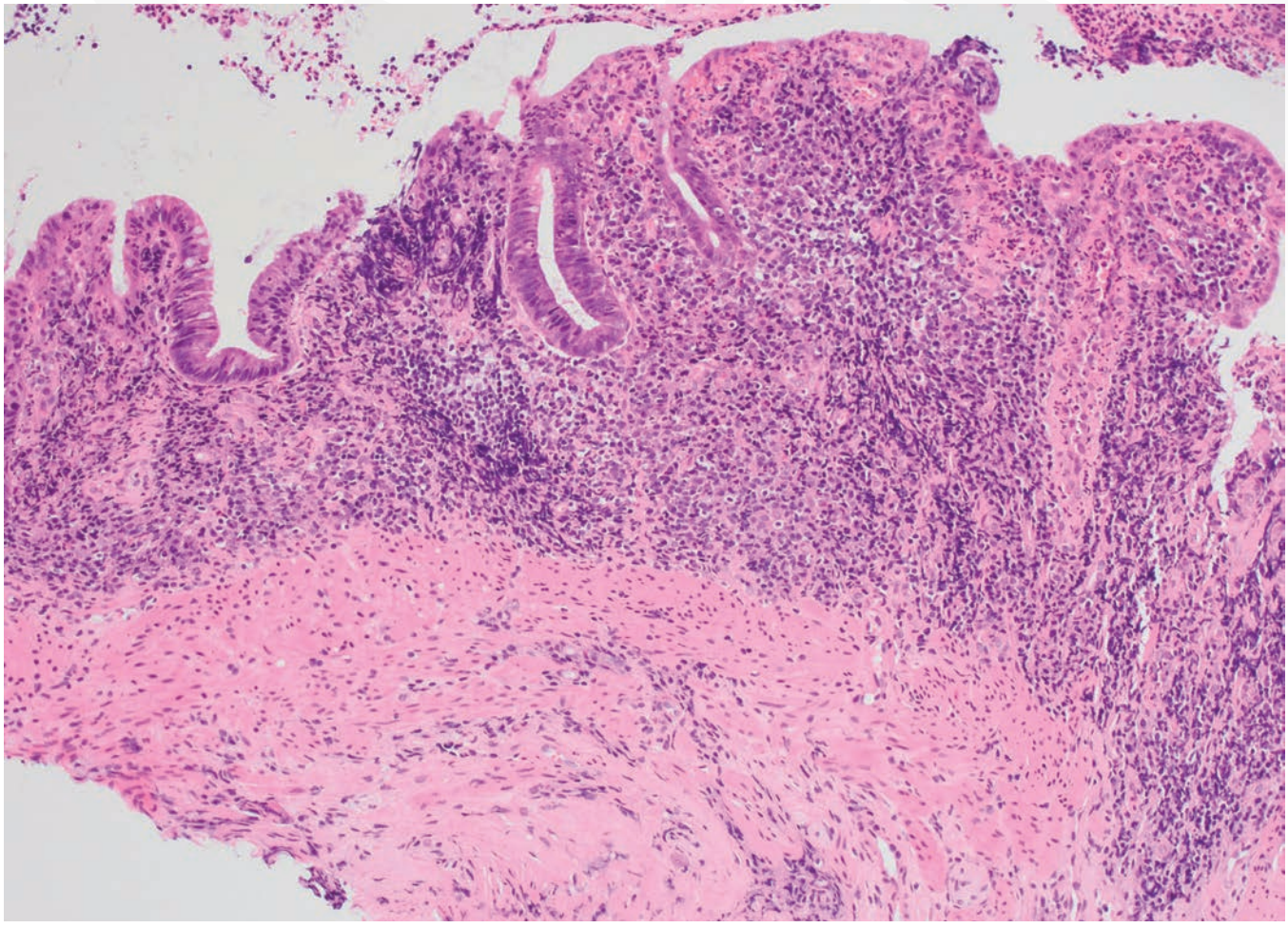
Full ileocolonoscopy is now standard practice for the investigation of suspected new IBD, allowing endoscopists to take biopsies of multiple sites from the ileum to the rectum. The pathologist can then assess the histological appearance at each site, determine the anatomical and intra-site distribution of any abnormalities, and compare the findings with the endoscopic observations. This helps to confirm, refute, or refine the diagnosis at presentation. Biopsy assessment is also important for follow-up after therapy (see Table 1).

There are specific pathological changes in a biopsy that can support a diagnosis of IBD, such as architectural distortion of the mucosa and chronic inflammation (in the form of basal plasmacytosis). There are also features that help distinguish UC from Crohn's disease; for instance, granulomas (strongly favoring Crohn's disease) and the anatomical distribution of changes (typically continuous in UC and discontinuous in Crohn's disease). In addition, histology helps to diagnose or exclude the many clinical mimics of IBD, such as diverticular colitis, tuberculosis, amoebiasis, other chronic infections, ischemia, radiation damage, and drug-induced colitis (2–4). Colitis as a result of the relatively new immune checkpoint inhibitor antineoplastic drugs can be a very close mimic, as can diverticular colitis.

IBD that is difficult to classify may be labelled "IBD unclassified (IBDU)" in biopsies or "indeterminate colitis" in resections. High-quality pathology helps to reduce the size of these categories, allowing better tailoring of management to the individual patient.

IBD patients have a high risk of dysplasia and malignancy compared with the general population, particularly when the disease is longstanding (5–7). Endoscopically, dysplasia can form an obvious mass or polyp – or it may be flat and difficult to detect. The endoscopist may suspect dysplasia, especially with the assistance of new methods such as dye sprays for highlighting abnormal mucosa. However, no investigation other than histology can reliably diagnose or grade dysplasia. Diagnosis, grading, and assessment of the extent of dysplasia play a major role in determining follow-up – whether observation, local excision, or more radical surgery. Furthermore, the histological classification of IBD-associated dysplasia and its contribution

"Clinical assessment, imaging, blood tests, and endoscopy all play an important role – but robust histopathology support is essential."



A biopsy from a patient with new ulcerative colitis showing distortion and atrophy of crypts and extensive chronic inflammation.

Credit: Roger Feakins.

to prognosis is a continually evolving area of knowledge (8). Confirmation of a suspected diagnosis of colorectal carcinoma, small bowel carcinoma, or other type of tumor also requires pathology (9).

Additionally, longstanding IBD and medical therapy increase the risk of some infections. Corticosteroids increase the risk of intestinal cytomegalovirus (CMV) infection, which has the potential to worsen clinical outcomes (10). Diagnosis of CMV relies on several tests, including histopathology.

Resection of part of the bowel may be necessary for several reasons, including IBD that is refractory to medical therapy, severe fulminant IBD, a stricture, or IBD-related neoplasia. Pathological assessment helps to confirm or refine an existing diagnosis of UC or Crohn's disease and exclude neoplasia. Specifically, it often helps surgeons decide whether ileal pouch anal anastomosis (IPAA) is appropriate after colectomy, because this procedure is a satisfactory solution for UC, but is contraindicated for Crohn's disease, in which there is a high risk of pouch breakdown. Therefore, histological confirmation of UC is important prior to IPAA.

There is considerable current interest in the ability of histological abnormalities to predict the clinical course of IBD after drug therapy. Assessing histological activity and histological remission ("histological healing") complements the assessment of endoscopic and clinical activity in this setting and histological remission is an accurate predictor of a good outcome (though often difficult to achieve in practice). However, the best way to record histological remission or activity

Role of histology	*Comment*	*Histology's contribution*
Diagnosis of IBD	New > longstanding IBD	Adds to clinical/endoscopic assessment May diagnose a mimic of IBD
Classification of IBD as UC or Crohn's disease	New > longstanding IBD Prior to pouch surgery (a pouch is suitable for UC patients only)	Adds to and may change clinical assessment
Degree of histological activity	No universal grading scheme exists	Adds to clinical/endoscopic assessment
Anatomical distribution of disease	Assists classification as UC or Crohn's disease	Adds to clinical/endoscopic assessment
Anatomical extent of disease		Adds to clinical/endoscopic assessment
Cytomegalovirus (CMV)	Especially with corticosteroid therapy	One of several investigations that can diagnose CMV
Dysplasia: presence and grade	Longstanding > new IBD	Necessary for diagnosis, grading, and classification of dysplasia Necessary to exclude underlying malignancy Helps to assess mucosa adjacent to a lesion and determine resectability of the lesion
Malignancy	Longstanding > new IBD Colorectal carcinoma most common Small bowel carcinoma Lymphoma	Necessary for diagnosis and classification Necessary for staging of cancers in resections Adds considerably to prognostic predictions
Assessment of response to drug therapy	No agreement on the best approach to histological assessment for this purpose Several scoring schemes exist Not a formal aspect of clinical practice	Histology complements endoscopic assessment and is a good predictor of outcome after drug therapy
Assessment of Crohn's disease strictures	May provide useful information after therapy	Adds to clinical assessment

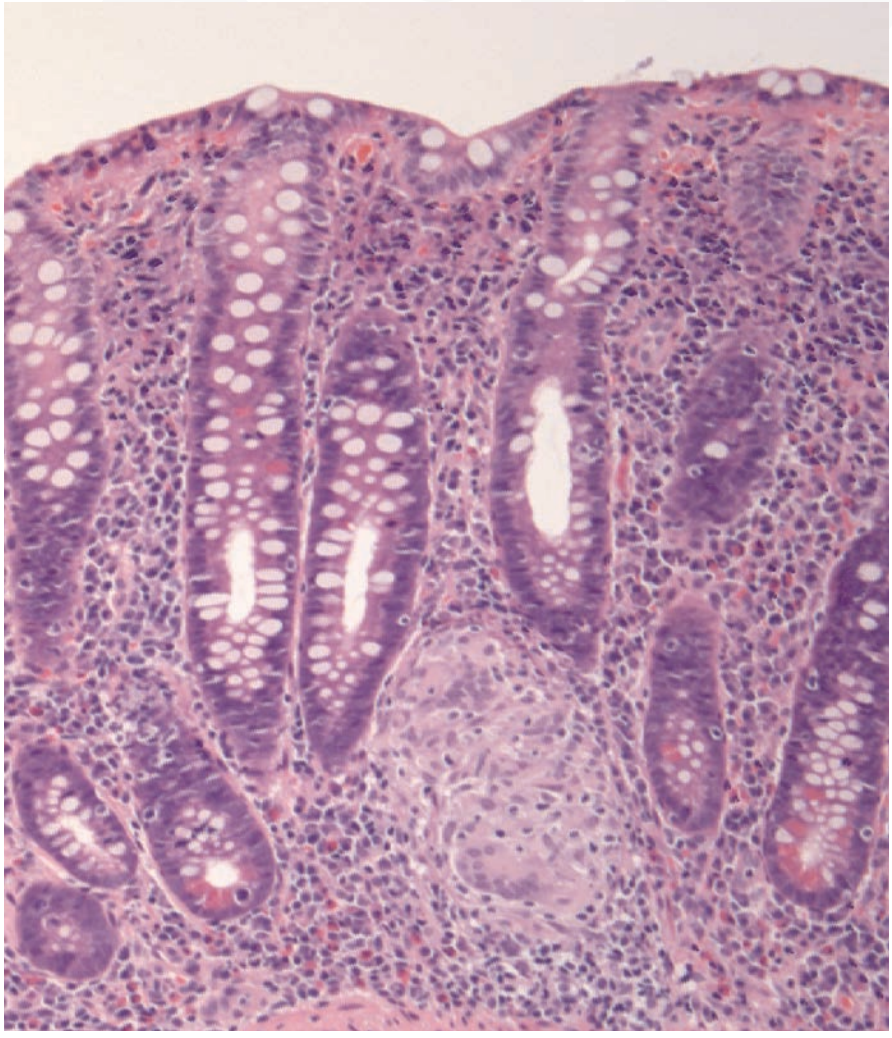
Table 1. The role of histology in IBD.

in this context is the subject of much discussion. Histological scoring systems exist, some of which – like the Nancy histology index – are relatively simple and others – such as the Geboes score or the Robarts histopathology index – are more complex (11–13). Publications with titles such as "Histological remission: under the microscope is the cure" (14) exemplify the enthusiasm some clinicians and researchers have for histology. Furthermore, histology may play an important role in the assessment of the effects of new antifibrotic drugs on strictures in Crohn's disease.

A final consideration is that a good working relationship between clinical teams and pathologists greatly enhances the quality of IBD care. Feedback occurs in both directions, enhancing knowledge, and multidisciplinary meetings are usually rewarding. Unfortunately, clinical teams, pathologists, and managers often perceive IBD clinicopathological meetings as a waste of time if there are more pressing priorities.

In the UK's National Health Service, histopathology departments, gastroenterology services, and endoscopy units are often understaffed. When a histopathology service is under pressure, outsourcing of biopsies and even resections to offsite laboratories may be a temporary (or longer-term) solution. This process often disproportionately affects gastrointestinal pathology; third-party reporting services may have little opportunity to liaise with clinical colleagues and may have less specialization and experience in IBD diagnosis. As a result, several recent consensus papers have explored the best ways to improve all aspects of IBD care (15–17).

To optimize their contribution to IBD services, histopathology departments need adequate space and equipment, high-quality staff, and robust funding. Comprehensive training of pathologists and technical staff is also a factor. Above all, there should be enough time for thoughtful and meaningful interpretation of histological samples and for productive communication between pathologists and clinicians. Those responsible for improving IBD



A biopsy from a patient with Crohn's disease. A granuloma is present (center of image).
Credit: Roger Feakins.

services locally and nationally will reap many rewards from a decision to maintain high-quality pathology input as part of the process.

Roger M. Feakins is Consultant Histopathologist at the Royal Free London NHS Foundation Trust, London, UK, and Subspecialty Adviser for Gastrointestinal Pathology at the Royal College of Pathologists.

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Upconverting Tissue Diagnostics

Lumito's novel imaging technology offers a new approach to cancer diagnosis

Early and accurate diagnosis is the key to stopping cancer in its tracks. That's why Lumito, a tissue diagnostics company based in Sweden, develops a product that has potential to release resources, increase accuracy, and minimize error margins at diagnoses of cancer indications. "We want to support pathologists across the globe in the fight against cancer and other severe diseases," says CEO Mattias Lundin. "We are still in the development phase and are eager to verify and validate where our technology creates the most value, build that into the final product, and launch a valuable solution that makes a difference in healthcare."

Lumito's technology combines a nanoparticle-based reagent kit with a whole-slide imaging scanner that captures histological samples with both brightfield and upconversion nanoparticle (UCNP) illumination to visualize cell and tissue morphology and the locations of specific protein markers. The result? High-contrast digital images with no background.

Björn L. Isfoss, chief physician, has worked with surgical pathology in laboratories in the USA, UK, Sweden, and Norway. He says, "Lumito's UCNP immunolabelling method provides more accurate visual presentation of signals than chromogenic IHC can. The signals appear more granular than in traditional IHC, reflecting punctate occurrence of target molecules. Immunolabelling presentation is clearer than with immunofluorescence. The target-to-signal ratio appears more linear than is possible with traditional IHC, which promises an improvement in target molecule quantification via digital image analysis."

Isfoss continues, "This is widely relevant for histopathology practice, which today is limited by fuzzy immunolabelling signals and imperfect quantitation of target molecule load. It is possible that pathologists will serve cancer patients better with Lumito's method because it seems to allow more robust target molecule quantitation, which is essential for the selection of patients eligible for hormonal therapy or immunotherapy."

Although Lumito's technology is still pending clinical validation, it seems to have arrived just in time for digital pathology to hit the mainstream – both in academic and in clinical laboratories.

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The technology can potentially be used in various applications and we are developing the Acri-scanner, which is an WSI scanner, and reagents for routine use in digital pathology.

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How Not to Lose Your Mind

Lessons I learned while awaiting my COVID-19 test results

By Christina A. Arnold

I had incredible New Year's plans. The weather in Denver was supposed to be perfect! I was planning on welcoming 2021 by hiking in the mountains, enjoying the delicious fresh air and sunshine.

And then it happened.

At 9pm on New Year's Eve, I started sneezing and developed a runny nose.

Two years ago, a sneeze would have meant that I was coming down with a simple cold. No biggie. A sniffle during the COVID-19 pandemic triggered all sorts of dangerous thoughts.

This essay is about how not to lose your mind. For me, these lessons helped me manage my emotions while awaiting my COVID-19 test results, but I suppose they can help in any situation: the stress of residency training, the promotion process, your annual review, connecting with your in-laws, a difficult divorce, navigating your kids through virtual school…

Stay present-focused

If you ever want to experience fear, think about the future. It's filled with all sorts of unknowns. Where was I going to find a COVID-19 test center? How long would I need to wait for the result? What would I do if I couldn't be at work as scheduled? What if I had to be hospitalized? What if I died of COVID-19? The future is ruthless.

If you ever want to experience shame, think about the past, because hindsight shows us that we could always have made better choices. How did I get sick with my N95 on almost all the time? Where was I not careful? How was I to blame? Did I get anyone else sick? The past is ruthless.

Although thinking about the past and future is natural, none of the above thoughts served me. In these situations, I encourage you to take a lesson from your big toe. It's just sitting in a sock at the end of your foot. It isn't asking about the future or the past. It simply exists in the present. The present is not scary. At the peak of my fear and regret, I kept bringing myself back to the present moment. I was quarantined in my bedroom. I felt physically okay. I was safe. All I had to do was breathe in and out. I could totally handle that.

As you stay present-focused, it can be helpful to develop a soothing behavior and mantra to help anchor you. For me, I put my hand on my heart, take deep breaths, and say, "I can figure it out." What helps anchor you to the present?

What is the real worst-case scenario?

When your brain starts to panic, let it explore the worst-case scenario in a constrained way. I find it helpful to journal the scary thoughts so that the ideas stop spinning in my head and move onto paper, where I can objectively review them and intentionally decide which thoughts to keep and which to discard. As frightened as I was, only a few thoughts were driving the fear. I could handle a few thoughts.

I liken this process to cleaning out the junk drawer. First, take out all the junk (write all the thoughts down), then decide which treasures (useful thoughts) you want to keep and which junk to throw away. While quarantining in the bedroom, I realized that I was afraid I would be hospitalized and die of COVID-19. Once I saw those words in my journal, I realized that my worst fear was death. I reminded myself that I wasn't even sure I had COVID-19, I had no comorbidities, and I was unlikely to die from that illness at that time. I was watching my favorite television show in my favorite reclining chair while wearing my favorite pajamas. I was actively enjoying my life. I was okay.

When your brain starts to panic, listen to your thoughts and then talk to your brain to help it calm down. When you feel panic, what are your worst-case scenarios? What are you telling your brain to bring it back to neutral?

"When your brain starts to panic, listen to your thoughts and then talk to your brain to help it calm down."

Give equal airtime to positive possibilities

It was true that I could have had COVID-19, but it was equally true that I might not have it. Even if I had COVID-19, it was at least as possible that I would survive without any complications as it was that I would die. As you navigate a crisis, understand that it is your brain's job to protect you by showing you all the possible dangers. Make sure you balance out "worst-case scenario" thoughts with positive thoughts that are at least equally true.

Our brain's job is to find evidence that it is correct

Your thoughts are powerful – so be careful with them. Our brain's job is to find evidence that we are correct. If you think, "I will die of COVID-19," your brain will find evidence of that – and that will lead to fear and panic. If you think, "I will figure this out no matter what," your brain will similarly find all the evidence of that thought, giving you a feeling of peace.

What thoughts are holding you back? How can you shift to positive thoughts to create positive feelings that drive positive actions that end in positive results?

"As you navigate a crisis, understand that it is your brain's job to protect you by showing you all the possible dangers. Make sure you balance out 'worst-case scenario' thoughts with positive thoughts that are at least equally true."

There are never any guarantees

The pandemic is challenging because it immediately and dramatically changed everything. Many of us questioned our mortality. Many of us lost loved ones. It was frightening to realize that we couldn't control our health and, even now, there is no universal cure.

It helped to remind myself that, in some ways, nothing has changed because there never were any guarantees. We never could control the future with any degree of certainty. All of us are born with an expiration date; none of us will live forever. In this regard, nothing is different. Death is, and always has been, an inevitable part of life.

The worst-case scenario, I believe, is to waste our precious time worrying about the future or shaming ourselves about the past instead of enjoying the beauty all around us in the present – and that's one big reason I love going to the mountains. No matter how much panic our human brains create, nature is big and resilient. The mountains were here long before we were and they will be here long after we are gone. They are not worried or panicked about human existence. Like your big toe, they just exist.

Look around your life. What gifts are lying in plain sight?

You either get the results you want or the lessons you need

Because I certainly didn't want to be sick, I tried to explore what I could learn from the experience. After a bit of thinking, I realized that it allowed me an opportunity to manage my mind, to be okay with not being in control, to process my feelings of fear, and to rest.

What could you learn from the areas in your life that are less than ideal?

You can't control reality, but you can control how you show up in your life

Sitting in my bedroom, I realized there was nothing I could do to accelerate the process of waiting for the test results. Although I couldn't control the testing process or the outcome of my illness, I could control how I showed up in my life. I decided that, of all the feelings in the world, I wanted peace while I waited for my test results. The thought that generated peace for me was, "I can handle this."

I leaned into the waiting. If I had to spend the weekend in my closet, I would make it the best weekend in my closet ever. I created four podcast episodes, reviewed two papers, submitted revisions on a paper, and read several papers and a book. I enjoyed a marathon of trashy television. I called all my best friends. I rested and took naps. I allowed myself to accept the circumstances (because I couldn't change them). I generated a feeling of peace. It was a beautiful weekend.

What feeling do you want to cultivate in your life? What thoughts would help create that feeling for you? If you have a hard time finding the right thoughts, think back to when you last intensely experienced the feeling you want. What were you thinking to create that feeling? If that doesn't work, go to your future self who is many years wiser and already has all of those feelings; borrow her thoughts to create the feeling you want.

Life is 50-50

Half of life is painful (or worse, boring); the other half is beautiful. Trying to make every day of your life amazing will lead to disappointment. Not every day can be amazing. Some days are just "meh" because this is the human experience.

On New Year's Eve 2020, I signed multiple clients to my coaching program.

And I developed a runny nose.

It was a gorgeous day in Denver.

And I was quarantined in my closet.

It was the dawn of a new year.

And I might have COVID-19.

Life is 50-50.

And isn't that contrast beautiful?

Spoiler alert: I took a COVID-19 test and received the results in less than 12 hours. My test was negative. I missed zero days of work. I had a beautiful weekend in my closet. I created tremendous value for my academic career and coaching practice. I rested and watched television. The very next hike I went on was the most stunning hike of my life because of the lessons I learned waiting for my COVID-19 test.

All thoughts and feelings are available to you.

Choose the ones that serve you.

Christina A. Arnold is an academic GI pathologist and professional coach. She can be reached at YourPathInFocus.com.

Spotlight on...

Technology

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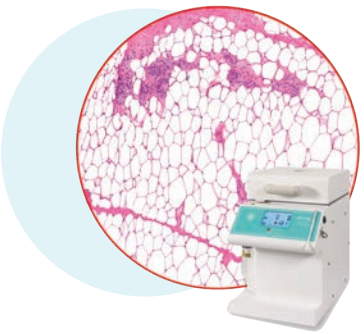

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The Digital Pioneer

Sitting Down With… Rajendra Singh, Professor of Pathology and Dermatology, Director of Dermatopathology, and Associate Chair of Digital Pathology at Northwell Health, New York, USA.

You're a pioneer in digital pathology – what led you to the field?

When I worked at the University of Pittsburgh Medical Center, we had residents, fellows, and visitors come from all over the world to train with us – and we had a lot of slides being digitized. I believe that, once you look at a digital slide, you realize it's going to change the way pathology is practiced and taught. I came to the US because I didn't have the resources to train myself, but digital pathology suddenly opened a lot of doors. Digital slides could be uploaded to the cloud so that anybody sitting in any country could log onto the platform and start teaching themselves pathology.

What inspired you to create PathPresenter?

I realized that I needed to make the resources we had at large academic institutions available to people anywhere in the world, but that was extremely difficult because the slides all came from different scanners that produced different file formats and therefore needed different viewers. To remedy this, we built a platform in which we could put the slides on the cloud, have the back-end software convert them into a single format, and then make them available on a single viewer. At first, it was just for our own use – so that we could use these digital slides for teaching – but, when other people saw the platform, they told us it was the sort of resource they had always needed. After that, institutions became interested and wanted to use the platform for their own internal teaching. That's when PathPresenter became a company and we hired people to build these platforms for interested institutions.

Last year, you hosted the first online pathology review for residents on PathPresenter. How did it go?

When COVID-19 hit, the entire medical education system had to go online – the question was, "How can we do it in a way that's easy to use and can bring together files from different scanners?" I reached out to a few people who are prominent on social media and, together, we built a conference in which we showed people how they can use these files for teaching – all for free. All the conference speakers volunteered and had the opportunity to pre-record their lectures if the timing didn't suit them. We also built a Q&A session that included even the pre-recorded lectures – when an attendee entered a question on the platform, the speaker received an email and could go online to answer the question. These tools weren't even heard of two years ago – and now we have an online community of renowned experts who are willing to put in the time to teach the entire world. More than 6,000 people registered for the conference (which is usually unheard of!) and we received a lot of good feedback that we'll be using to improve the platform.

Tell me about the new initiatives coming up on PathPresenter…

We are creating a section called "high yield" with the bread-and-butter cases that every trainee should know. We have teamed up with various societies and institutions whose members are going to build these high-use cases in which experts will point out features on the digital slides that helped them make a diagnosis. Because they're doing it on the cloud instead of on a multi-headed scope, it becomes an "infinite-headed scope!"

How did you end up on the editorial board of the WHO Classification of Tumors, 5th edition?

I was presenting at a conference in Chicago, talking about how PathPresenter can be used for data sharing in education. Ian Cree, the current pathology leader at WHO and the person in charge of the 5th edition, was sitting in the audience. Afterwards, he approached me and said they were moving the Blue Books to an online digital format, but wanted to make sure they were in line with how pathology is taught. Of course, there is no way you can teach pathology without having access to the slides. When he saw how PathPresenter worked, he realized it had the same mission as the WHO – to facilitate the spread of information around the world and democratize availability of resources, especially to low- and middle-income countries. Because of that, he asked me if I'd like to be on the editorial board – and, of course, I accepted.

"In the end, it is all about patient care."

Do you have any time management tips for lab medicine professionals?

It has to be a passion. It's not about making money – do your job and money will come. If you have a passion, it becomes much easier because you're not worried about how much time you're putting in. Not everyone can put all of their time into building platforms like PathPresenter; I have been lucky enough to have institutions support me along the way. But there is no magic formula for time management – the more you want to do it, the more passionate you will be about your projects, and I believe then you will find the time to fit them around your day-to-day work. In the end, it is all about patient care – and if there is anything we can do to help our patients, the world is going to come together to help you achieve your goals.

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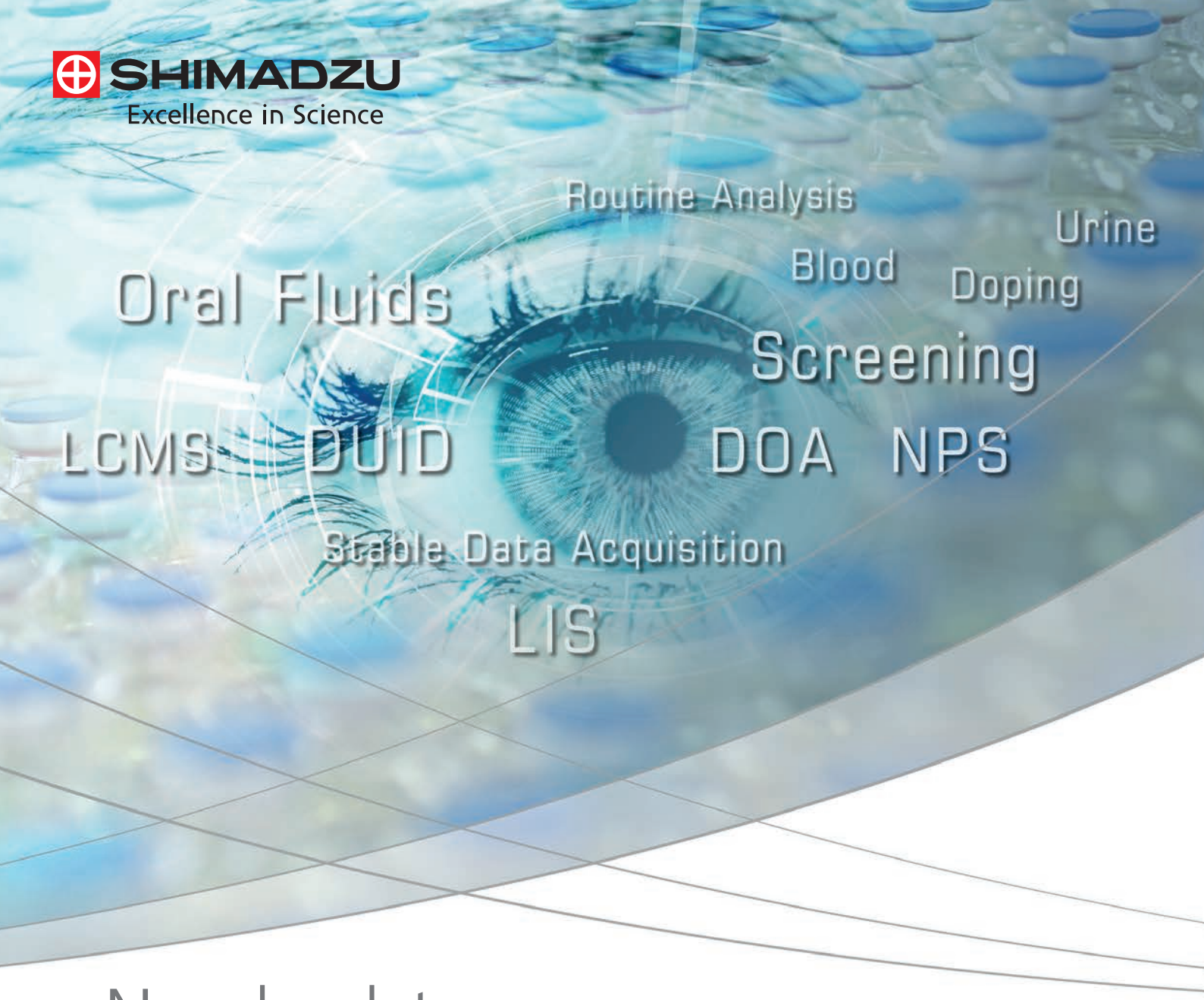

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