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Pathology's Stories – in Our Own Voices

Podcasting gives us the opportunity to interact with others in a brand-new way

My most vivid memory from medical school is a lecture from an ear, nose, and throat surgeon, who began by asking us, "What did Oscar Wilde, the famous 19th century poet and author, die from at the age of 46?" Such questions immediately attract my attention because the straightforward answer, or the consensus view, is suddenly cast in a new and suspicious light. As the lecture progressed, the intertwined worlds of medicine, surgery, and pathology appeared.

Textbooks nowadays provide an unparalleled wealth of knowledge about diseases, including their presentations, clinical manifestations, and treatments. A single disease, aspect of a disease, or even a simple statement of "fact" may take a lifetime to discover – a concept often overlooked when we are faced with remembering thousands of different diseases to pass our exams.

But it's the personal approach that makes pathology and its stories memorable – and that's where pathology media, and especially podcasts, shine. There is a wide range of pathology-focused podcasts to explore, and you'll learn more about several of them in this issue (see page 18). Mine – This Pathological Life (1) – focuses on the stories of our medical forefathers. We delve into each episode from a historical perspective and trace a path to the present to explore what we knew, what we know, and what we soon hope to know.

Our pathology predecessors were real people with real struggles – and we're fortunate to be the beneficiaries of their efforts. I am constantly amazed at the boldness, perseverance, and sheer luck that has shaped our understanding of medicine and disease. As a general pathologist, I have the privilege of exploring the many disciplines of pathology and inviting specialists from every subfield to speak on the show. It's this diversity of topics throughout pathology that lets our discipline's podcasts reach beyond our colleagues to inform other health care professionals, researchers, and even patients. And it's the uniqueness of the podcast medium that lets us explore the personal side of pathology, honoring the discoveries of those who came before us and celebrating the contributions of those who work alongside us.

If our listeners enjoy our episodes half as much as we enjoy recording them, we podcasters know they'll have a great time. Now – if you'll excuse me – having once again recalled that Oscar Wilde lecture, I believe I have a new podcast to record…

Travis Brown

Travis Brown is a general pathologist at Clinpath Pathology, Mile End, South Australia, Australia. He hosts the podcast This Pathological Life and can be found on Twitter at @DrTravisBrown.

Reference

1. *T Brown, "This Pathological Life" (2021). Available at: https://bit.ly/2NbGuSm.*

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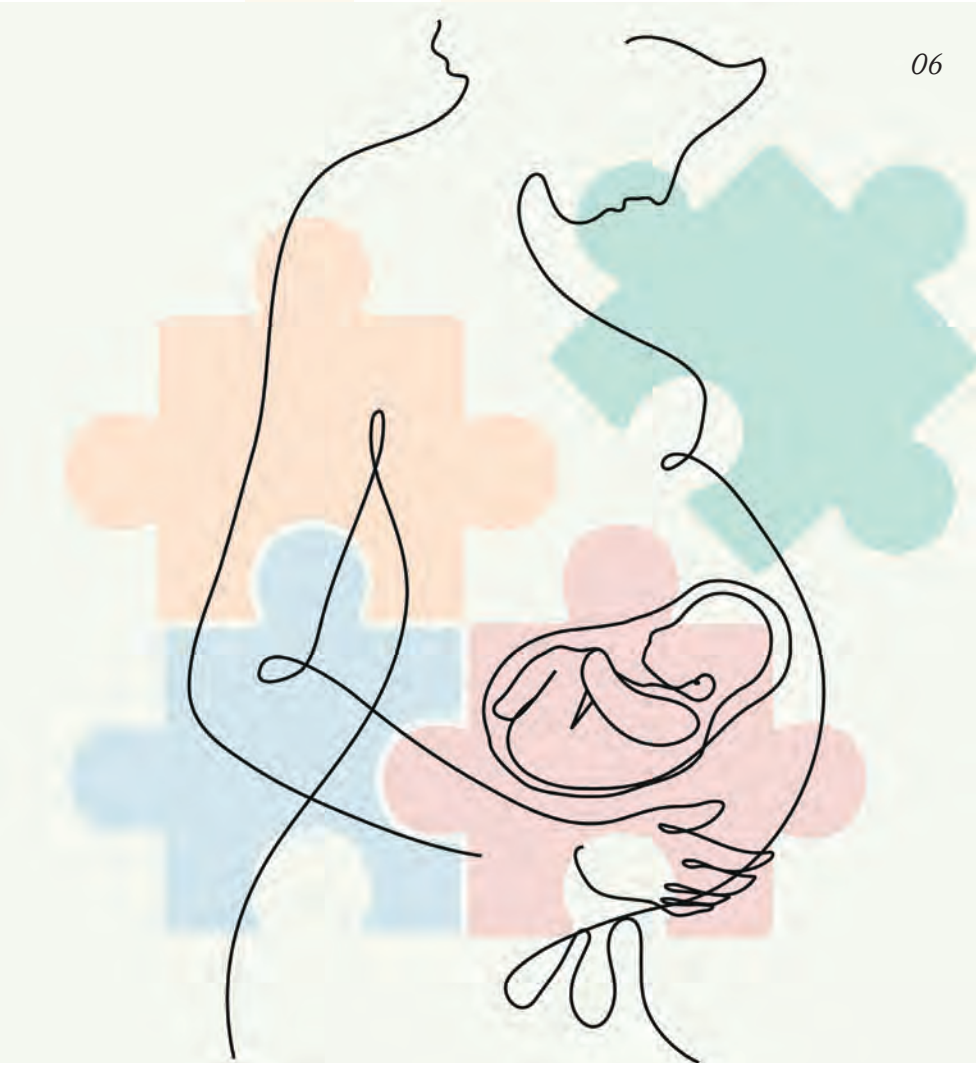

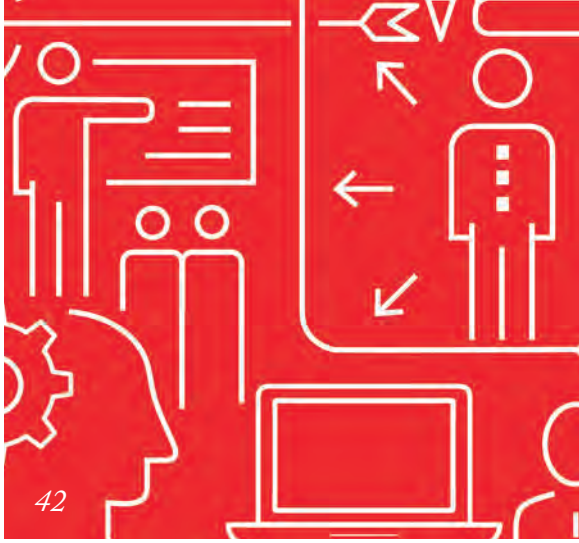

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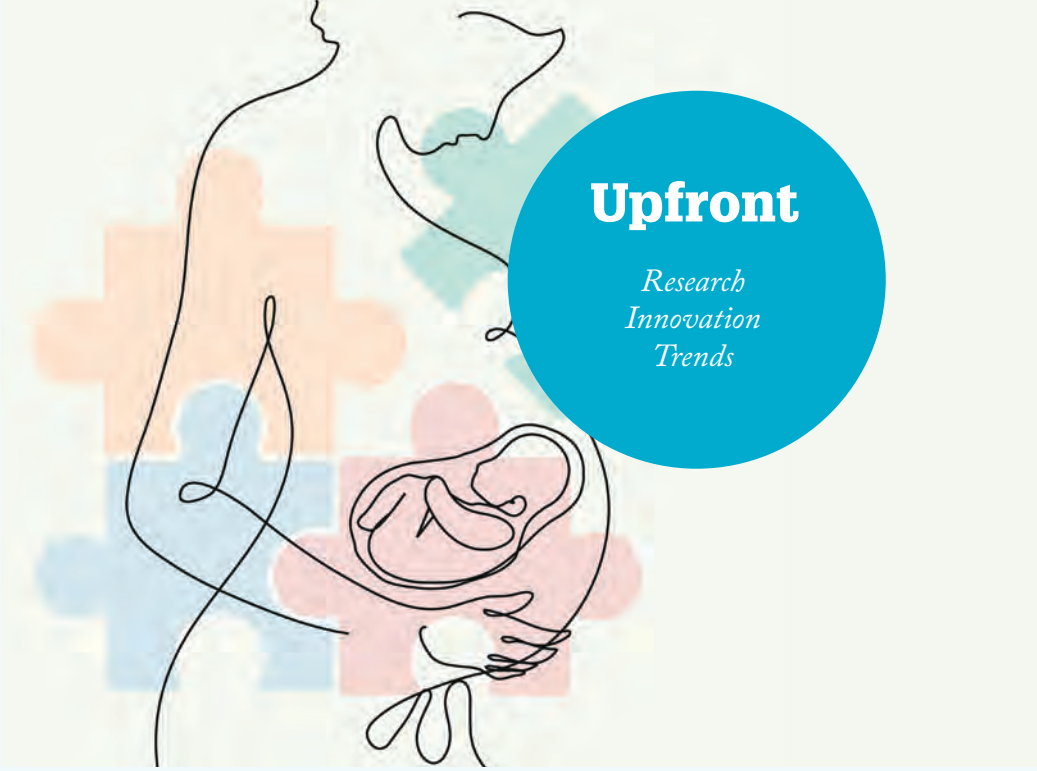

Pieces of the Puzzle

Four new studies contribute to our growing understanding of autism spectrum disorder

Methylation clues

Genetics may be heavily involved in ASD etiology – but now, researchers are also considering the role of paternal epigenetics. A team at Washington State University collected sperm samples from fathers of children with or without ASD to analyze changes in DNA methylation (1). Genome-wide analysis revealed 805 significant differential DNA methylation regions that could be used as biomarkers to predict paternal offspring autism susceptibility.

AI on autoantibodies

But what about mothers? Maternal autoantibodies of fetal brain proteins specific to ASD have previously been identified – a subtype now known as maternal autoantibody-related ASD (2). Researchers have developed a serological assay with machine learning to identify the reactivity patterns of ASD-specific maternal autoantibodies against eight proteins highly expressed in the fetal brain (3). The highly accurate test has the potential to predict a woman's likelihood of having a child with ASD.

Beyond inheritance

Mosaic mutations that occur after conception may also be implicated in ASD. Using whole-genome sequencing to investigate mosaic mutations in the frontal cortices of participants with and without ASD, researchers have found that most brains have similar rates of "point" mosaic mutations – but, in participants with ASD, mutations were more likely to affect parts of the genome involved in brain function (4).

Copy number variants (CNVs) in mosaic patterns also differ in people with ASD (5). Larger CNVs (involving 25 percent or more of a chromosome) have been found in people with ASD and CNV size is linked to ASD severity. Surprisingly, smaller CNVs that are associated with ASD when found in all cells were no longer correlated when found in mosaic mutations.

It's clear that no one factor causes ASD – and that only by stepping back and assessing each piece of the puzzle can we develop accurate screening and diagnostic tools.

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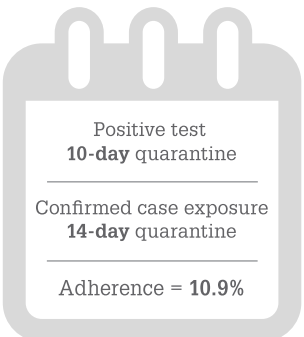
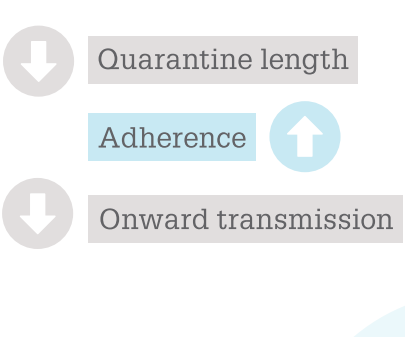
INFOGRAPHIC

Lifting the Burden of Quarantine

A test-to-release strategy may reduce quarantine length of uninfected COVID-19 contacts





LABORATORY LEARNINGS

The latest breakthroughs in pathology and laboratory medicine research

Looking at Lipids

At present, diagnosis and stratification of asthma patients is performed using blood tests, X-rays, lung function tests, and examination of allergies – hardly simple. But new findings show that urinary eicosanoids can accurately distinguish type 2 asthma, opening the door for direct, noninvasive phenotyping of the condition (1).

We the Jury

Artificial intelligence (AI)'s role in digital pathology is on the rise – and now, researchers have found that jurors are less likely to find a physician liable for malpractice if they have accepted AI's precision medicine recommendations rather than rejected them (2).

Miscreant Monocytes

Despite their role in inflammation, monocytes and monocyte-derived cells are poorly understood in sarcoidosis. Now, research has found higher levels of these mononuclear phagocytes in the blood and bronchoalveolar lavage fluid of pulmonary sarcoidosis patients (3) – indicating their potential role as predictors of disease outcome.

Complementary Proteomics

Researchers have used a nanoparticle-based protein enrichment technology to identify a highly sensitive and specific protein signature of early-stage breast cancer (4). The assay could be used in conjunction with mammography to improve screening for the disease and reduce false positives.

New Day, New Disease

A new genetic disorder has been discovered: linkage-specific deubiquitylation deficiency-induced embryonic defects syndrome, or LINKED syndrome for short (5). The multiple-congenital-anomaly disorder is characterized by developmental delays and brain, heart, and facial malformations caused by a mutation of *OTUD5* that disrupts key molecular stages during embryonic development.

Computational Cancers

Researchers at St. Jude Children's Research Hospital have developed a new computational framework – MethylationToActivity – to infer gene promoter activities from DNA methylation signatures in adult and pediatric cancers (6). The deep learning tool may improve precision treatment decisions by factoring in genetic variants and epigenetic deregulation.

See references online at: tp.txp.to/lablearnings

Do You Know?

COVID-19 statistics – revealed!

What percentage of patients who died of COVID-19 in the intensive care units of major US medical centers (up to May 1, 2020) suffered from respiratory failure?

a) 15 percent
b) 35 percent
c) 50 percent
d) 93 percent

Answer: d) 93 percent

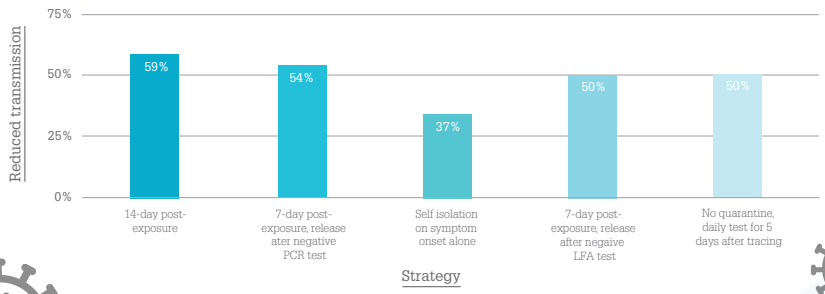
These data were reported by the multicenter STOP-COVID research group (Study of the Treatment and Outcomes in Critically Ill Patients with COVID-19). The study included a cohort of 2,215 COVID-19 patients admitted to the ICUs of 65 participating US hospitals (1).

Reference

1. *S Gupta et al., JAMA Intern Med, 180, 1 (2020). PMID: 32667668.*

New model assumes adherence levels of

Estimating reduced transmission with test-to-release strategies



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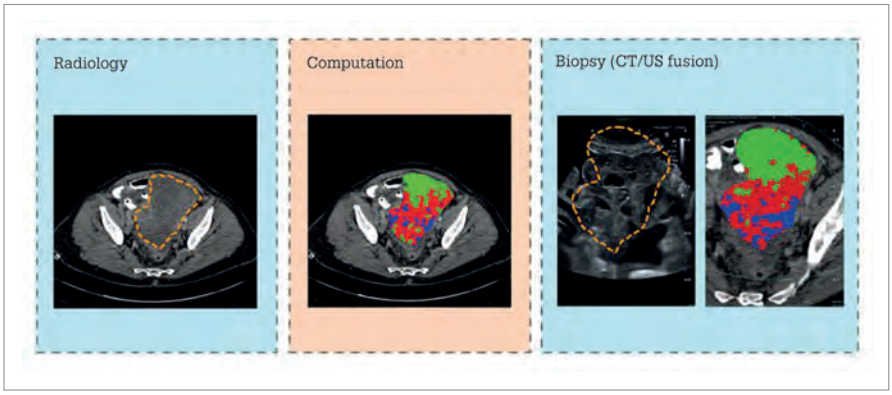
Two Is Better Than One

Combining CT scans with ultrasound images for more accurate tumor biopsies



Credit: Evis Sala, University of Cambridge, UK.

Cancer diagnostics are advancing rapidly, but for patients with high-grade serous ovarian cancer (HGSOC) – in which high genomic heterogeneity is common and associated with reduced progression-free survival – disease stratification needs a major overhaul.

A multidisciplinary team at the Cancer Research UK Cambridge Centre – with expertise in radiology, physics, oncology, and computer science – previously found that computed tomography (CT) scans can show high heterogeneity of HGSOC lesions that indicate different molecular profiles (1). "To study this relationship further, we needed to be able to selectively sample the regions – or 'habitats' – of interest, which requires imaging guidance," says Mireia Crispin-Ortuzar, a researcher on the study. "However, habitats are extracted on CT scans, whereas biopsies are most commonly obtained using ultrasound guidance. This prompted us to develop a technique to target ovarian cancer habitats using CT-ultrasound fusion."

The team used radiomics to spatially identify the habitats from the CT scans, then superimposed the maps onto CT images and co-registered them with ultrasound images to guide biopsies (2). In doing so, they successfully captured the diverse range of cancer cells within the tumors – leading to a more accurate biopsy.

Though a tremendous step forward for the research community, those who feel it most will be the patients. "When you are first undergoing the diagnosis of cancer, you feel as if you are on a conveyor belt – every part of the journey being extremely stressful," said Fiona Barve (3), who was diagnosed with stage four ovarian cancer in 2017. "This new, enhanced technique will reduce the need for several procedures and allow patients more time to adjust to their circumstances. It will enable more accurate diagnosis with less invasion of the body and mind. This can only be seen as positive progress."

So what's next for the team? "The technique enables us to obtain tissue samples that are accurately matched to regions of well-defined characteristics on CT scans," says Crispin-Ortuzar. "We plan to explore the correlation between imaging parameters and tumor biology dynamically – at different points during treatment. This will form the foundation for a more strategic, targeted approach to ovarian cancer biopsies."

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1. *L Rundo et al., Comput Biol Med, 120, 103751 (2020). PMID: 32421652.*
2. *L Beer et al., Eur Radiol, [Online ahead of print] (2020). PMID: 33315123.*
3. *University of Cambridge (2021). Available at: http://bit.ly/2MqC9vT.*

Detect, Distinguish, Diagnose

A spectroscopic technique offers potential for noninvasive cancer screening

Oral squamous cell carcinoma (OSCC): common, but difficult to detect early – leading to poor prognosis. To address this challenge, researchers from the University Medical Center Hamburg-Eppendorf used shifted-excitation Raman difference spectroscopy (SERDS) to evaluate the molecular composition of OSCC, non-malignant lesions, and physiological mucosa – and whether they can be differentiated by Raman spectroscopy (1).

Based on physiological tissue of the oral cavity, they found that non-malignant and cancerous lesions can be distinguished with high accuracy using SERDS. The method also yielded high accuracy in identifying non-malignant lesions that required confirmation by surgical biopsy. "Although it won't replace biopsies any time soon, the technique could help reduce the lapse of valuable time as well as the number of invasive procedures," said lead author Levi Matthies (2).

See extended article and references online at: tp.txp.to/OSCC

IMAGE OF THE MONTH

Keep on Folding

Previous efforts to visualize RNA folding were based on approximations and assumptions, but researchers at Northwestern University have captured the data using their new tool – Reconstructing RNA Dynamics from Data (R2D2) – and used computer models to produce videos of *Escherichia coli* signal recognition particle RNA folding (1). In the R2D2 video, the RNA molecule folds itself into knots before quickly untying itself and finding the correct structure – something that has never been seen before. "We think the RNA has evolved to untie itself from knots because if knots persist, it can render the RNA nonfunctional," said Julius Lucks (2), lead researcher on the study.

Check out the video and full references at tp.txp.to/rna-fold

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

QUOTE of the month

"Medical students: Pathology is not 'supplementary' to your medical education – it is the foundation of your medical education! Pathology is the language of medicine [...] All medical knowledge stems from when we were all generalists and everyone performed 'pathological' examinations. The physical exams you learn? Those are gross examinations! You need to understand what you are looking for when you examine a patient."

Karleen Meiklejohn
Read the full thread at: tp.txp.to/kmei-twt

Sewage Clues to SARS-CoV-2

By tracking virus levels in wastewater, experts can identify areas where COVID-19 is more prevalent

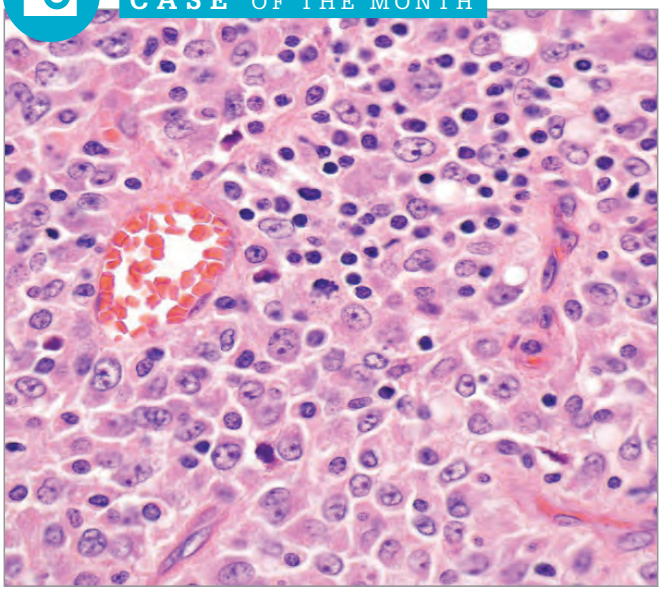
Population testing for COVID-19 can be costly and logistically difficult – but it is also crucial to understanding the spread of the disease. To use diagnostic resources more efficiently, the industry has turned to innovative methods – such as wastewater-based epidemiology (WBE) – to understand where infections are occurring even before symptoms appear.

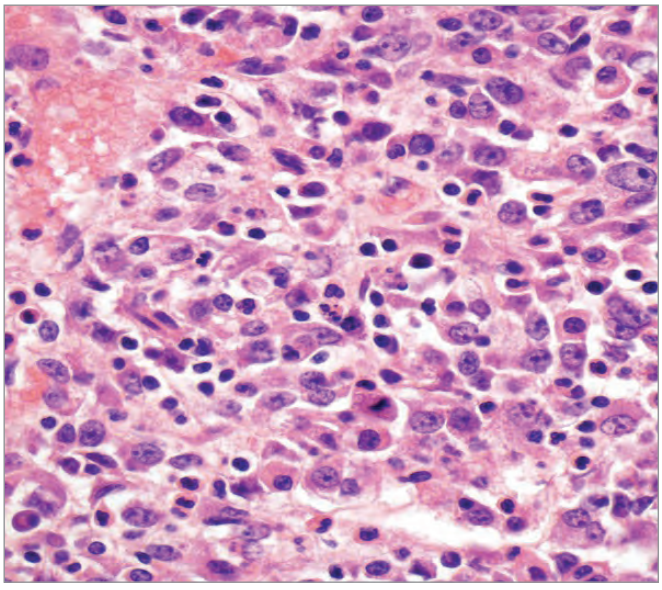
WBE involves pinpointing areas where SARS-CoV-2 is heavily prevalent by measuring viral RNA shed into wastewater through the feces of infected individuals. Epidemiologists use methods such as RT-PCR or ddPCR to test wastewater samples for the presence of viral RNA – but, because samples are diluted, methods must be highly sensitive. A recent case study showed that ddPCR could detect SARS-CoV-2 RNA between levels of 101 to 104 copies/100 mL (1). New approaches like WBE could help us conserve diagnostic resources, improve public health measures, and better understand COVID-19.

Reference

1. *R Gonzalez et al., Water Res, 186, 116296 (2020). PMID: 32841929.*

CASE OF THE MONTH





A 35-year-old male presented with abdominal pain and was found to have a 12 cm retroperitoneal mass invading the kidney and involving multiple lymph nodes. Among other stains, the tumor was positive for CD4, CD68, and CD163 and negative for pancytokeratin, S100, and CD1a.

What is the best diagnosis?

a) Langerhans cell sarcoma
b) Follicular dendritic cell sarcoma
c) Histiocytic sarcoma
d) Interdigitating dendritic cell sarcoma

Answer to last issue's Case of the Month…

b) *Treponema pallidum*

The lymph node shows syphilitic lymphadenitis, a clinical manifestation of syphilis.

Syphilis is a disease with three stages; syphilitic lymphadenitis can be seen in any stage. The most commonly observed histologic changes accompanying syphilis include follicular and paracortical hyperplasia, interfollicular plasmacytosis, capsular thickening (frequently prominent, as in this case) with plasma cell infiltration, and obliterative vasculitis. Some cases can show collections of epithelioid histiocytes or well-formed granulomas and stromal and vascular hyperplasia. In the tertiary stage, lymph nodes can show gummatous lymphadenitis, characterized by prominent necrosis surrounded by epithelioid histiocytes and multinucleated giant cells. In the affected lymph nodes, spirochetes can be demonstrated using Warthin-Starry staining, immunofluorescence, or immunohistochemical stain (the preferred method).

Submitted by Anamarija M. Perry, Associate Professor of Pathology, and Lauren B. Smith, Professor and Director of Hematopathology at the University of Michigan, Ann Arbor, Michigan, USA.

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To register your guess, please go to http://tp.txp.to/0321/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.

AIRA MATRIX

Step Beyond the Current Digital Paradigm

AUTOMATE

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- Detecting & grading Pancreatic Intraepithelial Neoplasia

OPTIMIZE

- EBUS TBNA adequacy assessment
- Comprehensive radical prostatectomy reporting

PREDICT

- Precision Diagnostics & Predictive Analytics:
  - Prostate Carcinoma
  - Lung Carcinoma

AIRA Matrix operates beyond the current digital AI paradigm and strives to harness the true potential of deep learning in Pathology. We provide automation tools, operational efficiency solutions and predictive analytics – all to aid cancer diagnostics, prognostics and build better prediction models.

Interested in learning more or collaborating? Contact us at info@airamatrix.com

In My View

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

Your Brain on Paper

Mind maps for efficient memorization and retention in pathology

By Vishakha Pardeshi, Pathology Resident at Wayne State University, Detroit, Michigan, USA

Diagnosis is an art – and, like any art, it requires the right supplies and technique. Rather than paints and brushes, our supplies are the information we gather about a lesion – for instance, its site or histological characteristics. And rather than careful brushstrokes or energetic splatters, our technique is the approach we take to organizing our thoughts. With so many different tissues and lesions, we need a simple approach to categorizing them. And for me, that's where mind maps come in.

Put simply, a mind map is a visualization tool focused on a central concept. It breaks the monotony of data collection and helps categorize individual pieces of information into colorful, memorable items. As pathologists, it's not enough for us to read the details of a case – we must also retain those details and draw connections between them to create a "big picture" overview. Mind maps allow us to visually represent and sort those connections. After all, to quote Robertson Davies, "The eye sees only what the mind is prepared to comprehend (1)."

I realized as a student that, if I knew in advance what I needed to see under the microscope, I would be able to see it. But pathology is a vast field – and only by organizing and conceptualizing the material could I hope to understand it fully. And so, in my second year of pathology residency, I started making mind maps. But they're not only useful for studying – they helped me with assignments. I even used a mind map to formulate this article!

"Do you need special software? Not necessarily; mind maps are so easy and versatile that the least you require is paper and a pencil."

Do you need special software? Not necessarily; mind maps are so easy and versatile that the least you require is paper and a pencil. My first mind maps – just drawn on paper – work wonders! Anyone can make a mind map, but following a defined process makes it easier.

First, you need to know your subject matter. Mind maps can't replace reading, but they can replace re-reading. On your first examination of the subject matter, you can identify i) a central concept, ii) the ideas that revolve around that central concept, and iii) any further ideas that connect to those thoughts. The next time you want to review the subject, just take a look at your mind map. You'll find revision easier, quicker, and more effective.

I share my mind maps on Twitter and on my website (pathfiles.com). However, I recommend that you make your own; it's not just the map itself, but the creative process that aids in comprehension and retention. Mind maps – and the brain work involved in creating them – exist to make life simpler. They can help you with not only education, but also other aspects of your career – researching, framing a report, or even planning your day. I encourage you to give mind maps a try. You will be amazed at the results!

Read an extended version of this article online at: tp.txp.to/mindmap

Reference

1. *R Davies, Tempest-Tost. Clarke Irwin: 1951.*

So Near and Yet So Far

Despite advances in the field, remedial human germline editing still has a long way to go

By Eli Y. Adashi, Professor of Medical Science and Former Dean of Medicine and Biological Sciences, Warren Alpert Medical School, Brown University, Providence, Rhode Island, and I. Glenn Cohen, Deputy Dean and James A. Attwood and Leslie Williams Professor of Law, Harvard Law School and Faculty Director, Petrie-Flom Center for Health Law Policy, Biotechnology, and Bioethics, Harvard University, Cambridge, Massachusetts, USA.

"[...] we might anticipate the in vitro culture of germ cells and the direct control of nucleotide sequences in human chromosomes, coupled with recognition, selection, and integration of the desired genes (1)."

It was 1963 when Joshua Lederberg, one of the finest minds to grace American science (and a Nobel prize awardee for the discovery of bacterial conjugation), wrote those words in Man and His Future.

We can only speculate as to the functionality Lederberg envisioned, but it is likely that he had in mind what we would today call "word processing" – a system in which we replace one letter, word, or paragraph with another using simple commands such as "cut and paste."

Transmuted to the genome editing arena, Lederberg's construct would have permitted the substitution of one base (or gene) for another, using commands such as "delete," which would give rise to a knockout, or "delete and insert," which would lead to a knockin. The CRISPR-Cas9 endonuclease fits this bill perfectly. What sets CRISPR-Cas9 apart from its predecessors is its supreme targetability, fidelity, malleability, and versatility (2) – and that brings us to remedial editing of the human germline genome.

"The deepest promise of this technology is transitioning from chance to choice."

There are some basic questions we must ask ourselves when discussing such a therapy. For example, what is the objective of remedial human germline editing? Simply put, it is to prevent disabling and life-truncating heritable monogenic maladies – although there are formidable philosophical questions as to whether this is achieved by correction or substitution (in other words, is the pre- and post-edited embryo the "same person"). The deepest promise of this technology is transitioning from chance to choice – a lofty goal which, if taken to its logical conclusion, would rid humanity of the so-called "monogenic scourge."

But what universe do we envision ourselves occupying with this new technology? Aside from the moral imperative of human germline editing, would we want to tackle the over 10,000 human monogenic disorders that are currently listed in Online Mendelian Inheritance in Man (3)? Indeed, we would be well-advised to assume a more focused approach, beginning with edit-suitable maladies for which peri- or post-natal medical therapy is infeasible, those for which peri- or post-natal somatic editing is ineffective, or those for which preimplantation genetic diagnosis is either associated with a rate-limited embryo complement or of no use at all. Preference should also be afforded to genes or alleles that are highly penetrant, ideally singular and, of course, CRISPR-accessible. It is worth emphasizing that we are discussing the desirability of this treatment for terrible monogenic diseases only, because bodies like the National Academies are appropriately wary of its extension to perfectionistic human enhancement (4).

The final question we should pose concerns the present state of remedial human germline editing. The simple answer is "nascent" – or, as the title would suggest, so near and yet so far. Much remains to be optimized in the process of gene editing – efficiency, specificity, and uniformity being top of the list (5). Once we overcome these technical challenges, safety and efficacy will be assured. Then – and only then – will remedial human germline editing become a reality in the service of the Hippocratic ideal.

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2. *M Jinek et al., Science, 337, 816 (2012). PMID: 22745249.*
3. *Online Mendelian Inheritance in Man. Available at: https://bit.ly/362acBa.*
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Opportunity in Education

How virtual learning benefits pathology and laboratory medicine

By E. Blair Holladay

The challenges presented by the COVID-19 pandemic have not left any area of our lives, personal or professional, untouched. In pathology and laboratory medicine, we've seen an evolution of testing and research. Advocacy efforts have grown as we've amplified the voices of medical laboratory scientists, making ourselves heard and stepping into the spotlight to show patients and healthcare colleagues the critical work we do every day. Where we were a year ago is barely recognizable compared with where we are – and what we know – now.

As the landscape of the laboratory continues to evolve, we are seeing significant progression in the way we educate and train our current and future workforce. Traditional in-person learning is not always possible in today's pandemic environment. Over the past year, there has been a significant pivot to online education to maintain the standards and knowledge pathologists and medical laboratory scientists need to provide high-quality care.

At the beginning of the pandemic, establishing a footprint in virtual education was not without pitfalls. But, as we developed a sense of normalcy around living our lives online when we couldn't be together in person, educating and learning in a virtual environment got easier, more expansive, more creative, and more targeted toward meeting the needs of the community. From the start, ASCP committed to bringing virtual education to the pathology and medical laboratory community in multiple formats. We launched a series of Town Hall events as a resource for the most up-to-date information on advocacy efforts, laboratory test developments, and health disparities affected by COVID-19. Knowing that pathology and medical laboratory professionals are working tirelessly under the weight of the pandemic, we offer a free course on burnout prevention. And, starting this March, we are launching our newest educational experience to date, Virtual Pathology Grand Rounds, which brings academic Grand Rounds directly to the learner.

As virtual education grows, it benefits the pathology and laboratory community not only in the US, but around the world. Virtual educational events allow people to join in who would not otherwise have been able to attend. Expanding our educational opportunities to include virtual learning gives the information we share a broader reach and improves patient care globally.

COVID-19 has pushed us all to innovate in ways we never thought possible – and access to education is one of the benefits. Whether online or in person, educating the future of our workforce – as well as continuing our own education throughout our careers – is essential. Education lets us provide the critical knowledge our patients rely on and establishes our seat at the table of effecting change in healthcare. At this time of unparalleled challenges, continuing to expand virtual education opportunities is essential to not just our patients, but healthcare as a whole.

A Comprehensive Answer for Cancer

Is comprehensive genomic profiling always the right approach?

What is comprehensive genomic profiling (CGP)?

CGP is the simultaneous detection of all classes of genomic alterations across hundreds of genes with a single test – and a single sample. This forward-thinking technique was enabled by the advent of next-generation sequencing (NGS) and its ability to deliver ultra-high throughput and scalability.

Why is CGP so important for precision oncology research?

Cancer is "a disease of the genome," driven by the sequential accumulation of genetic and epigenetic changes in oncogenes and tumor suppressor genes. The more we learn about cancer, the more such changes we discover – and the more these variants, or biomarkers, become relevant to translational and clinical research into new cancer treatments. It's now clear that many of them must be interrogated together so that we can understand as much about the molecular makeup of a tumor as possible. This type of simultaneous interrogation is sometimes only possible using CGP.

Take, for example, breast cancer, in which we have long been testing single-gene biomarkers, such as *ERBB2* (Her2) amplification, *BRCA1* and *BRCA2* mutations, and, more recently, *PIK3CA* mutations. Now, we are also beginning to examine homologous recombination repair (HRR) pathway gene mutations and complex biomarkers such as genomic instability to assess HRR deficiency (HRD).

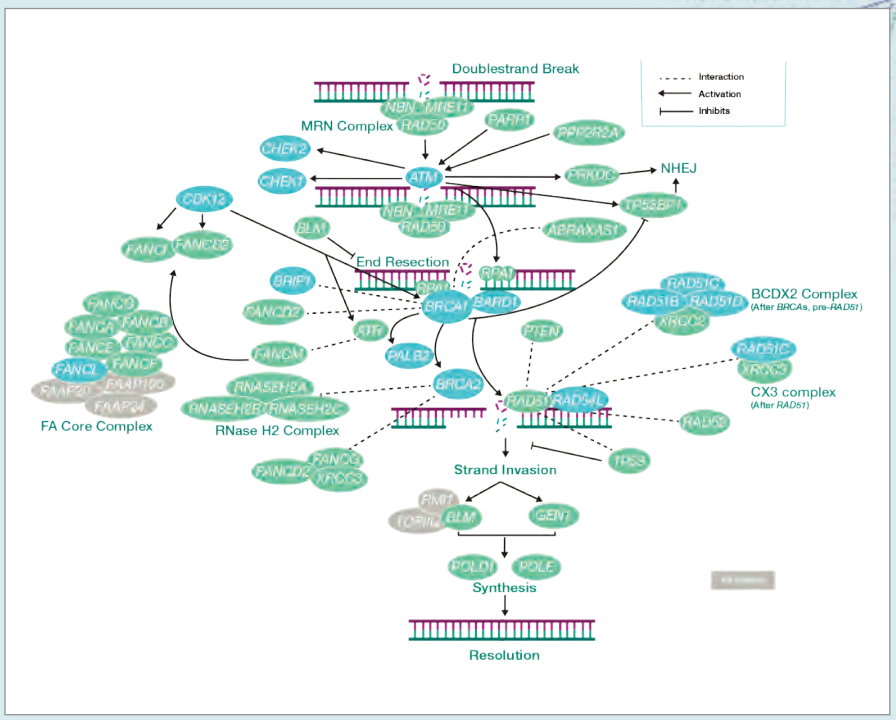


Figure 1. HRR pathway. Non-grey genes are covered in the Oncomine Comprehensive Assay Plus. Purple genes were included in clinical trials with prostate cancer clinical research samples

Is CGP a technique for every lab?

Not every approach to CGP is suitable for every laboratory. Until recently, labs' ability to generate the increasing amounts of CGP data needed has been hindered by the technical limitations of the available techniques. Some hybrid capture-based NGS CGP techniques are complex workflows with up to five different instruments (and five corresponding sets of software) that must be stitched together. This requires significant expertise and extensive hands-on lab work – thus preventing broader adoption of the technique.

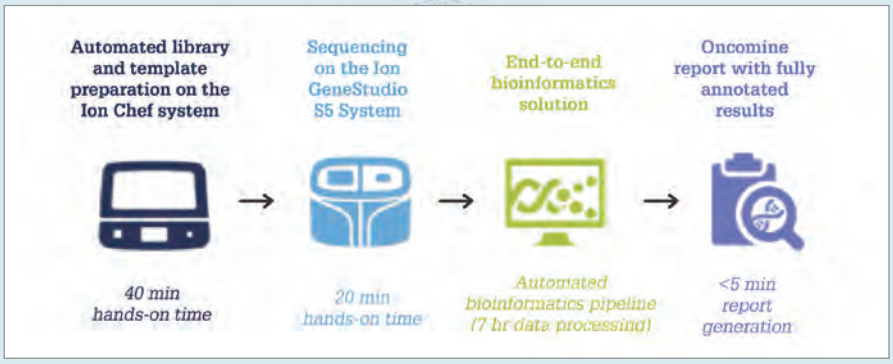
But now, Thermo Fisher's new and enhanced Ion Torrent Oncomine Comprehensive Assay Plus comes as a complete, highly automated (60 minutes of hands-on time) solution with streamlined data analysis and reporting – all from a single supplier, enabling end-to-end protocols. This will allow many more labs to implement CGP.

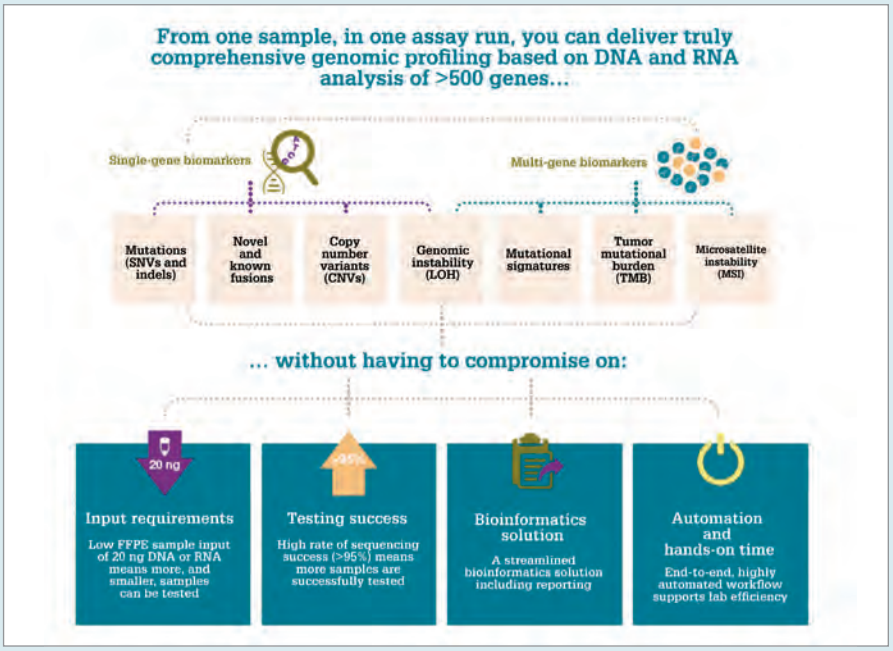
Is CGP the right choice for all cancer sample profiling?

Not necessarily; based on pure common sense, one size does not fit all. Let's take non-small cell lung cancer (NSCLC) as an example. All biomarkers relevant for clinical research into NSCLC can be tested by one 50-gene targeted panel. It's cheaper, faster, and requires less sample input than CGP – which is critical in NSCLC, where "tissue is still an issue." Some hybrid capture-based NGS CGP techniques require so much tissue that over half of normal clinical research samples cannot be analyzed (1). If all of the necessary information can be obtained from a single targeted panel, why risk attempting CGP and potentially ending up with no results at all? Even in genomic profiling, bigger is not always better.

When is CGP the right choice?

There are four key scenarios in which comprehensive genomic profiling is most impactful.





Oncomine Comprehensive Assay Plus enables truly comprehensive genomic profiling without the limitations of other CGP technologies.

1. *You have evaluated your sample with a smaller targeted panel and the results came back negative.*
   Reflexing to CGP increases the chance of finding less common variants with potential relevance.
2. *You need to analyze complex multi-gene biomarkers as well as single-gene biomarkers.*
   In many scenarios, complex multi-gene biomarkers such as microsatellite instability (MSI) or tumor mutational burden (TMB) are required as well as mutations, fusions, and copy number variants. Clinical immuno-oncology research (for example, using colon cancer samples) is one such scenario.
3. *You are assessing the HRR pathway.*
   HRD can be assessed using two main strategies: i) detection of genetic causes, such as germline or somatic mutations of HRR genes, including *BRCA1* and *BRCA2*; and ii) evaluation of "genomic scarring" representing genomic instability, such as the analysis of genome-wide loss of heterozygosity.
4. *You are working with cancers of unknown primary.*
   Interrogation with a broad, comprehensive test will deliver maximum insights in the shortest amount of time, potentially uncovering information that can help identify the cancer.

Which is the right CGP solution for you?

Although there are multiple CGP solutions on the market today, many are technically complex and require large amounts of starting sample material. They also are not truly "comprehensive" in that they may not enable analysis of all complex biomarkers or mutational signatures – despite the fact that they are becoming standard in some clinical research.

That's why Thermo Fisher Scientific developed the Ion Torrent Oncomine Comprehensive Assay Plus. Requiring only 20 ng of formalin-fixed, paraffin-embedded sample – the lowest sample requirement for CGP on the market – it analyzes over 500 genes. Including both DNA- and RNA-based variants and all relevant single- and multi-gene biomarkers, the Oncomine Comprehensive Assay Plus is truly comprehensive genomic profiling, without compromises.

Reference

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Learn more about the Oncomine Comprehensive Assay Plus and the value of HRD assessment in a CGP assay in our on-demand webinar at tp.txp.to/thermo-web/11.3.21

For Research Use Only. Not for use in diagnostic procedures

HAVE *You* HEARD?

Podcasting – the audio revolution taking over informal pathology education

By Michael Schubert

Long gone are the days of learning medicine solely by didactic lecture, seated in crowded halls, pen in hand, notebook on desk. The educational revolution has brought forth practical experiences, simulated autopsies, virtual grand rounds, and a host of innovative educational tools. But it's not just formal education that has seen a sea change; nontraditional learning has also fed into revolution. And among the fastest-growing informal training tools are podcasts – audio recordings that can be listened to anytime, anywhere, on any subject. From true crime tales to hobby how-tos, there is a podcast for every interest – and pathology is no exception. We spoke to a panel of pathology podcasters to find out what inspired them to take on the challenge of hosting a modern-day radio show – and why they think the medium is so popular.

The PANELISTS

LORI RYAN
(ScopeMD)
scopemdpodcast.com

DENNIS STRENK
(People of Pathology)
peopleofpathology.podbean.com

NATALIE BANET
(Deeper Levels)
deeperlevels.natalieba.net

JORDAN TAYLOR AND NICOLE CROOM
(Dead Men Do Tell Tales)
deadmendotellpodcast.com

XIAOYIN (SARA) JIANG, CHRISTINA ARNOLD, MICHAEL ARNOLD, AND KAMRAN MIRZA
(PathPod)
pathpod.podbean.com

LOKMAN SUNG
(Detroit's Daily Docket)
detroitsdailydocket.buzzsprout.com

WHO ARE THE PEOPLE BEHIND THE PODCASTS?

Lori Ryan (ScopeMD): I am an AP/CP trained pathologist with a master's degree in epidemiology. I am privileged to serve multiple patient populations as a pathologist; most of my workday is spent signing out lung pathology and cytopathology cases. I am director of the immunohistochemistry laboratory and also serve as Chair of Pathology at Abbott Northwestern Hospital in Minneapolis.

Dennis Strenk (People of Pathology): I'm a pathologists' assistant (PA) and was previously a histotechnologist. I started in the laboratory in 1997 – by accident. At the time, I had a degree in biology and wanted to go into microbiology. I ended up getting a job as a lab assistant in the histology department of a local hospital and found that I loved it. The more I learned, the more I enjoyed it – and I just kept going from there.

Natalie Banet (Deeper Levels): I'm an academic pathologist and I practice in Rhode Island. I specialize in gynecopathology and cytopathology. I have wanted to be a physician for as long as I can remember. In my journey through medical school, pathology – specifically, histology – was one of my favorite subjects, and I ended up in this career after realizing that not only is it the best fit for my style of learning, it also facilitates my love of teaching.

Jordan Taylor (Dead Men Do Tell Tales): My grandfather was a pathologist and, at the time, local pathologists covered forensics cases, so I grew up hearing some very interesting stories. You can't escape pop culture, either; I watched all the TV shows, including Crossing Jordan, which was about a forensic pathologist named Jordan in Boston, two hours from where I grew up – and I went, "That's me!" I loved the idea that there were doctors who could put "bad guys" away. I tried to keep an open mind throughout my education, but I pretty much always knew I wanted to be a forensic pathologist.

Nicole Croom (Dead Men Do Tell Tales): I also got interested in forensic pathology in high school. Unlike Jordan, I didn't have any firsthand stories, and although I really liked crime TV shows growing up, I never focused on the person doing the autopsy. It wasn't until high school, when I started asking myself what I wanted to do with my life, that I thought more deeply about it. In my senior year, I shadowed a deputy coroner and met Bennet Omalu, who was chief medical examiner at the time. He said I could come in anytime I was free, so during college breaks, I worked with him. He was a fantastic mentor. When I applied to medical school, I wrote my personal statement about wanting to be a forensic pathologist – and they still let me in! Like Jordan, I tried to keep an open mind, but nothing drew me the way forensic pathology had.

Xiaoyin (Sara) Jiang (PathPod): I am at Duke Health and do cytopathology and head/neck/endocrine pathology. I love

pathology because I get to solve puzzles every day, harness my love of science, and educate and network with amazing colleagues around the world.

Christina Arnold (PathPod): I am from the University of Colorado and I practice gastrointestinal pathology. I love pathology because it is visual, interesting, lets me think outside the box, and the field is full of wonderful educators.

Michael Arnold (PathPod): I am a pediatric pathologist and Medical Director of Anatomic Pathology at Children's Hospital Colorado. I am a visual person, so I love that anatomic pathology is a very visual field. Pediatric pathology is a relatively general subspecialty, so every day is a different learning opportunity.

Kamran Mirza (PathPod): I am a hematopathologist at Loyola Medicine in the Chicagoland area and serve as Vice Chair of Education in the Department of Pathology and Laboratory Medicine. I was always intrigued by the behind-the-scenes, but extremely powerful, role of pathology and instantly fell in love with the field.

LokMan Sung (Detroit's Daily Docket): I am an Assistant Medical Examiner at the Wayne County Medical Examiner's Office and a Clinical Associate Professor of Pathology at the University of Michigan Department of Pathology. My decision to pursue medicine evolved during my undergraduate education at Alma College. Before beginning college, I had every intention of studying chemical engineering. I had been to engineering camps and was pretty interested in the field. In my senior year of high school, I had been accepted into two Schools of Engineering and was all set to start down that path. However, for reasons that I can't really explain even today, I changed gears and headed off to a small liberal arts college. Through my years in college, my interest in medicine grew, ultimately leading me to medical school.

I distinctly remember when I decided to jump headfirst into forensic pathology. I attended Wayne State University School of Medicine, where a major portion of my second year was pathology. Admittedly, portions of it were pretty dry – but, for me, the lecture we received on forensic pathology was entirely different. Leigh Hlavaty was able to make the subject incredibly fascinating. From that point on, I was all in. I have the pleasure of working with Leigh Hlavaty now and she and I have had discussions about how a single person or event can alter the trajectory of one's life.

WHAT INSPIRED YOU TO START PODCASTING – AND HOW DID YOU BEGIN?

LR: The podcasts I listen to focus on the insights and experiences of women leaders, the majority of whom are entrepreneurs and CEOs. Though I have learned a lot from these podcasts, I really wanted to listen to a podcast focusing on women in healthcare. In late 2017, I began exploring the idea of creating a podcast for women in medicine as a way to give back to the medical community. My goal was to create a podcast that explored the scope of challenges and opportunities for women in medicine. Across 2018 and 2019, I researched podcast editing and recording equipment and created a list of potential episodes. ScopeMD launched in March 2020.

DS: I've been a fan of podcasts for a few years now, but it seemed there weren't any about those of us in the lab – at least, not in the interview format I enjoy most. My friend Alyse, a fellow PA, said I could interview her for practice because she was writing a book. That became the first episode. I researched hosting sites and recording software and picked whatever seemed easiest to use. Then I bought a good microphone and just went from there.

NB: I listen to podcasts all the time! I had been mulling over starting my own for a while, but I was finally prompted to get going when COVID-19 hit hard here in the Northeast. I had a more flexible schedule and I was eager to talk to others about the shared experience of the pandemic. The technical aspects were slightly overwhelming, but I am lucky to be married to a technically proficient partner who helped me pick the most user-friendly recording and editing software options. My first show was with one of my closest friends, who agreed to be my test subject.

"I listen to podcasts all the time! I had been mulling over starting my own for a while, but I was finally prompted to get going when COVID-19 hit hard here in the Northeast."

JT: Nicole and I talked about how true crime podcasts weren't particularly well-explained and jokingly said we should have our own podcast and cover the real science. One day we just went, "We should do it!" Nicole sent me a bunch of options for podcast names and cover art and, once we settled on what we wanted, we rented equipment from the university and got started. It was fun (but terrifying)!

XJ: It really began because the podcasts I most like to listen to are quiz show-type podcasts, and I've always thought pathology would make a wonderful quiz show. I'm so lucky to have already known the perfect co-hosts!

CA: I have always wanted to be a game show host. This was my chance!

MA: When Sara Jiang proposed the idea of PathPod, I knew it was going to be fun and interesting. I didn't know anything about podcasting, so I was excited to try and figure it out.

KM: This amazing PathPod team, led by Sara Jiang and her brilliant idea, had me sold from day one.

LS: There are several reasons we started the podcast, but one of the most compelling is education. Our office is focused on education. We have long-standing relationships with Wayne State University and local pathology residency programs, where we have a one-month rotation for residents and medical students. The rotation is entirely immersive; rotators are afforded the opportunity to perform autopsies, not just watch them. In addition, the staff give lectures on many different forensic pathology topics. In the past, our knowledge-sharing was more local; now, with the evolving world of podcasts, we have an incredible ability to reach far beyond our borders.

WHAT WAS THE PATHOLOGY PODCASTING LANDSCAPE LIKE WHEN YOU BEGAN – AND WHAT IS IT LIKE NOW?

LR: In 2017, I was not aware of any pathology podcasts. Now, multiple pathology podcasts are available. In my opinion, the exponential increase is due to technological advances that have made it easier to record, edit, and distribute podcasts, as well as work-related changes during the COVID-19 pandemic. I am particularly excited about podcasts by pathology organizations, such as IASLC's Lung Cancer Considered podcast. Podcasting is a great way to get new information out quickly to a large audience.

DS: At the time, there really weren't any pathology podcasts. But, as I came to find out, a few others had the same idea that I had at almost exactly the same time!

NB: I can honestly say I didn't see any other pathology podcasts when I began, but I now know that they were out there. There is such a diverse set of perspectives and interests – I think it's all lovely.

JT: We still feel like we're pretty new to pathology – and to podcasting. True crime podcasts are possibly some of the most popular and people who enjoy them want more information about the science, so we hit a good niche. There are a lot more medical-adjacent podcasts now than there were when we began – and certainly more pathology podcasts.

XJ: I think the podcasting medium is getting more and more popular not only with individuals, but also with organizations and journals working in this sphere. We are all looking for ways to learn more efficiently and I think podcasts really maximize our ability to learn on the go.

LS: There is huge interest in "true crime" and many of the podcasts were, and still are, focused on that. In comparison, pure pathology podcasts are not that common. For pathology, I

"I think the podcasting medium is getting more and more popular not only with individuals, but also with organizations and journals working in this sphere."

think podcasting is still in its early infancy. Podcasts that have a sharp focus on pure pathology have narrower audiences. An issue we all face is broadening to reach a wider listenership.

WHAT LIES AHEAD FOR PATHOLOGY PODCASTING?

LR: I anticipate that all medical journals and organizations will either have a podcast or consider having one – and I anticipate that future pathology podcasts will be niche-driven. Examples include podcasts for pathology trainees, monthly journal podcasts with episodes focused on article highlights, subspecialty-specific podcasts, and podcasts offering CME.

DS: I think video will be incorporated more. I could see live broadcasts from various conferences as they happen. That's not something I'm ready for just yet, though.

NB: I think it would be great if some of the flagship journals and educational organizations had podcasts and offered them as supplements to major publications and updates. Imagine how much an author or a committee would have to say about their work, the process of bringing the information to the page, and the advice they could share for those interested in pursuing similar projects!

JT: I hope things get more focused. We have a couple of big-picture podcasts, but I think pathology needs a more intellectual approach – but that, in turn, makes it hard to find an audience beyond pathologists themselves. We got lucky; forensics is one of the few pathology subspecialties that captures the attention of a wider audience.

I also hope things will become more interactive. I've had to learn how to describe something that's visual using only words, because so much of pathology is visual. Maybe we could upload virtual slides or other media for people to refer to while listening. That said, I feel like images and video – although useful – go beyond the scope of a podcast. It's not really a podcast anymore.

NC: We don't always correlate what we're doing in our episodes with our social media. Perhaps we could post more on social media in weeks when we don't release an episode – but it's hard to balance residency life with not just the podcast, but also its many social media platforms.

LS: I have a very positive outlook for pathology podcasting. With a broad stroke of the brush, pathologists are a reclusive bunch. We can do a better job reaching out to the community at large. This is easier with a large, established listener base, but one arena that we can explore in the future is live shows with audience participation and call-ins.

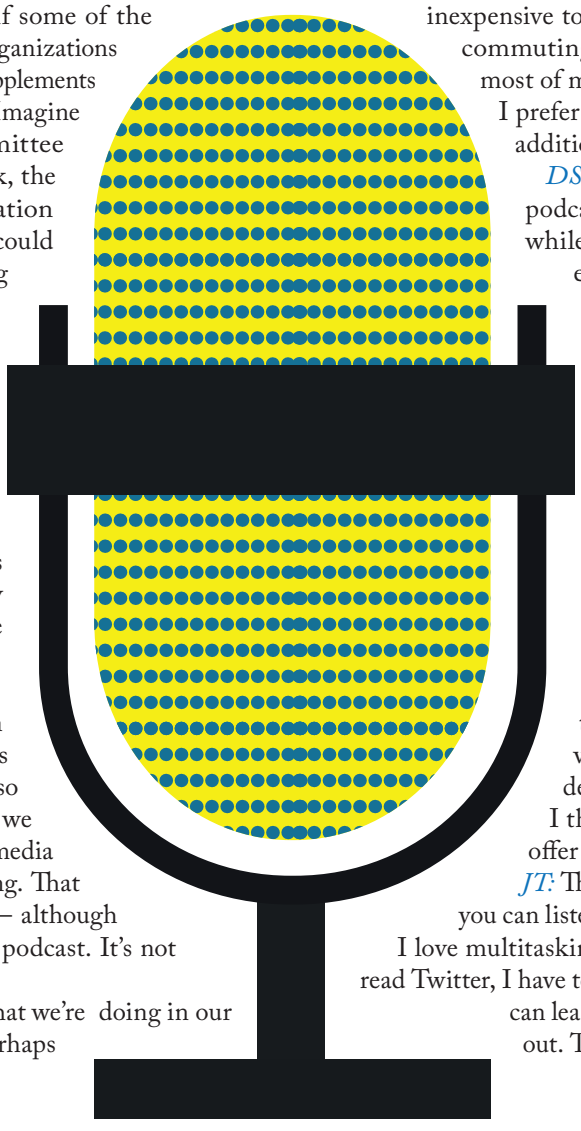
WHAT ARE THE STRENGTHS OF PODCASTS IN COMPARISON TO OTHER INFORMAL EDUCATIONAL TOOLS?

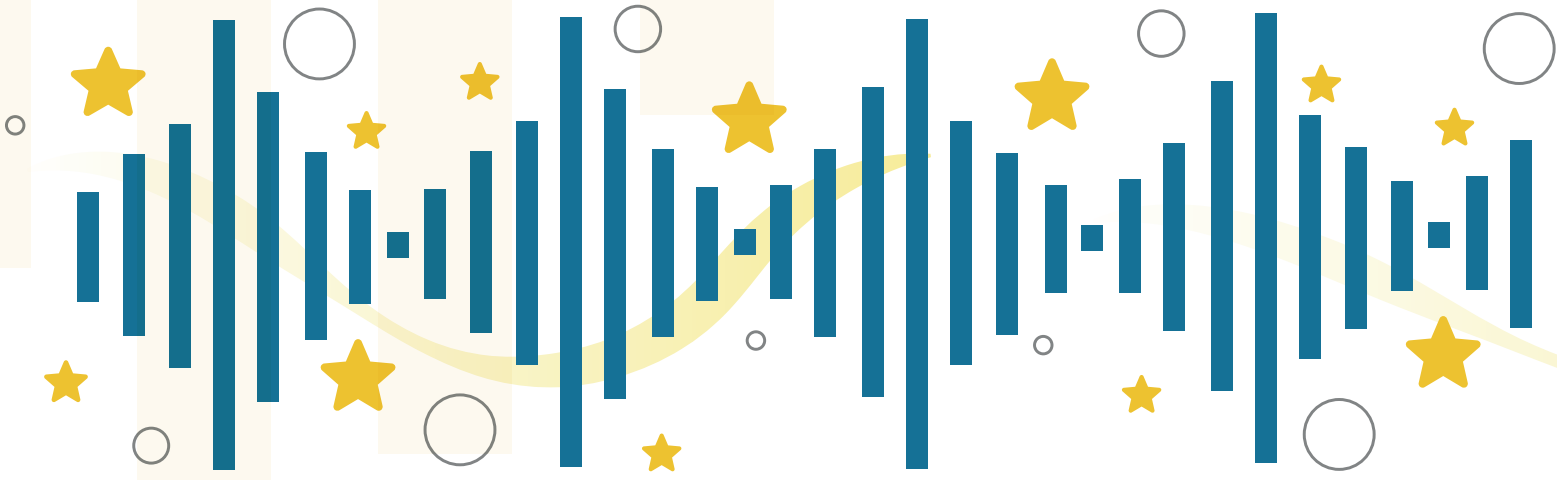
LR: Podcasts are portable and are relatively easy and inexpensive to produce. I listen to podcasts while commuting and exercising. Because I spend most of my day in front of a computer screen, I prefer podcasts because they don't require additional screen time.

DS: To me, one of the strengths of podcasts in general is that you can listen while doing other things – commuting, exercising, and so on. That's true of pathology podcasts, too. Other formats have their place, but podcasts allow you to listen wherever you are.

NB: Podcasts are so easy to access – both in the "click and listen" sense and in the didactic sense. They expose the basic truths of situations and allow for nuance in tone and meaning that is missing from the written word. I came to love some of my favorite journalists because I heard them talking about their work and now, when I read their words, I have a deeper appreciation for their meaning. I think podcasts give folks the space to offer their opinions without limitations.

JT: The great thing about podcasts is that you can listen while you're doing something else. I love multitasking, but if I want to watch a video or read Twitter, I have to look at the screen. With podcasts, I can learn while cooking, driving, or working out. There are only so many hours in a day!





"I was always taught that you don't completely understand something until you can explain it to a child. Podcasting has been good practice."

NC: I also like the auditory component. My preferred learning methods are interactive, so I enjoy multitasking while listening – and a dynamic speaker grips your attention and keeps you focused. Social media is interactive and often image-based, but limited by character count – and it's easy to get distracted. A well-done podcast is gripping and educational at the same time.

XJ: I think the strength of podcasting is that it allows us to have more in-depth conversations and for people to tell their stories in their own voices.

CA: Podcasting allows us to connect the way we used to pre-COVID-19. We are having conversations, engaging, sharing ideas, and laughing.

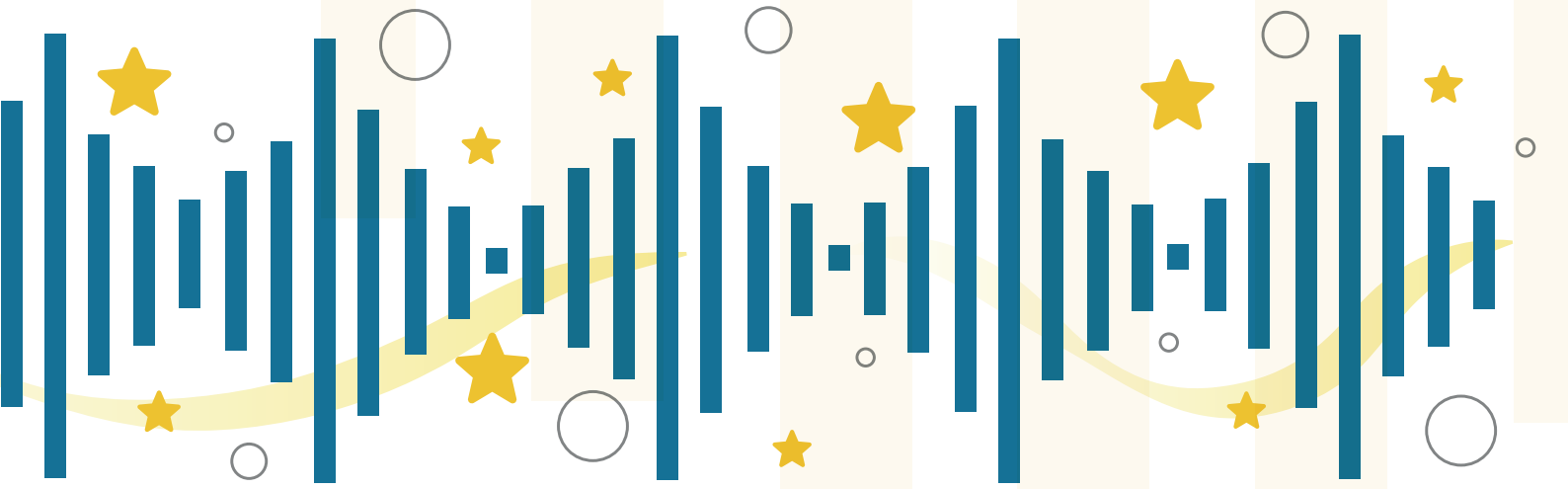
MA: I think podcasting provides a platform where you can hear people talk through a topic in a conversational style. It keeps things interesting for the listener, and I've loved hearing people give their candid thoughts about everything from how they got into medicine to what they are doing now.

KM: The ubiquity of podcasts is a powerful element – in contrast to other, less prevalent methods of disseminating information.

LS: People consume media in all forms; each has its benefits and drawbacks. I don't tweet or read blogs much, but I have spent countless hours watching YouTube videos. All three of these forms of media require visual focus. Podcasts can be listened to anywhere. They are perfect for people with any type of commute. If you download them to your media device, you can be offline and still enjoy them.

HOW DO YOU FIND THE EXPERIENCE OF PODCASTING – AN AUDIO-ONLY MEDIUM – IN A DISCIPLINE AS VISUAL AS PATHOLOGY?

LR: Podcasts have very few distractions, allowing the



audience to really focus on the conversation. I find that my guests are more candid because there is no video component. Our conversations are like going out for coffee – and the audience gets to listen in on the conversation.

I think all pathology and laboratory medicine topics are amenable to the audio-only format, which lets the conversation focus on interesting and challenging issues – what terminology should we use? Is this entity clinically important? What's the role of ancillary testing? How do new technologies impact our work? If additional resources are needed, podcast show notes are a perfect place to put links to references and photographs.

DS: It can be difficult at times. I include links in the notes for each episode so that listeners can learn more about the topics that might be more visual. Twitter is useful for that, too.

NB: My podcast, when it focuses on pathology, does so from the human perspective – the stories behind ideas and people's journeys into the field. I don't think that pictures of actual diagnostic entities can be replaced by podcasts, but they supplement one another well.

JT: I was always taught that you don't completely understand something until you can explain it to a child. Podcasting has been good practice, especially because, as forensic pathologists, we're going to have to testify someday – and that often involves explaining complicated things without visual aids. We'll be explaining complicated scientific concepts to laypeople for the rest of our careers, so this is a great start.

NC: The advantage we have as a forensic pathology podcast is that a lot of our findings are going to be gross findings, which are easier to describe. People know what organs and bodies look like, whereas they may not be familiar with cells and tissues. Fortunately, much of our training has involved learning to communicate our findings using words instead of pictures. A pathology report is a verbal description of what we see on the slide.

In a residency interview, I was asked, "How would you describe orange to a blind person?" They wanted to gauge my ability to communicate – so it's clearly an important skill.

CA: We actually record over Zoom, but we only broadcast the audio recording. I think that's the best of both worlds. Recording over Zoom allows us to see and react to each other's facial expressions and body language, which are lost on an audio recording. But listeners want a medium they can consume while doing other activities, so audio-only is a good fit.

MA: I think pathologists are naturally skilled at talking about our visual field. Our work products are pathology reports, books, and manuscripts, so it has been easy to have discussions about many topics without a visual component. It feels like the casual conversations that happen in small groups at national meetings.

LS: I don't think podcasting detracts from highly visual subjects – in fact, they may even carry benefits. For example, some people have visual deficits that make audio input a major source of information acquisition. Also, certain learners gain the most by listening. Pathology is a visually driven discipline, but that doesn't mean you can't convey a message through audio. I'm certain any podcaster's goal is to deliver a narrative that is sufficiently descriptive for the listener to use their imagination to construct an image that fits the audio. They can then take that foundation and search other sources of (perhaps visual) information.

WHAT WAS YOUR PROUDEST, FUNNIEST, OR MOST UNEXPECTED MOMENT AS A PATHOLOGY PODCASTER?

LR: I have had the opportunity to interview amazing people in healthcare. I can honestly say that I am proud of every single episode of ScopeMD. It has been humbling to have listeners ask me to produce an episode focusing on a challenge or opportunity impacting their careers. Interestingly, the most challenging episode for which to find a guest was the "history of women in medicine" episode. The most unexpected moment was when one of my children burst into the room during an interview, sat on my lap, and learned about immunotherapy. My guest was completely unfazed.

DS: There are so many. I'm certainly proud of the fact that I set out to create a podcast and, 40-plus episodes later, I'm still here. I research my guests in advance, but they still often say something unexpected that turns out to be the most interesting part of the interview. The funniest was probably the crossover episode with Natalie Banet at Deeper Levels when we talked about our theme songs.

NB: I was recording an early episode with a physician from Spain and she took her laptop out on the balcony to let me hear folks clapping for healthcare workers. I had a lump in my throat for the rest of the episode. Throughout the pandemic, I have really appreciated my podcasts as a way of filling in the gaps that human-to-human connection has left in everyday life.

JT: I think the proudest is just the fact that we have over 300 listeners. I don't have that many friends and family who will listen to me drone on for up to an hour! In terms of humor, I love how well we can riff off of each other. I wouldn't describe myself as a funny person, but when you're with a friend, it's easy. I know what makes Nicole laugh.

NC: We've gotten to interact with some really cool people – and podcasters with relatively popular shows have asked to do crossover episodes with us. They have thousands of listeners. "Sure!" we say. "Yes, please!"

XJ: My proudest moment is definitely the fact that this got off the ground (thanks to the amazing team working on it) and that people are listening to it and sharing it. I am amazed that something like this came together so quickly. It's one of the silver linings of the pandemic.

LS: One of my proudest moments happened very early on. In fact, it was before we even went live with our podcast. It dealt with finding a name for our podcast and its announcer. We very much wanted to get the whole office involved in this project, so we had a contest. Leigh Hlavaty, Omar Rayes, Milad Webb, and I came up with three names each and then had the whole office vote on them. It was a tough choice because we have some great entries, like "Forensics

"I was recording an early episode with a physician from Spain and she took her laptop out on the balcony to let me hear folks clapping for healthcare workers."

in the D," "Motor City Forensics," and "The Y-Incision." We also put out a casting call for everyone who wanted to stretch their vocal cords and be the voice to introduce the episode. When we did it, I was worried that we wouldn't get any people, but I was wrong. I can't remember how many auditioned, but there were a lot. Then we had a pizza party for the whole office to vote on the name and announcers. It was a fun time, and I was really proud that the whole office took such an interest in the project.

IF YOU COULD DO AN EPISODE ON ANY SUBJECT YOU WANTED, WHAT WOULD YOU CHOOSE?

LR: I would really like to host a roundtable of women who are CEOs of healthcare systems. I would like to know more about their leadership journeys and their insights regarding future challenges and opportunities in healthcare.

DS: I'm interested to learn about pathology in other countries. I know my job as a PA doesn't exist in most other countries. I'm curious about other differences.

NB: I would do a show about all of my esoteric interests – like science fiction, mystery novels, or a show in which I could ask my favorite political journalists what they really think about their subjects.

JT: I would probably choose a crossover with My Favorite Murder where they ask forensics questions based on cases they've talked about. There are many times I've gone, "I would love to be the person who could answer those questions" – and it would be special because they got us into podcasting.

NC: If I could do an episode on any subject I wanted, I'd like to tackle emerging infectious diseases. A crossover episode with This Podcast Will Kill You would be interesting. I've also seen a book about how fashion has killed people over the years – for instance, with carcinogenic dyes – and I think that would be a fascinating topic for an episode.

CA: I would love to hear a "Beyond the Scope" segment with Vinay Kumar, one of the authors of Robbins.

MA: I've always been interested in astronomy and physics. I'd love to interview Neil deGrasse Tyson.

KM: I would love to interview Michelle Obama. Not sure how that would fit under our PathPod umbrella, but I would make it happen!

LS: Expanding on the auditory experience of a podcast, I would like to go much more in-depth on the sounds of an autopsy room. The actual performance of an autopsy holds little mystery for a pathologist, but it is something that others rarely experience accurately. I would like to present classic sounds, such as the X-ray machine, bone saws, and the shutter of a camera, and then have discussions on each of those sounds to expand on where they fit into an autopsy. As with the other four senses, hearing can produce a very visceral reaction.

DO YOU HAVE ANY ADVICE FOR READERS WHO WOULD LIKE TO BEGIN LISTENING TO PODCASTS?

LR: With so many podcasts to choose from on almost every topic imaginable, I would suggest that they reach out to their friends and colleagues for recommendations.

DS: It can be overwhelming, because you can find a podcast about nearly any subject. I'd say to pick a few favorites and then branch out from there.

NB: I would say that, no matter how niche you think your interest is, there is likely a podcast about it. Anything you want to feel a sense of community about, you can find in podcasting. It's a really nice way to learn from very smart people – and it sure passes the time during chores and exercising!

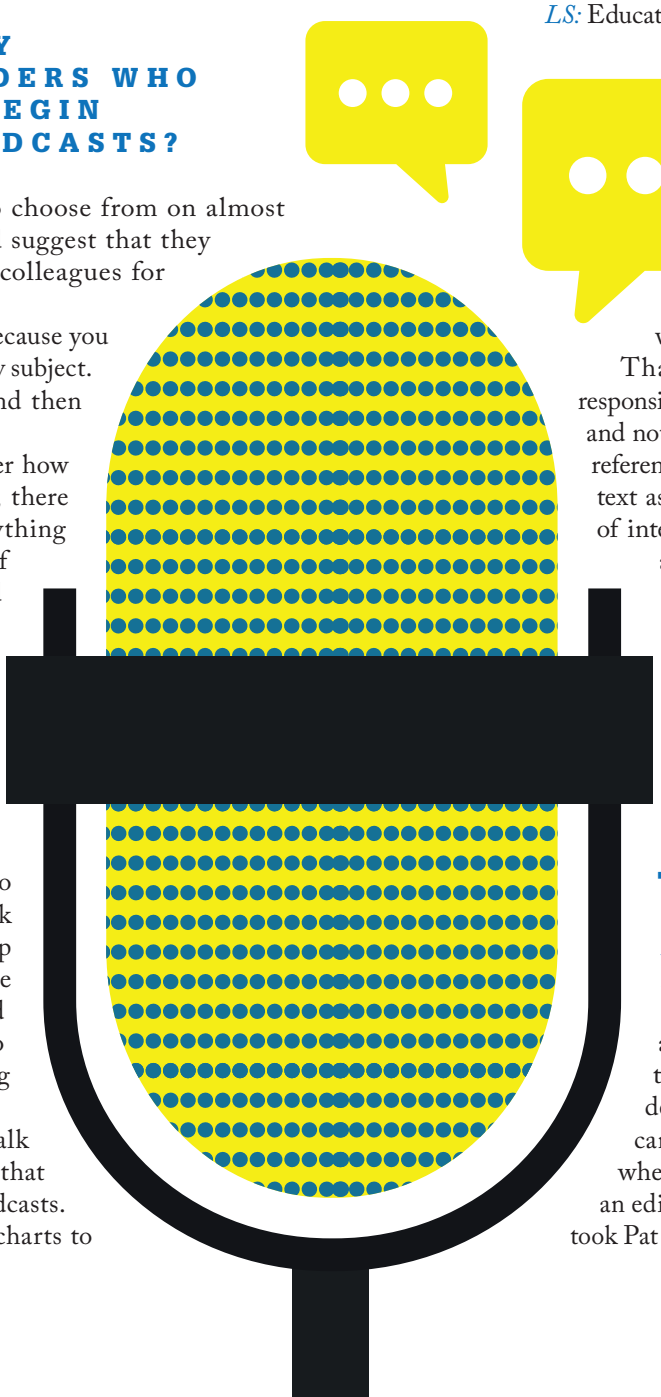
JT: Start with a subject you really like. Don't try to sit down and listen to it, because humans are very distractible. Do something else, like go for a walk or cook – anything that will keep you physically occupied – while listening. If I try to sit quietly and listen to a podcast, I'm going to pick up my phone and start looking at Instagram.

NC: I agree with going for a walk or doing dishes; those are things that work for me when listening to podcasts. I also recommend checking the charts to see what podcasts are highly rated. Popular podcasts are popular for a reason! It's a good sign that the creators are dynamic enough to get other people engaged. If you can find a topic that you love presented by informative or engaging speakers, you know it will be good.

XJ: There are so many podcasts out there, and they're great to listen to when unloading the dishwasher, putting away laundry, or exercising!

MA: I agree. There are so many good podcasts – download a bunch and try them out!

LS: Education and entertainment are not mutually exclusive. If someone is interested and seeking out knowledge, a podcast can be an excellent introduction to a topic. They can be valuable sources of information. That said, it is the listener's responsibility to do additional research and not take a podcast as a definitive reference – but that is true of written text as well. There are always levels of integrity to the materials we us as references.



DO YOU HAVE ANY ADVICE FOR READERS WHO MIGHT LIKE TO START A PODCAST OF THEIR OWN?

LR: I would encourage anyone interested in podcasting to consider how much time and money they would like to commit. This will help determine how often episodes can realistically be released and whether they want to work with an editing and production vendor. I took Pat Flynn's Power-Up Podcasting

course, which I found extremely helpful.

DS: The hardest part is just to start. You don't need fancy equipment. Basically, all you need is a good microphone and a way to record. There are many options for hosting sites and they're fairly inexpensive. If you have a good idea, just give it a try!

NB: Just go for it! Don't wait for the perfect time or assume that you will ever feel all the way "ready." You will learn so much along the way. And it's so much fun!

JT: Just do it! We had a good brainstorming session and, once we got started, it was a blast. If you're not sure you want to invest in it, start by renting equipment. One of our biggest hurdles was looking at equipment, because it seems so overwhelming at first. I've also read that you should set yourself a minimum length of time to do it – that stops you from doing it once or twice and then giving up because you hate the sound of your own voice.

XJ: If we can do it, you can too. All it takes is ideas, some time, and a good headset!

MA: There are lots of ways to make it happen, and capturing audio is much easier now that most people have access to Zoom for recording. The first episodes will take a lot more time to figure out than later ones.

KM: Be targeted and know your audience!

LS: Equipment is no longer a barrier if you wish to start a podcast. If you have a recording device and broadband access, you can start podcasting. Beyond that, you need to go back to basic interrogatives: who, what, when, where, and why. Take some time and really think about why you want to start a podcast, who your audience is, and what your topics of discussion are. What is the message you want to send? Do you have a twist that sets you apart from other podcasts?

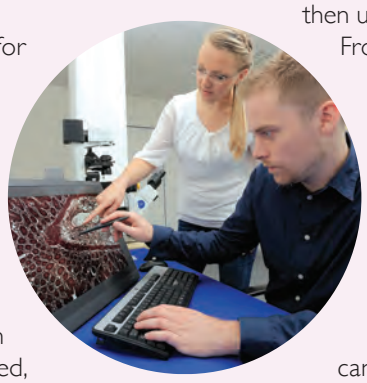
One of the largest hurdles to overcome is capital investment – and the greatest investment is time. A significant amount of time and effort goes into the preproduction, production, and post-production of a podcast. I cannot emphasize this point enough. I encourage anyone who wants to start a podcast to do so – but you must be able to dedicate the time to create a high-quality product.

OPTIMIZING CANCER RESEARCH WITH THE MMI CELLCUT

Advanced laser microdissection technology empowers high-precision cancer research

The Molecular Machines and Industries (MMI) CellCut system is the latest technology in advanced laser "CapSure" microdissection. But how? It's simple: combined, its high-precision laser and CapSure technology reliably isolates single cells from tissue sections to extract RNA for transcriptomics and sequencing. The low-damage laser protects the sample's surrounding areas, but it is also precise – creating a cutting edge that delivers unprecedented results, while the patented adhesive isolation caps enable contamination-free isolation of single cells and ensure no excised cells are lost.

The MMI CellCut has huge potential for applications in oncology. "Our translational cancer research focuses on particular mechanisms of tumorigenesis for the identification of novel tumor biomarkers and therapeutics," says Shawn Baldacchino, a member of the molecular pathology research team at the University of Malta. "The MMI CellCut enables us to selectively isolate specific tumor cell populations based on morphology from H&E-stained, formalin-fixed, paraffin-embedded tissue sections for RNA analysis. Using this method, we have isolated distinct malignant clones within heterogeneous tumors and microdissected normal breast duct tissue to establish physiological expression levels. Based on gene expression, we classify breast cancer tumors to identify biomarkers towards novel effective therapeutics."



Intratumoral heterogeneity is a major challenge for clinicians. With the MMI CellCut, researchers can specifically excise morphologically different areas of a tumor to understand cellular heterogeneity and optimize treatment plans. This can be applied to any cancer type that displays tissue heterogeneity.

Moreover, the role of invading immune cells in cancer progression is still not fully understood. By integrating the MMI CellCut onto a fluorescent microscope, invading tumor cells can be identified via immunofluorescence microscopy and subsequently cut with laser microdissection. The combination of spatial and molecular information on these cells can be then used to better understand tumor immunology. From a mixed-cell culture with tumor cells and immune cells, homogeneous cell populations can be isolated with the MMI CellCut for further cultivation or molecular analyses. For example, T cells could be isolated when inducing apoptosis in the tumor cells they interact with, allowing for analysis of specific gene regulation processes that might not be detected in bulk experiments.

For a seamless digital workflow, the system can be equipped with the MMI CellScan to save high-resolution, whole-slide digital images – in brightfield and fluorescence – and preserve detailed spatial information on target cells before and after extraction.

Cancer is still a major threat to human health and MMI wants to empower scientists by contributing its technology to support those studying tumor development – helping them establish a precise diagnosis, identify optimal treatments, and get one step closer to curing patients.

www.molecular-machines.com

IBEX

THE PROOF IS IN THE TRAINING

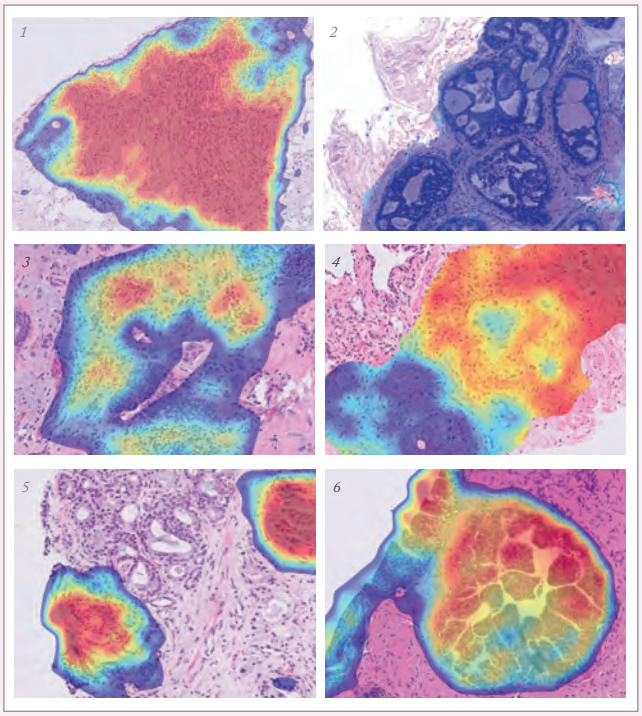
Best practices for training artificial intelligence algorithms for cancer diagnosis

Congratulations! You've just hired a new pathology resident – but, before teaching her how to analyze a tissue biopsy, you may wish to assess which approach will be better:

1. Ask the trainee to diagnose slides, telling her whether a slide is cancerous or benign without explaining what a tumor looks like or its key features, or
2. Jointly analyze slides that include all significant features and morphologies, explaining in detail what nerves and blood vessels look like, how to identify atypical ductal hyperplasia versus ductal carcinoma in situ or invasive ductal carcinoma versus invasive lobular carcinoma in breast biopsies or look for different Gleason grades, high-grade prostatic intraepithelial neoplasia, and perineural invasion in prostate biopsies.

Few would argue that the first approach is optimal – especially given that residents will need to complete full pathology reports and not just identify cancer. Moreover, to accurately detect all cancer types, they also need to be trained on specific – possibly rare – cases that contain structures and cells similar to cancer.

With today's tidal wave of digital pathology, more and more companies and researchers are developing artificial intelligence (AI)-based tools to improve cancer diagnostics. Like any assistant, AI must be trained – but how? Should algorithm developers train it based only on slide-level information from the pathology report (e.g., cancerous or benign)? Or should they dive deep with expert pathologists who rigorously annotate features prior to training and then highlight the model's incorrect predictions?



Results of analysis by strong AI algorithm. Heatmaps of breast biopsy images showing invasive lobular carcinoma (1), low-grade DCIS (2), and tumor infiltrating lymphocytes (3); and prostate biopsy images showing Gleason grading (4), perineural invasion (5), and high-grade PIN (6). All images courtesy of Ibex Medical Analytics.

Again, the first option is tempting – it is less time-consuming, easier to access the necessary data, and requires fewer resources. Unfortunately, it results in "narrow AI" – an algorithm that can handle only one task, such as cancer detection or grading, often with limited accuracy. The second, albeit more meticulous and requiring more effort, results in "strong AI." Strong AI is far more comprehensive and explainable and can support pathologists across a wider range of tasks including finding and grading cancer, identifying subtypes, and detecting other clinical features.

AI offers great promise to pathology and laboratory medicine, improving the quality of cancer diagnostics while enabling more efficient workflows. The secret to developing strong AI that becomes the pathologist's trusted advisor lies in the quality of the training – and, like your next resident, pathologists make the best teachers.

Chaim Linhart is Chief Technology Officer and Co-Founder of Ibex Medical Analytics, Tel Aviv, Israel.

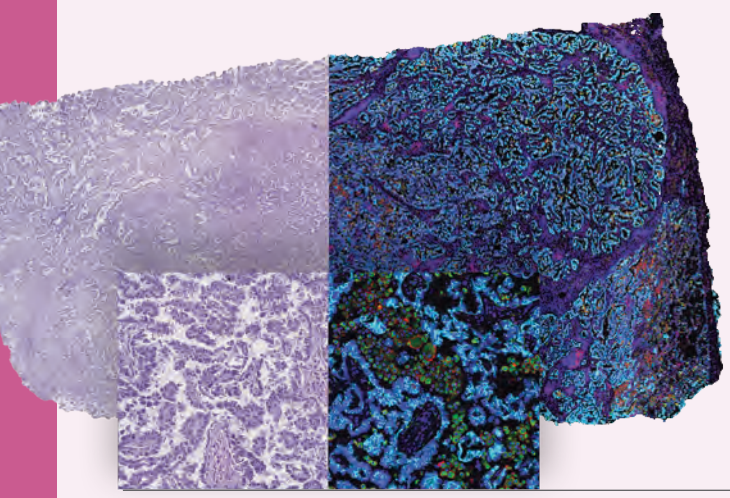
ULTIVUE

RIDING THE NEXT WAVE OF INNOVATION IN DISEASE DIAGNOSIS WITH INSITUPLEX

Ultivue's new multiplex immunofluorescence method optimizes standard anatomic pathology workflows and accelerates assay development

As a young startup company, Ultivue stands at the center of the ever-evolving world of biotechnology – charged with delivering new cures for diseases. Modern therapy development requires insight into mechanisms of disease and patient stratification strategies that will fuel the next wave of innovation in diagnostic testing. Ultivue is perfectly positioned to drive these discoveries – but how? It's simple: InSituPlex.

InSituPlex is a new, robust multiplex immunofluorescence assay technology, conjugating DNA barcodes to antibodies and using sequence-specific DNA-DNA hybridization to label antibodies in tissue sections. Multiplex detection is achieved through standard fluorescent slide scanners and can be analyzed with a wide variety of software.



Multiplex detection has been used in research for several decades, but with limited uptake in diagnostic anatomic pathology. However, Keith Wharton, Vice President Medical Director at Ultivue and anatomic pathologist, says, "Rapid progress in the field of immuno-oncology and techniques such as single-cell phenotyping are creating an urgency around multiplex investigations with single-cell resolution that retain tissue context."

The past decade has witnessed the growth and maturity of these methods – but none are well-suited to the equipment and workflows commonly used in histology laboratories. InSituPlex assays can be automated on standard robotic autostainers in a workflow that mimics traditional immunohistochemistry. Furthermore, the InSituPlex nucleic acid hybridization-based signal amplification and detection means the tissue only needs to undergo mild antigen retrieval conditions during staining and restaining. This preserves tissue morphology and enables precise co-registration of multiplex images with the same H&E-stained tissue section used for pathologic diagnosis – allowing pathologists to correlate the appearance of every cell in the tissue section with its marker profile.

By using DNA barcodes to amplify weak signals, InSituPlex assays generate a high signal-to-noise ratio that enables sensitive, robust detection of any marker used for conventional immunohistochemistry. Critical time savings are also achieved: first, assay development times are reduced from months (using traditional immunofluorescence methods) to two to three weeks; and second, assay run times on automated stainers are reduced from days to around five hours – you can go from marker discovery to optimized assay in just a few weeks!

But remember, it's not technology that's driving the need to multiplex – it's biology. Ultivue believes that tissue context is vital for accurate disease characterization and, given the growing need (especially in immuno-oncology) to associate the co-expression of multiple markers with specific cell phenotypes, InSituPlex is well-positioned for wider adoption by providing unparalleled insight into diseased tissues.

Ultivue's current reagents and service offerings are for research use only, not for use in diagnostic procedures.

www.ultivue.com

Lunaphore technologies

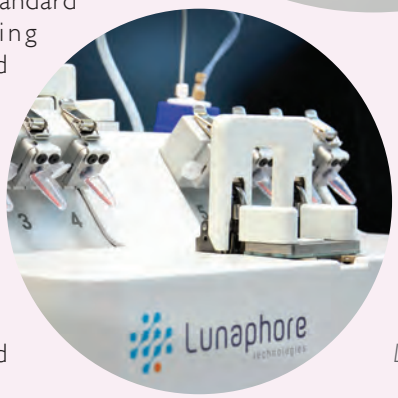
TRANSFORMING IMMUNO-ONCOLOGY RESEARCH APPLICATIONS

Lunaphore's microfluidic technology empowers small- to medium-sized laboratories to accelerate cancer research

Fast Fluidic Exchange (FFeX) is the latest microfluidic technology from Lunaphore – a company transforming cancer research with in situ tissue analytics. Their novel microfluidic chip is based on FFeX technology that, when clamped against a regular glass slide, forms a low-volume chamber for the user to incubate tissue samples and perform in situ staining.

Speed sets FFeX apart from its competitors, with protocols running 10 times faster than standard techniques – reducing reagent diffusion times and increasing reaction speed. This is made possible through LabSat® – a single-slide automated staining tool based on microfluidic technology.

Thanks to precision fluidics, LabSat® offers many benefits. Besides rapid turnaround, short incubation times contribute to tissue preservation – even when performing multiplex protocols – which leads to high-quality staining results. Furthermore, an active reagent flow circulates inside the chamber to ensure high staining uniformity. Finally, the system is fully open; users can load their reagent of choice onto the instrument, including any off-the-shelf, label-free primary antibodies. This is all made possible by a compact, single-slide staining tool in reach of small- and medium-sized laboratories.



LabSat® is designed for research laboratories that are not currently automated – enabling them to develop automation and gain independence from core facilities. That's not to say that other laboratories can't benefit as well – it is particularly useful for those that require rapid results for few samples without disrupting their high-throughput workflow.

Lunaphore aims to democratize its robust automation, equipping laboratories with a tool that allows them to rapidly access clinically relevant data and accelerate cancer research. "I was extremely impressed with the quality of results we achieved with Lunaphore's technology," says Spencer Watson, postdoctoral fellow in the Johanna Joyce Laboratory at the Ludwig Institute for Cancer Research. "It would normally take us two days to perform a five-color immunofluorescence tissue staining, but with Labsat® it took us only 30 minutes."

Cancer is one of the most burdensome diseases in the world, requiring constant support and innovation from the industry. With Lunaphore's dedicated focus on immuno-oncology research applications, its FFeX technology has great potential for wider application.

LabSat® is for Research Use Only. Not for use in diagnostic procedures.

NextGen

Research advances
New technologies
Future practice

In Search of the Perfect Test

Fast, effective, affordable, portable… Can new technologies tick all these boxes in a single test?

By Paolo Actis

Fast, effective, and affordable: an ideal triumvirate of characteristics for a diagnostic test. It may seem impossible to achieve all three in a single test – but I don't believe it is. As a community of technologists, my peers and I have been working on rapid, low-cost biomarker disease detection for many years. Of course, the COVID-19 pandemic has brought the issue into the limelight – but there are many other diseases and use cases that make this technology valuable. For instance, we can glean a great deal of valuable information for diagnosing or monitoring cancer via a blood test to measure the concentration of circulating biomarkers. In many cases, the sooner you detect the presence of cancer biomarkers in blood, the higher the chance of survival and the more conservative the treatment options. And that's why my colleagues and I decided to develop a technology that can detect biomarkers with single-entity resolution.

Once our test is ready for use, I believe it will change the lives of both patients and practitioners. Our goal is to empower patients to monitor their own health, reducing the number of hospitalizations without placing an additional burden on pathology labs. For instance, nurses who work with cystic fibrosis patients often travel miles to their homes just to take a blood sample for CRP testing (an early marker of inflammation that can signal a need for medical intervention). Why put nurses through hours of driving, laboratory medicine professionals through hours of work, and patients through days of waiting for a single result? I think point-of-care testing has incredible benefits to offer pathologists, patients, and health services as a whole.

How it's done

Our discovery was a combination of community and serendipity. Scientists all over the world have been trying to use DNA structures as protein carriers because the former is much easier to detect than the latter – we just had the good fortune of finding a way to make it work.

We use nanopore technology to measure one biomarker at a time. Essentially, we run an electrical current across tiny holes (nanopores) and measure changes in the current as the biomarker of interest passes through. The beauty of the technology is that it's completely electrical – meaning that it's both portable and quick. We've even developed it as a USB-powered device that can be plugged in anywhere for on-the-spot biomarker testing. At the moment, the technology measures nucleic acids accurately – but, in the future, we want to expand the analysis to proteins as well. That will be a game-changer. Take cancer, for instance; you'll be able to go to your doctor's office, have your finger pricked, and get a biomarker test result in about 20 minutes. That will then guide the doctor on whether to order more in-depth testing.

Of course, point-of-care protein testing is not easy. Our approach marries nanopore technology with DNA origami (a way of using DNA as a "Lego brick"). We build a structure that looks like a picture frame in the center of which we can capture a protein biomarker. Capturing that protein significantly changes the electrical signal across the DNA origami frame – allowing us to measure the protein level in a sample.

Early detection difficulties

In the research stage, biomarker detection technologies often perform well – but, when it comes to translating them from a controlled laboratory to a real-world environment, complications arise. And we know the same may be true of our technology; it is a new approach, so we are trying to partner with hospitals and companies who can test it in a clinical setting.

Traditionally, validating a medical technology takes years – often a decade or more. Since COVID-19 struck, the world has completely changed and we've seen a lot of technology fast-tracked to the end user. Can we speculate that, in the next few years, we'll see more and more of this speed-validating? Perhaps – but let's not forget the complexity of the challenge we face. When we provide clinical information, we need to have complete confidence in its accuracy – and that means carefully evaluating, standardizing, and controlling our tests, and ensuring that they are within acceptable margins of error.

"Once our test is ready for use, I believe it will change the lives of both patients and practitioners."

The key difference between our proposed test and others is that ours has no optical component – it's all electrical. Imagine the miniaturization – and the power – of a smartphone applied to a biomarker testing tool. Because we can create a tiny device with integrated wireless connectivity and data analysis, we can turn a time-consuming laboratory procedure into a point-of-care test. This vision is further helped by the fact that our testing requires only a few microliters of blood – so not only is it minimally invasive (a fingerprick suffices), but it also means we don't need expert assistance from a nurse or phlebotomist. Finally, we measure biomarkers at the single-molecule level –

Pandemic Plans

Right now, the entire diagnostic world is working on COVID-19 testing – and we're no different. We're trying to adapt our testing concept to detect SARS-CoV-2 proteins. Originally, we wanted to detect antibodies – but that seems less useful now than it did four months ago, so we're focusing on viral proteins instead.

We've spoken to hospitals who have told us what they need. For example, our test may work on COVID-19 patient serum, but we aren't allowed into the lab to perform it. Therefore, we need to make sure that our device is easy for their staff to use with minimal training, but that is not easy. Usually, we develop really cool things in an academic setting – but they don't travel well and their operation is complicated. We're trying to solve that now!

one protein at a time – and build a signal by counting those proteins. Unlike a test that requires millions or trillions of individual proteins, this approach has the advantage of high sensitivity.

From concept to reality

To measure a specific protein, we start with a blood sample and pre-processing – at a minimum, to isolate a plasma sample. Then, we incubate the processed sample in a vial of our DNA origami to allow the biomarker to bind to the "frame." After incubation, we place the sample into a cartridge with a nanopore filter; then, the cartridge goes into a machine roughly the size of a book, which measures the electrical current. Within one or two minutes, we have the raw data we need. Finally, we analyze the data offline. Total time? About 35 minutes – perfect for rapid or point-of-care diagnostics.

The catch is that each protein biomarker needs its own specific, custom-designed DNA origami – so there will be different vials for the different "frames." Moreover, our technology currently detects one protein at a time, but for many diseases a single biomarker is not enough for clinical decision-making. We're working on measuring multiple proteins at once by combining different DNA origami "frames" into a single vial, but I anticipate it will take us another five years to get there. And that's why we need to ask ourselves if we truly need to enable the detection of multiple markers. Are there any applications for which just one would be useful – and would those applications be commercially viable? After all, we will need funding to support the development of our technology. We're talking to clinicians to find out what they need most.

Our current prototype is not optimized for routine clinical use – something we realized pretty much immediately. We are now working with industry partners who can help. For instance, we recently joined forces with a company that provides disposable cartridges for digital measurement – an approach that will be much more suitable in the clinic. Single-use equipment means that every new measurement would be in a completely sterile environment. Our initial experiments look promising, but now we need to validate the test for clinical use.

The future of biomarker research

These days, everyone is talking about liquid biopsy. We typically use liquid biopsy to analyze nucleic acids circulating in the blood, helping us detect and diagnose certain diseases. But why focus on nucleic acids when so many technologies already measure DNA and RNA? In my opinion, it's time to focus on proteins. Our approach to protein analysis is an unusual one; rather than examine the sequence that underlies the protein, we simply look for its presence.

Fundamentally, the presence of an unexpected protein – or the absence of an expected one – tells you that something is wrong. Nucleic acids tend to provide information about risk factors for disease; you might never develop the disease itself. Protein detection, in contrast, allows you to intervene when there is an active problem – and the earlier we can detect a protein biomarker, the better the outcomes (and the lower the stress) for the patient.

> *"Only by involving everyone can we create a test that is beneficial for both professionals and patients."*

Another key is engagement with medical professionals. We need our clinical colleagues to co-design assays and devices with us to ensure they are accessible and easy to use. And that means we need to involve everyone – from nurses to consultants – so that anyone who might be using the technique has the opportunity to inform its development. As engineers, we're very good at overcomplicating things, so it pays to get as much input as possible from end users. Only by involving everyone in the process can we create a test that is beneficial for both professionals and patients. And, after all, that's what diagnostics development is all about.

Paolo Actis is a University Academic Fellow in the School of Electronic and Electrical Engineering, University of Leeds, UK.

Embracing Pathology's Digital Revolution

Deep Bio stands at the front and center of digital transformation with DeepDx® Prostate

Digital pathology is on the rise – and, with it, artificial intelligence's role in the pathology workflow. Many pathologists are embracing the change – often young pathologists who understand that progress is inevitable.

Dedication to the cause

Deep Bio is among the companies leading the charge by developing deep learning algorithms tailored for pathologists. A biotechnology startup based in South Korea, Deep Bio was established in 2015 with the vision of integrating artificial intelligence (AI) into cancer diagnostics. Now with 34 employees, Deep Bio boasts a multidisciplinary team of medical experts, machine learning engineers, data scientists, and entrepreneurs – all working to harness the AI-driven transformation in pathology.

Deep Bio first made waves in the medical AI-space by taking first place in CAMELYON17, a global competition to assess the performance of algorithms in localizing breast cancer metastasis in the sentinel lymph node. Since then, it has continued to build on its deep learning technology to engineer algorithms for various cancer types – producing 13 registered patents and 14 pending. Through its diverse software offering, Deep Bio empowers pathologists and supports real-time clinical decisions.

Its flagship product, DeepDx® Prostate, is an AI-powered software that automatically detects prostate cancer. Once the pathologist uploads digitized whole-slide images of H&E-stained prostate biopsy specimens, the tool generates automatic cancer detection, colored overlays of Gleason scoring, and tumor quantification within seconds. Notably, DeepDx® Prostate made headlines when it became the first AI-based cancer diagnostic support software to receive MFDS (Korean FDA) approval. "The Korean pathology community has been at the forefront of adopting AI to improve the quality of patient care," says Sunwoo Kim, CEO and founder of Deep Bio.

What were the drivers behind this medical AI adoption? Kim explains that a clinical validation study of the algorithm, published in Cancers, played an instrumental role. "Our clinical validation study showed high diagnostic concordance between DeepDx® Prostate and the reference standard of three pathologists (0.907 quadratic-weighted Cohen's kappa coefficient)." He continues, "This shows that our model can provide pathologist-level diagnostic support or second opinions."

But it is not just the performance of Deep Bio's technology that sets it apart; it goes above and beyond for its customers, too. "When we first implemented DeepDx® Prostate, Sunwoo took the initiative to bring his team with him to the US to meet our lab. When someone makes that kind of effort, it makes it much easier to work together," says Matthew Leavitt, CEO of PathNet, a network of independent pathology practices.

Moving forward

Deep Bio shows no signs of slowing down. "There has been a high demand in the US for our software. We have already processed more than 244,000 cores from CLIA labs for testing purposes," says Kim. "We have more AI models in the pipeline for the diagnosis of breast cancer, bladder cancer, and lymph node metastasis of breast cancer. More excitingly, our technology can quantify clinically meaningful data, such as the proportion of Gleason pattern 4, which has prognostic significance."

Tried and tested

With Deep Bio's years of experience behind it, DeepDx® Prostate offers a seamless process for the pathologist, bringing value to its users. "We have been using DeepDx® Prostate for a couple of years now," says Leavitt. "Deep Bio's initial willingness to integrate into our workflow and laboratory information system means that, after I have analyzed tissue, I can instantly check the results from DeepDx® Prostate with a simple click of a button – sometimes revealing small areas of concern that I would have missed had I not had the tool running in the background."

DeepDx® Prostate's speed and analytic features enable pathologists to confidently make diagnostic decisions in real time, but Leavitt understands that the company behind the algorithm is an integral part of the partnership. "DeepDx® Prostate is truly revolutionary, but it takes a lot of trust, experience, and feedback between the user and the AI developers. That's why we have formed such a nice relationship with Deep Bio – because it handles that interaction between the user and AI developer so well."

Min-Sun Jin – a pathologist at South Korea's Bucheon St. Mary's Hospital with experience using DeepDx® Prostate – eagerly agrees. She says, "DeepDx® Prostate helps pathologists diagnose cancer with increased accuracy and speed. In particular, it reduces inter- and intra-observer variability. In hospitals without pathology residents, using DeepDx® Prostate for screening will allow pathologists to spend more time and energy on their research."

Sunwoo Kim is CEO and Founder of Deep Bio, Inc., Seoul, Korea.

Matthew Leavitt is CEO of PathNet, Little Rock, Arkansas, USA.

Min-Sun Jin is a pathologist at Bucheon St. Mary's Hospital, The Catholic University of Korea, Bucheon, Korea.

Profession

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How to Flatten the Forgetting Curve

Virtual learning can increase knowledge retention – and learner satisfaction

By Stephanie Post

As laboratories bring in new instrumentation, excitement quickly fades to stress and scheduling hassles for many. In addition to space modifications and laboratory information system connections, training staff on the new system while maintaining current workload demands can be a daunting task.

For over half a century, labs have sent staff for offsite training to operate their new systems. In this train-the-trainer model, those staff members are expected to be the key operators on the system and to transfer knowledge to others for the life of the system. Vendors set out to arm trainees with everything they need to know to operate, maintain, troubleshoot, and train others on the system – but that doesn't always happen.

Why doesn't the material stick in these trained operators' minds? Why aren't the dozens of books, guides, and manuals lining the shelves of the laboratory cutting it? The answer may lie in a phenomenon called the Forgetting Curve.

What was that?

In 1885, Hermann Ebbinghaus demonstrated that knowledge retention decreases up to 40 percent in just a few days if that knowledge is not applied (1). Adding this theory to our experiences with training created an "Aha!" moment.

When customers travel to our headquarters for training, they often return to their labs to juggle running their current system with implementing the new one. It might be weeks or months before they go live on the system they have just learned everything they need to know about – meaning they will naturally lose a significant fraction of that knowledge.

Is there a way to train basic operators so that they don't lose knowledge as soon as they hit the tarmac of their home city?

> *"Knowledge retention decreases up to 40 percent in just a few days if that knowledge is not applied. Adding this theory to our experiences created an 'Aha!' moment."*

In 2009, we tested the use of webcams with select customers for "just in time" training – a remote basic

training experience that customers could attend when they needed the information. Pilot successes and failures led us to think bigger – a lot bigger. We formulated a strategy to deliver professional-level training online – live – and gave it a prescient name: virtual instructor-led training (VILT). Our goal was to train everyone who operates our hematology systems. VILT would be divided into tell-show-do segments where the instructor tells the learners, then shows the learners on camera, then sends the learners to their instrument to do the exercise. When learners come back to class, they complete retention poll questions and participate in a question-and-answer session. The tell-show-do process is repeated segment after segment

"We designed a 'continuum of education' structure with levels ranging from basic training to advanced curricula."

In 2010, we sought out space (and consultants) and began to build two television studios. The next three years were spent learning a new craft and navigating technology changes and challenges along the way. Beyond technology and construction, we had to transition our instructors to become not just on-camera talent, but educators who now taught to that camera without the benefit of classroom nonverbal cues.

By mid-2013, we were ready to kick off a pilot with a small analyzer and a few select customers. Their early feedback was used to polish our VILT classes and add support tools, such as documents to explain VILT streaming needs and ensure patient data was kept private. In January 2014, we decided it was time to rip off the bandage and launch our new hematology systems training in VILT.

Customers could now self-enroll through our online learning management system (LMS) for classes that worked for their schedule. Classes were shortened from five days to two and a half for more complex platforms and a half day for smaller systems. Because these classes are offered live, we quickly learned to modify start times to accommodate the east coast, west coast, and even Hawaii time zones. Surprisingly, we learned that these varied hours often allowed early morning or afternoon shifts to take VILT as well.

Come one, come all

How did we get customers to attend? We didn't want to completely eliminate our in-person training, but we wanted to make it more like a Masters of Business Administration course involving networking, information sharing, advanced learning, and troubleshooting.

We designed a "continuum of education" structure with levels ranging from basic training to advanced curricula, including an in-person class. The customer was given travel training slots as part of their analyzer contract and had the option to complete basic analyzer training through VILT and save the travel slot for an exclusive, invitation-only advanced class at our training facilities. Within a year, 99 percent of basic training was conducted through VILT and we replaced those in-person classes with advanced training where experienced customers could learn together at a higher level.

Through the years, VILT attendance numbers began to double, triple, and now quadruple compared with the number of customers we could train in a classroom. For example, in-person classes may be restricted to eight customers to optimize hands-on experience with the four analyzers in the room. Now, our largest class includes 64 customers working on their own instruments in their own labs. But even with the apparent success of VILT and a 93 percent customer favorability rating, a question still remains: how does this training help us achieve our goal of not only training everyone, but also driving retention?

Initially, we worried that having too many customers at the same site in a VILT class might be challenging, so we did what every scientist would do – a study. We had an opportunity with two different labs in the same integrated hospital system who were willing to try VILT. Lab A sent one operator to VILT; Lab B sent six. Upon assessing feedback from the customer and our implementation staff, the data showed that Lab B, with its six trained operators, was more prepared at instrument go-live time than Lab A. Furthermore, data from memory studies suggest people retain 50 percent more information when learning in groups (2,3).

In addition to the group learning benefits VILT offers, we noted something we hadn't predicted: learners weren't just taking VILT, but completing our self-paced e-learning courses as well – at an average rate of 250 completions per day! The e-learning we offer is available 24/7, so customers who can't attend VILT or who want to review certain sections of the training can access it anytime.

Today, we have trained more than 18,000 technology users with VILT and have even increased our training operation based on an expanded product portfolio and customer demand for additional curricula. We've now established an educational site, the Sysmex Center for Learning, that houses seven professional production studios, large interactive advanced learning classrooms, and technical training classrooms built with VILT capabilities. Even now, we're just scratching the surface of the future of training – but there's still plenty of room to expand.

"Data from memory studies suggest people retain 50 percent more information when learning in groups."

Stephanie Post is Senior Director of Marketing Communications, Commercial Operations Training & Development & Program Management, Sysmex America, Lincolnshire, Illinois, USA.

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Long-Distance Learning – With a Heart

In the midst of a pandemic, a virtual pathology lecture series stepped up to fill the training gap

By Christina A. Arnold, Adam L. Booth, Ashley Holloman, Kamran M. Mirza, Michael A. Arnold, and Teresa S. Burgin

The COVID-19 pandemic has forced near-immediate changes to all aspects of daily life. To limit transmission of the virus, some cities have adopted travel restrictions and social distancing policies that have made office-based work all but impossible. On top of that, many hospitals have created policies that require trainees to work from home. For pathology trainees, these measures have disrupted traditional educational activities, including sign-out at a multi-headed microscope and attending (often crowded) didactic and slide conferences. Training programs were forced to go virtual (1–3), but the transition strained an already-pressured group of faculty tasked with conforming to the new restrictions while simultaneously managing the pathology laboratory through the pandemic.

On April 1, 2020, the College of American Pathologists (CAP) launched the CAP Virtual Pathology Lecture Series to help sustain residency program education in these unprecedented times. To date, more than 9,500 individuals have registered for the series and it has garnered more than 76 million impressions on Twitter. A CAP survey found that 97 percent of the 1,347 respondents found the lecture series "satisfactory or very satisfactory" – and all surveyed faculty described a very positive experience, saying that they would lecture again and recommend the series to their colleagues (4).

What did we learn from launching an international lecture series in under a week during the pandemic? Here are our top eight lessons.

1. Identify the need

To solve a problem, you have to see the problem.

On March 13, 2020, the CAP began to receive reports from pathology trainees and faculty across the country, warning them of the looming educational crisis. The CAP identified a need for free pathology education that could be accessed by thousands of learners from all parts of the world – immediately.

2. Assemble a team

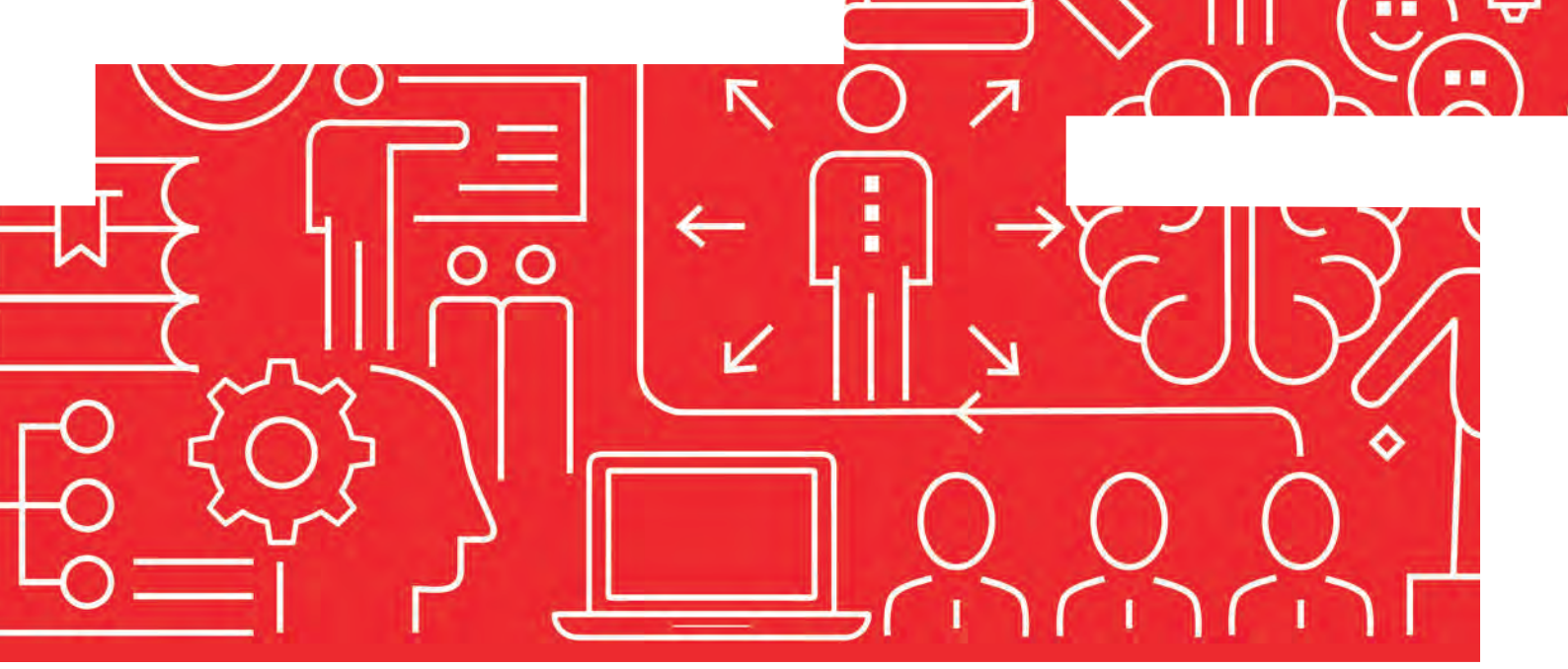
"Look for the helpers." – Fred Rogers

Just two weeks later, Teresa Burgin suggested a CAP-sponsored virtual lectureship series during a Curriculum Committee conference call. "I heard Teresa Burgin describe the lecture series and I recognized this as the perfect solution to multiple crises," says Christina Arnold. Later that day, the two identified key educational topics and strong educators who could be mobilized quickly. Arnold solicited faculty volunteers and, within 24 hours, more than 30 educators had volunteered more than 40 topics. The CAP Virtual Pathology Lecture Series was born – and its launch was a mere five days away.

3. Get the word out

"This will be a success if we have 40 learners." – Teresa Burgin

Developing projects for large organizations typically involves setting out a clear mission, outlining objectives with deadlines, recruiting key people, establishing goals for success, vetting these programs through experienced committees, and promoting them widely via member directories, email, and social media. These processes are important – but they take



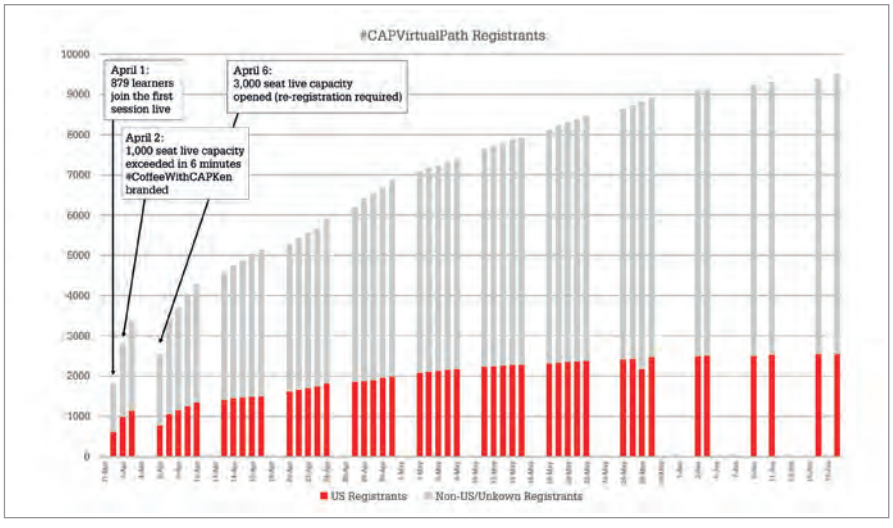


Figure 1. Registration data by geographic location, with key events highlighted.

"All promotion was exclusively through [social media]. Would anyone attend the sessions?"

time, a resource that was in short supply. Instead, a fast-moving ad hoc committee replaced the traditional workflow.

To recapitulate the daily lecture series most training programs offered before the pandemic, the CAP decided to offer free one-hour lectures Monday through Friday, with an additional 30-minute question-and-answer session for each lecture. Burgin worked with Kamran M. Mirza, Adam L. Booth, Michael A. Arnold, and Christina A. Arnold to produce balanced, high-yield educational content for the April schedule. The CAP team scheduled lectures based on priority topics and educators' schedules, secured a virtual platform to host up to 1,000 learners, enlisted technical support, and developed artwork and digital assets for promotion. At this point, all promotion was exclusively through the social media platforms of the involved pathologists. Would anyone attend the sessions?

"This will be a success if we have 40 learners," said Burgin.

Arnold was more optimistic. "I think the numbers will be much higher, but I am not sure where we will land."

The first promotional tweet went out less than 24 hours before launch. Within four hours of opening registration, more than 400 people had registered. Within 72 hours, that number had well exceeded 3,000 – surpassing all expectations. According to CAP President Patrick Godbey, "This program has been a tremendous success, with an average daily attendance of more than 1,000 in April."

4. Forget perfect – just get it done

"Perfection is the enemy of progress." – Winston Churchill

Launch day arrived. The lecture series was not formally promoted until a half-hour before the first presentation. The remaining April schedule was still in progress.

"We are building this plane as we fly," Burgin commented.

"Expect hiccups," Arnold added. "These things never go perfectly."

Nervous anticipation set in. Would anyone tune in to listen? Would people stay for the whole hour? Would anyone ask questions? Would the technology execute smoothly? Would learners come back for day two?

Barbarajean Magnani, the first scheduled

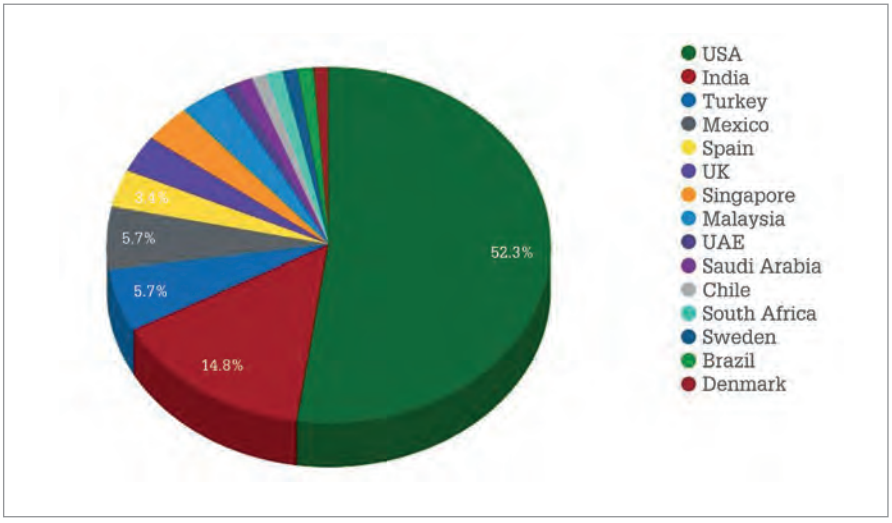


Figure 2. Geographic distribution of learners at the CAP Virtual Pathology Lecture Series.

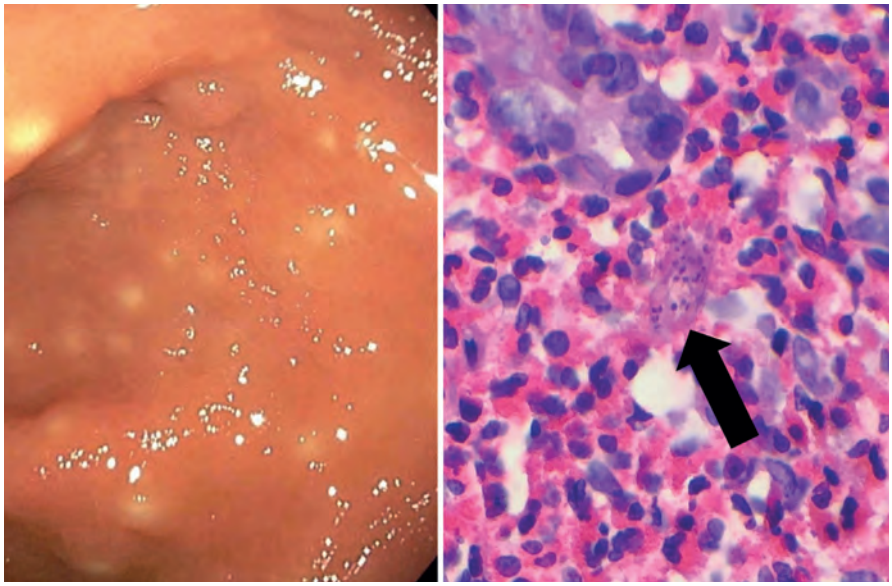


Figure 3. A remote case with similar features to the *Strongyloides* case described by Feely, including white nodules in the colonic mucosa (left panel, yellow box), and intense eosinophilia. Deeper sections into the tissue block revealed a single *Strongyloides* fragment (right panel, arrow).

speaker, delivered the first of a three-part toxicology primer on April 1, 2020. An international clinical chemistry and toxicology expert, Magnani commanded an audience of 879 on day one.

Was this a fluke? Would the lecture series have staying power?

The next day, Michael A. Arnold offered a "Survival Guide to Pediatric Tumors" – a specialized topic that rarely garners high viewing numbers. Nonetheless, the room reached its 1,000-learner capacity within six minutes. Every subsequent day of that week was similarly overbooked, with senior faculty members often exiting to make room for trainees. "I would make sure that I logged in 30–45 minutes early just so I could secure my place. The live lecture series had already become part of my routine and I didn't want to miss it!" says Ashley Holloman, a fellow in neuropathology. Although all lectures were recorded for learners to access at their convenience (5), people wanted to be "in the room" during the live lecture. Ultimately, the lecture capacity was increased to 3,000 (see Figure 1).

5. Make space for mistakes *#CoffeewithCAPKen*

Ken Molay, the webcast moderator for the lecture series, arranged to meet with each speaker 30 minutes prior to the lecture to run through audio checks and familiarize presenters with the software controls. During the pre-broadcast set up on the very first day, Molay and Magnani accidentally found themselves in broadcast

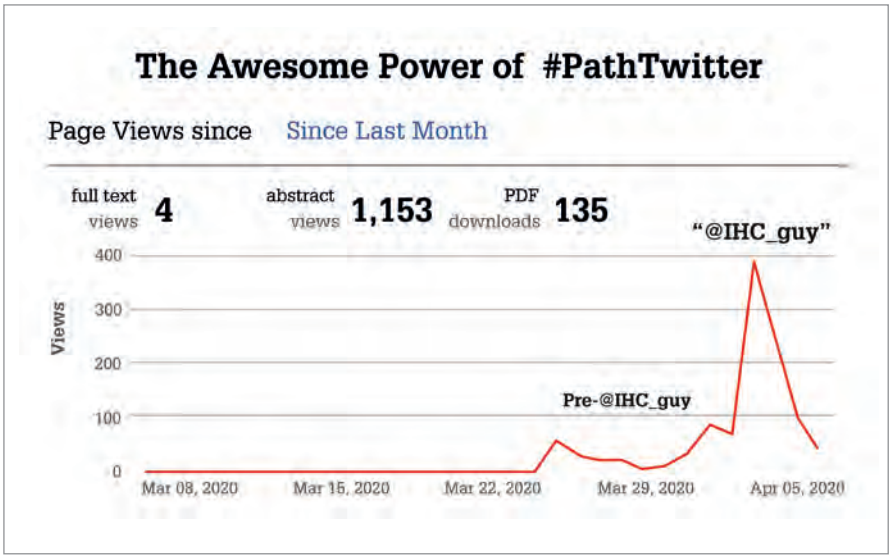


Figure 4. Increase in views of Andrew Bellizzi's publication (6) after joining Twitter and presenting a lecture on April 3.

mode. It was 9:45 AM, with 15 minutes until the lecture officially started, and the speakers were unexpectedly broadcasting live to hundreds of people… with no planned content.

Molay didn't miss a beat. He engaged with the audience. He asked them to type their locations into the comment box and shared them live. People tweeted photographs of their "classrooms" and Molay described them to listeners. Lockdown restrictions had isolated people – but the chat brought them back together.

By the next day, the pre-session dialogue was branded #CoffeeWithCAPKen and became an important fixture of the series. Topics included the learners' favorite music, diagnosis, pet, hobbies, movie, childhood game, non-pathology career choice, cell, and more. "#CoffeewithCAPKen had an amazing sense of community and a message of humanizing the medical field, promoting hobbies and work-life balance," one anonymous survey respondent shared. And the organizers felt the same. "I love #CoffeeWithCAPKen," says Mirza. "I have to admit, some days when I am very busy, I only tune in for that."

6. Look for surprise wins

Building future leaders

Well-established leaders with excellent teaching skills draw large audiences and deliver quality educational content. However, the pace of building this lecture series sometimes required finding a presenter within 24 hours – often impossible with a senior faculty member's busy schedule. This need for flexibility prompted us to include junior faculty as educators, and they did not disappoint. The arrangement was a win-win; early-career pathologists had a global platform on which to demonstrate their knowledge and educational skills – and we found a group of lecturers with flexible schedules, recent training, and comfort with online educational tools.

Sustaining trainee programs

As the COVID-19 crisis continued, residency programs across the nation built the CAP Virtual Pathology Lecture Series into their calendars. Many asked, "Can we count on this to continue?" It was clear from the audience size, social media presence, and feedback that the series resonated with learners. Lectures were described as "a once-in-a-lifetime opportunity," "the best thing that has happened in 2020," and even the "pathology version of Netflix!" One anonymous survey respondent said, "For two and a half months I was ordered to work as an emergency doctor. In this process, your lectures kept me connected to pathology and continued my education."

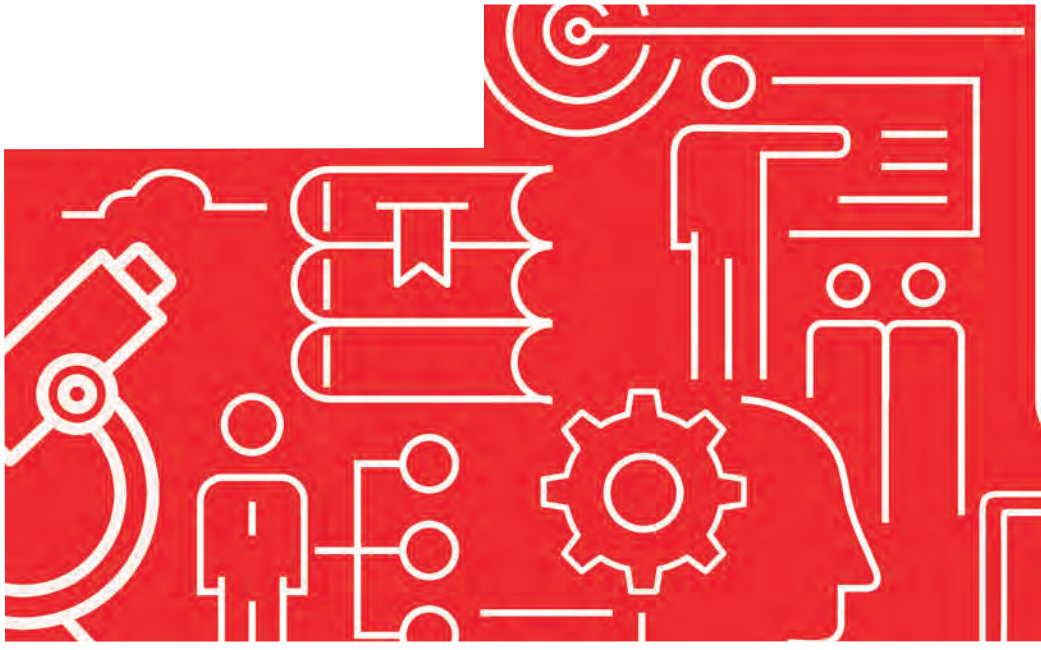
By making free, high-quality lectures by known experts accessible to all, the lecture series removed barriers to education – hopefully elevating and unifying pathology training. No matter where a person trained, how small their training program, or how many senior pathology leaders were at their institution, they could all learn the latest techniques from leaders in the field – on their own time in their own homes. In fact, the series was so popular and so successful that it was ultimately extended throughout May.

An international experience

Although CAP members are predominantly American, the CAP Virtual Pathology Lecture Series drew an international audience. By the end of April, almost two-thirds of the audience was outside the US (see Figure 2). The steady audience of global learners showed that the combination of an easy-to-use platform, quality educational content, and an evolving social community was contributing to pathology education not just among CAP members, but worldwide.

Beyond residents

The CAP Virtual Pathology Lecture Series was originally referred to as the "CAP Virtual Resident Lecture Series," but the team quickly realized that their audience was more than just residents. Medical students, technicians, fellows, practicing pathologists, and other professionals also found the series worthwhile. "Really learning a lot from tonight's #capvirtualpath lecture! Lots of things that I don't think I was



able to learn even during residency," tweeted Philippines-based pathologist Celestine Trinidad. Brian McMillen, another long-time pathologist, echoed her sentiments. "These are great not only for trainees, but practicing pathologists as well… I've listened to the talks by @RaulsGonzalezMD and @Williams_SR; both were full of great practice points."

Giving back to the pathology community

Pathology educators who would ordinarily travel as part of visiting professorships or to lecture at national or international meetings had their trips canceled in the pandemic. "The CAP gave me a way to give back to the community on a scale and platform that I could not have done on my own. While quarantined at home, I could share my prepared lectures with hundreds of learners across the globe and feel like I was doing what I could to help others in a time where almost everything was uncertain," says Arnold.

Improving patient care

The CAP Virtual Pathology Lecture Series did more than educate learners and build a social community. It also had an immediate, positive impact on patient care. How? On April 29, 2020, the CAP Virtual Pathology Lecturer was Michael Feely, a gastrointestinal and liver pathologist whose topic was "Infectious Diseases of the GI Tract." He shared that gastroenterologists often note numerous white nodules in the colonic mucosa of patients infected with *Strongyloides*. Sometimes, he cautioned, the biopsy may only show a small portion of the worm – difficult to recognize in a background of intense eosinophilia – and deeper levels can better clarify the pathology. Adam Booth immediately recalled a colon biopsy from three years prior, featuring intense eosinophils, that had been signed out descriptively. With his pathology attending, they retrieved the case and learned that the patient had an unexplained multi-year history of chronic diarrhea and eosinophilia. Deeper sections into the tissue block revealed a single fragment of *Strongyloides* (see Figure 3). Booth shared the updated information with the gastroenterologist, who immediately contacted the patient, ordered *Strongyloides* antibody serum IgG, and prescribed ivermectin.

"Social media not only helped launch the series, but also became an integral part of the experience."

7. Social media is a powerful catalyst

There's no doubt that social media was a key factor in successfully launching the CAP Virtual Pathology Lecture Series. With the launch coming only days after the idea first arose, there was no time to work through the usual channels of committees and advertisements. Instead, the pathology Twitter community stepped up. By June 21, 2020, the Twitter phrase "#CAPVirtualPath" had garnered more than 76 million potential Twitter impressions from over 23,000 tweets – numbers we don't think any other pathology initiative has reached.

Social media not only helped launch the series, but also became an integral part of the experience. Nearly one-third of survey respondents participated in Twitter-based discussions surrounding the lecture series. Learners "live-tweeted" key teaching points and images during the lecture so that the information and discussion could disseminate beyond the classroom. "[Twitter discussions] added so much to the experience," one anonymous respondent said. "Not only did the presenters often add valuable insight to the conversation, but the reviews and summaries helped build takeaway points to better understand the material."

To help everyone access the social media discussion around the lectures, the CAP hosted a Twitter workshop giving basic tips for navigating social media for pathologists. And learners weren't the only people dipping their toes into social media for the first time. Several of the faculty also joined social media to contribute to the online discussions. Andrew Bellizzi, GI pathologist at the University of Iowa and Chair of the CAP Immunohistochemical Committee, joined Twitter prior to his first lecture. Within 48 hours, he had more than 1,000 followers.

Within three days of his first lecture, the paper he discussed (6) had jumped from four abstract views to 1,153 (see Figure 4).

8. Adapt to a changing world

"The art of life lies in a constant readjustment to our surroundings."
– Kakuzo Okakura

COVID-19 changed all of our lives in every way. Would the CAP Virtual Pathology Lecture Series have existed in a pre-pandemic world filled with bustling service schedules, unrestricted travel, and scheduled didactics? It seems unlikely. Regardless, out of these dark times, something valuable was created. It started with CAP members voicing their concerns about the ongoing educational crisis. Next, their educational needs were connected to a supply of talented educators who were no longer traveling and wanted to help build the new normal. This lecture series grew organically into a social community through a series of happy accidents, organizers open to new ideas, and engaged learners eager to share. More than 9,500 learners across the globe shaped its presence on social media – and it is still evolving.

"As training slowly returns to 'normal,' we recognize that the new normal will be different," says Donald Karcher, Chair of the CAP Council on Education. "As a result, we're currently working on making the CAP Virtual Lecture Series a permanent resource for the pathology community."

But even pandemics are not forever. Now, the world is easing travel restrictions, learners are returning to medical centers, clinicians are ramping up services, and pathology services are bustling again. What role will the lecture series play in a post-lockdown world? At this point, it continues on a biweekly basis. The leadership team will become a larger and more formal committee. Although the details of the CAP Virtual Pathology Lecture Series are evolving in step with the needs of today's learners, the lessons it has imparted will stay with us as we build our new normal.

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Michael A. Arnold is Medical Director of Anatomic Pathology at Children's Hospital Colorado, Aurora, Colorado, USA.
Teresa S. Burgin is Senior Manager of Marketing Programs at the College of American Pathologists, Northfield, Illinois, USA.

The lecture series can be found on Twitter by searching for "#CAPVirtualPath" or visiting: https://www.cap.org/calendar/virtual-lecture-series-for-pathology-residents.

All lecture recordings are freely accessible at https://www.gotostage.com/channel/capvls.

See extended article and references online at: tp.txp.to/longdistance

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Pathology Education for All

How to teach pathology so that students learn

By Shivayogi Bhusnurmath and Bharti Bhusnurmath

Medical education is our opportunity to share our discipline with doctors of all stripes. How can we keep our teaching exciting, challenging, and relevant? A few simple tips can help:

- *Distinguish teaching from learning.* Pathology's role as the essential basis of all medicine makes it both exciting and meaningful – so students want to learn.
- *Challenge the students.* Our job is to introduce students to skills that underpin success in medicine. We must expect more than memorization.
- *Flip the narrative.* We use "flipped classrooms," small groups, and laboratory sessions to teach students to view each slide or sample as a whole patient.
- *Stay up to date.* Although not every student will be a pathologist, every student will be a doctor – and all of them must understand the value of pathology.

Read the full article online at: tp.txp.to/teach-path

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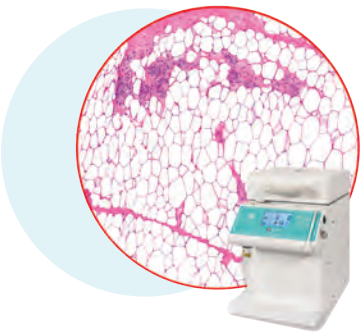

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An International Impact

Sitting Down With… Larry Wang, Professor of Clinical Pathology, Keck School of Medicine, University of Southern California, and Director of Surgical Pathology, and Associate Director of the Center for Global Health at Children's Hospital Los Angeles, California, USA

What led you to a career in pathology?

When I graduated from medical school, my dream was to become an internist – but the school assigned me to pathology. I was not happy at all. On my first day of work, the chair of pathology told me about being "the doctors' doctor" and recommended I read Arthur Hailey's The Final Diagnosis. I quickly realized that pathology included broad medical knowledge and incorporated a wide range of bioscience research fields and medical practices – and I came to love it.

What intrigued you about pediatric pathology?

When I was in graduate school, I participated in a research project on neurodevelopmental diseases. I discovered that childhood development was full of unanswered questions – and I love a challenge. After I finished my residency, I chose a pediatric pathology fellowship and really fell in love with the field.

My current research involves pediatric tumors and pulmonary developmental disorders. Working with the Children's Oncology Group as a member of the International Neuroblastoma Pathology Committee, my colleagues and I were the first to propose the concept of highly aggressive MYC-driven neuroblastoma. Recently, we investigated a rare and fatal lung disease, alveolar capillary dysplasia with misalignment of pulmonary veins, and found aberrant growth of extrapulmonary veins in the bronchovascular bundle (whereas septal pulmonary veins still exist without misalignment). The new findings challenge the current concept of "misalignment of veins" in this disease.

What's your advice to pathologists moving into a new region or culture?

When facing new challenges or a new environment, keep your spirits up; always have an enterprising heart; and strive to melt into your new life.

Everyone should know how to be grateful. As new immigrants, although we should work to integrate into our new environments, we should also know how to appreciate our homelands and our alma maters. Healthcare has no borders – think about how you can use what you learn in your new home to help the one you left behind. In this respect, many of my predecessors have served as excellent examples; their work has inspired me to participate in international projects.

Since 2008, I have worked with Chinese pathologists to train the next generation of pathologists. We have gradually improved the level of clinical diagnosis and laboratory management in China by holding workshops and inviting pathologists to American hospitals for short-term training. This has worked so well that I was invited to co-organize, co-edit, and co-write the pediatric pathology volume in the country's first pathology textbook series, which I hope will promote the discipline's development in China. I also went to India to attend CME courses for pediatric pathologists there. In the past decade, I have given more than 100 international lectures in pediatric pathology and trained 26 pediatric pathologists from seven countries. Next, my colleagues and I plan to conduct a one-year training program for international pediatric pathologists in accordance with general guidelines from the Fellowship Committee of the Society for Pediatric Pathology. In addition, I am helping Chinese children's hospitals train senior pediatricians, head nurses, and administrative personnel by organizing short-term training courses in the United States. The effects are impressive – and I hope they will benefit children around the world.

You're active in many professional societies – what are the benefits?

Pathology is a specialized subject that requires a wide range of knowledge. Especially in the current era of rapid technological development, we must maintain our curiosity and stay up-to-date on relevant professional knowledge if we want to be good pathologists. In particular, molecular genetics presents a significant challenge, because it changes many traditional concepts of pathology. With advances like this on the horizon, there is no way we can survive without continually updating our understanding.

"Pathology is not exactly overlooked; rather, it is seen as an auxiliary discipline."

How can pathology figure more prominently in medical education?

Pathology is not exactly overlooked; rather, it is seen as an auxiliary discipline. New imaging and molecular genetic technologies have replaced many traditional diagnostic methods, changed many traditional concepts, and gained a deep understanding of diseases – all very good things, but ones that present a major challenge to traditional pathologists. Molecular pathology is growing as a subspecialty – so it's more important than ever to master new technologies and incorporate them into routine diagnostic work so that we can remain "the doctors' doctor."

If you could give yourself one piece of advice at the start of your career, what would you say?

Follow your interests and instincts. Decide on a career path as early as possible. Choose a few things in your life that you love and focus on succeeding at them.

Read an extended version of this interview online at: tp.txp.to/lwang-int

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