SEPTEMBER / OCTOBER 2023 # 92

the Pathologist®

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Virus in Furs

How fashion-fueled mink farms are the perfect petri dish for a future pandemic

Ensure **Nucleic Acid Integrity** for **Accurate Molecular Results**

The Revos Tissue Processor prepares your samples for molecular test success

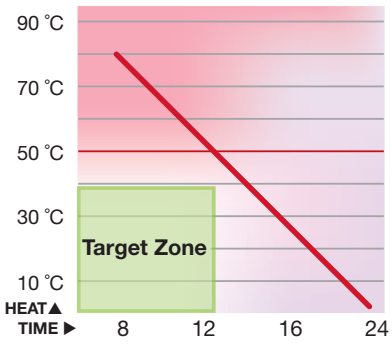
Molecular testing results, as with Next Generation Sequencing (NGS), can be inaccurate or incomplete when done on samples from tissue processors that use added-heat technologies to speed their results. The new Epredia™ Revos™ Tissue Processor overcomes this challenge with its unique canted-chamber design – the only rapid tissue processor on the market of this kind – that allows for rotational agitation within the chamber, processing seven times faster than the traditional processor without the need for added heat.

Through a recent internal study, we demonstrate how the ambient-temperature rapid processing with Revos allows for superior quality sample preparation and molecular testing results compared to added-heat processing. In this study, we compared high heat with ambient heat, as well as length of processing time. The tissues were trisected and processed in one of three protocols:

- Using Revos with ambient temperatures for 5 hours total time
- Using a traditional processor at 45 ºCelsius for 10 hours total time
- Using a traditional processor at 55 ºCelsius for 10 hours total time

The results? On average, the lower time and lower heat process of Revos delivered better RNA and DNA yields. Reducing heat and length of reagent time contribute to nucleic acid preservation, thus enabling higher quality molecular testing results.

Discover more on the benefits of the Revos Tissue Processor at **Epredia.com/Revos**



Positively impacting tissue processing quality
Reducing heat and time is beneficial to producing high-quality results for all downstream testing.

epredia LiveLab

Experience Revos for yourself, safely and conveniently with the **Epredia LiveLab**. If you are interested in a LiveLab session, please reach out to your Epredia Representative.

epredia
Enhancing precision cancer diagnostics

We've all heard the phrase, "beauty is pain." It's often thrown around in a colloquial manner, a joke when someone endures discomfort in the name of fashion. But the reality is less humorous. Behind the scenes of consumerism lurks a long history of disease that plagues the supply chain.

During the industrial revolution, illness was particularly rife among textile and cotton mill workers. Consistent exposure to cotton dust often caused severe respiratory and pulmonary diseases, such as byssinosis. And unsanitary conditions, overcrowded housing, and open sewers also meant that infectious diseases were commonplace.

The demand for fashion at the cost of health is not much different today. In July 2020, a fresh outbreak of COVID-19 tore through Leicester, UK, and the city became the first to undergo a second lockdown. Experts followed the trail of resurgence back to the garment manufacturing industry, where working conditions proved to be less than adequate. Investigations found that social distancing protocols were not rigorously enforced, and a handful of workers were made to work – regardless of their positive COVID-19 result. Trends like this are global, particularly in the developing world, where sickness and poor health are the price for a quick fashion fix.

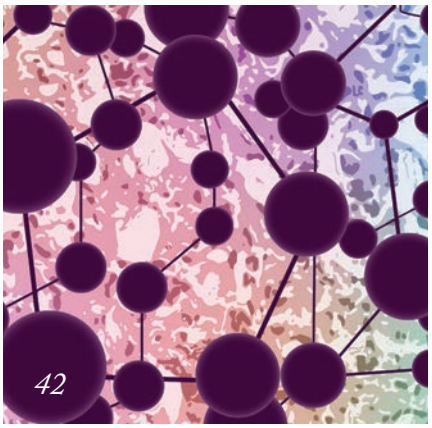
Lastly, it is well documented that animals are collateral damage of the fashion industry, born to die in stressful surroundings. At the same time, zoonotic spillover events are just waiting for the right mix of ecological, epidemiological, and behavioral factors to wreak global havoc – such as those present in certain farming practices (1). And as the human population increases and as the gap between people, animals, and the environment shrinks, many scientists are raising the zoonotic alarm. So, how uncomfortably close are we willing to get to such an event? If you flick to page 18, you'll see the topic of mink fur farming and pandemic potential explored in depth. Being a fashion fanatic myself, researching this topic made me realize that we need to rally now – more than ever – to support the anti-fur sentiment and mitigate the risk of a zoonotic crisis. Before it's too late – unfashionably so…

Georgia Hulme
Associate Editor

Reference

1. *R K Plowright et al., Nat Rev Microbiol, 15, 502 (2017). PMID: 28555073*

Contents



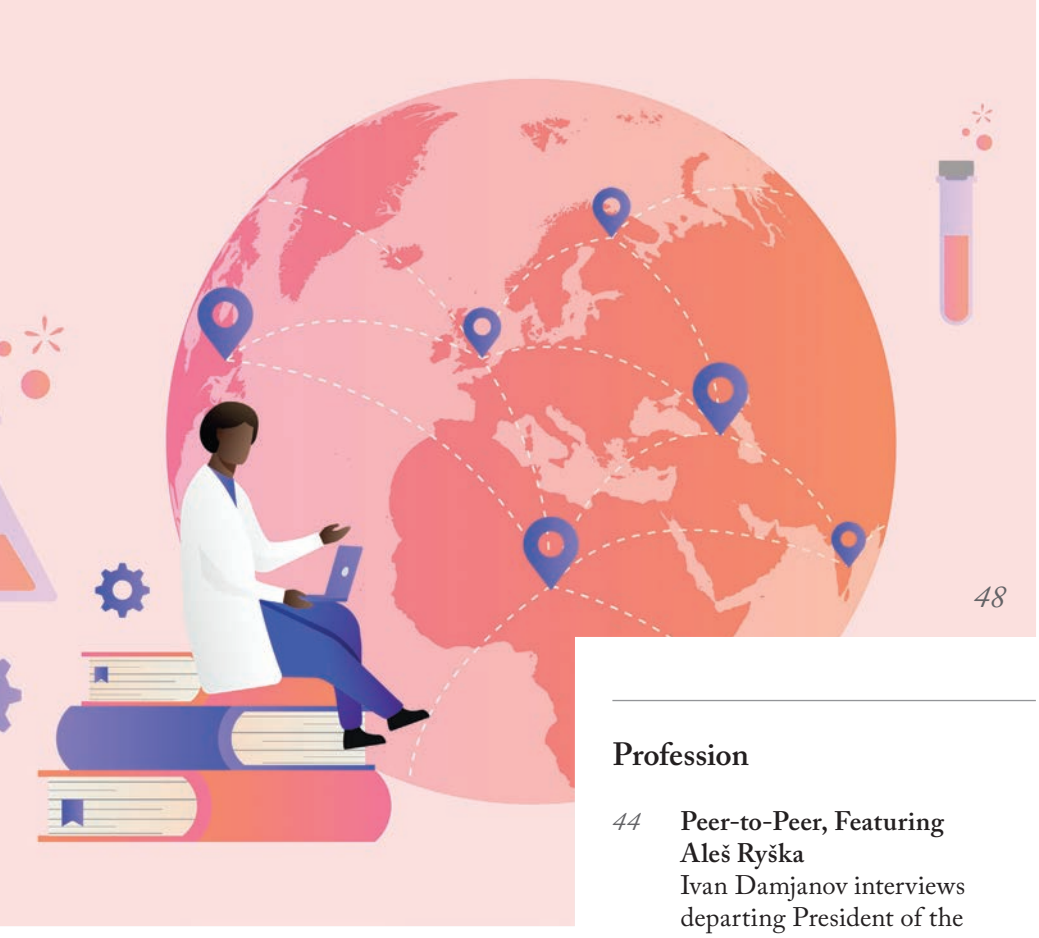
On The Cover

Examining the role of fashion in the next pandemic

Upfront

In My View

From The ASCP



Feature

Foundations

Profession

In Practice

Sitting Down With

Reports

the Pathologist

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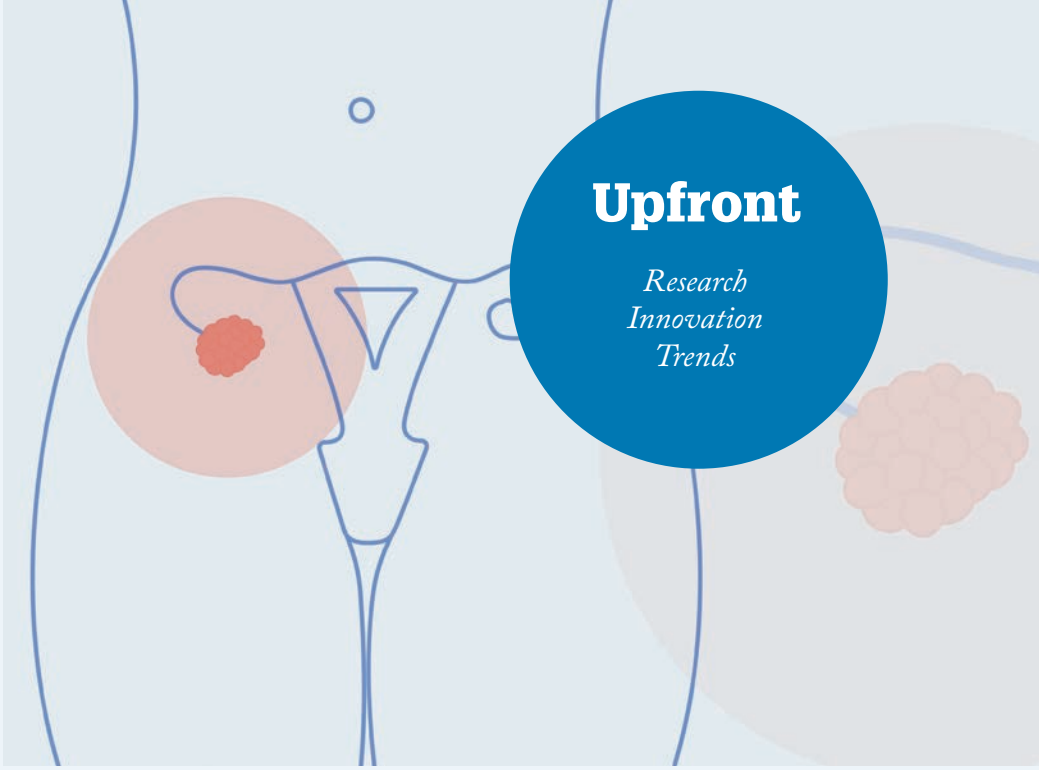


EVs for Ovarian Cancer Diagnosis

Three proteins identified as biomarkers for high-grade serous ovarian carcinoma

Ovarian cancer is the fifth most common cancer in US women, yet early diagnosis remains a global health care challenge. Often dubbed "the silent killer," its largely asymptomatic nature means that only 20 percent of ovarian cancers are found early, and there are no national screening programs available because of the unreliability and ineffectiveness of current tests (1). With that in mind, researchers from Nagoya University, Japan, have turned to ovarian cancer extracellular vesicles (EVs) – including exosomes – as promising biomarkers (2).

"We revealed the detailed protein information on ovarian cancer EVs and their diversity," says Akira Yokoi, Assistant Professor of Obstetrics and Gynecology at Nagoya University and lead author of the study. The research, which focused on identifying specific membrane proteins for high-grade serous ovarian carcinoma (HGSOC), used liquid chromatography-tandem mass spectrometry to analyze the proteins contained in small, medium, and large EVs. "Originally, the challenge was to find ovarian cancer-specific proteins in ovarian cancer EVs. We tested multiple methods, including unique ELISA for EV detection, western blotting or referring database for discovering targets and validating them," says Yokoi. They found that small EVs were more effective biomarkers than medium and large ones, and identified FR-alpha, Claudin-3, and TACSTD2 as proteins closely associated with HGSOC.

The team also developed a novel method of simple EV isolation using polyketone-coated nanowires (pNW). Indeed, the platform successfully purifies EVs from biofluids, making it well-suited for clinical application. The paper suggests "broad potential for pNW-based applications for isolating further specific EVs in circulating body fluids."

The one thing Yokoi wants laboratory medicine professionals to take away from these findings? "Deep understanding of EV biology can lead us to new applications in the clinic." The team aims to validate the performance of the identified biomarkers in clinical trials, and, in the future, they hope to apply this system to ovarian cancer screenings.

References

1. *American Cancer Society (2023). Available at: http://bit.ly/3OnXaEx*
2. *Akira Yokoi et al., Sci Adv, 9 (2023). PMID: 37418532.*

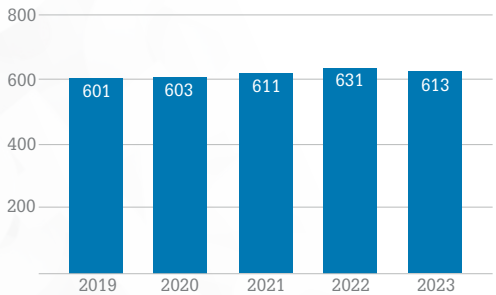
INFOGRAPHIC

Match of the Year: Residency 2023 in Numbers

A look at the data on Residency Match 2023

See reference online at: tp.txp.to/1023/match-of-the-year

Pathology positions offered in Match 2019–2023



Facilities with the largest variety of pathology quotas in 2023

Yale New Haven Hospital, Connecticut - **4**

Hospital of the University of Pennsylvania - **4**

RESEARCH ROUNDUP

We summarize five recent news stories in pathology and laboratory medicine

Transmission trends

Researchers have investigated the transmission of syphilis by linking national patient demographic, geospatial, and behavioral metadata to whole-genome sequencing of Treponema pallidum samples – the bacteria responsible for the disease. Analyses revealed that sublinegage 1 occurred throughout England and across all patient groups, and such trends prove how genomics can aid epidemiological insights (1).

Scoping out schizophrenia

Past genome wide association studies (GWAS) on schizophrenia have identified 145 genomic regions. Now, researchers have conducted a massively parallel reporter assay on 5,173 fine-mapped schizophrenia GWAS variants to figure out which have a causal effect in schizophrenia development. They found 439 variants with allelic regulatory effects (2).

Change for the better

New diagnostic criteria has recently been developed for metabolic associated fatty liver disease (MAFLD). The criteria was updated to be inclusive and applicable to all ages, regardless of age-related adjustment in some of the variables. The revaluation of MAFLD has increased awareness and bolstered research in the field – and will hopefully help increase diagnostic accuracy (3).

Stifling stiffness

Tissue stiffening is a mechanical alteration that occurs with the onset of cancer. It starts a chain reaction and causes deformation of neighboring cells and their nuclei – triggering cell proliferation closely related to tumor growth. Researchers have found that laminin – a glycoprotein of the extracellular matrix – mitigates the mechanoresponses of breast epithelial cells, therefore curbs the effects of stiffness and protects cells from tumor growth (4).

Deadly invasion

US researchers have found that the parasites that cause visceral leishmaniasis – *Leishmania donovani* – can infect non-immune cells. Single cell RNA sequencing revealed that the monocytes and macrophages of spleen tissue in mice were populated with the parasites. They were also found in the bone marrow of hematopoietic stem cells (5).

See references online at: tp.txp.to/1023/roundup

A Diverse Set of Discoveries

How do ethnicity and race affect the mechanisms behind liver cancer?

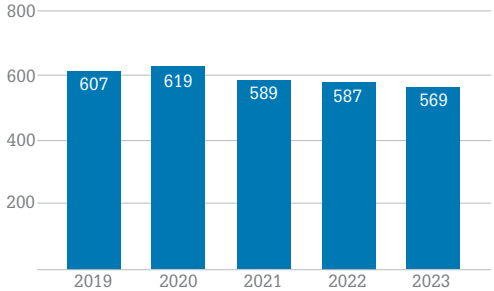
In a bid to pinpoint the specific causes of liver cancer among different racial and ethnic groups, researchers at the University of Miami School of Medicine analyzed each and every one of Florida's 2010–2018 liver cancer cases – more than 14,000 in total (1).

"Discovering differences in etiology can help detect racial-ethnic groups that have been overlooked in terms of liver cancer risk," says corresponding author Paulo S. Pinheiro. "Simply put, all Black people are not the same, all Hispanics are not the same, and all Asians are not the same."

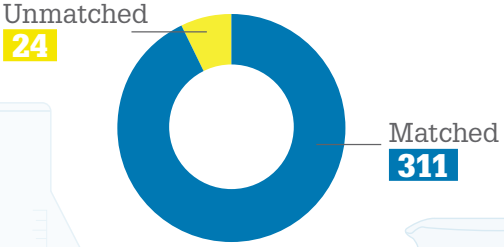
Rising causes of cancer, such as fatty liver disease and alcohol consumption, are high in Hispanic groups. On the other hand, causes that are generally decreasing – such as hepatitis C – are more common in US-born white and Black populations. Additionally, an overall rapid increase in hepatocellular carcinoma caused by fatty liver disease and alcohol is seen in men and women from all backgrounds – with the possible exception for Asians.

See references online at: tp.txp.to/1023/diverse-discovery

Pathology matches between 2019–2023



US applicants who put clinical/anatomical pathology as their only choice



Total: 335

Pathology popularity

For non-US applicants, pathology was the **5th** most popular speciality (185).

Doggy Diagnostics

These snouts have clout

Credit: Images sourced from Pexels.com

A review that examined 29 peer-reviewed papers on the power of pooches' noses has found that dogs' detection skills can rival standard RT-PCR testing (1).

"The collective results described in our review paper are quite impressive," says Tommy Dickey, first author on the paper. "The accuracy of the trained scent dog method is comparable to, or in some cases superior to, the real-time reverse transcription polymerase chain reaction test and the antigen test."

One of the studies reviewed in the paper found that tested dogs displayed a sensitivity 1000 times greater than scientific instruments. This, Dickey says, is the equivalent of detecting a single drop in a body of water bigger than 10 olympic size swimming pools.

"They can detect variants of COVID-19, along with asymptotic, pre-symptomatic, and long COVID-19, as well as symptomatic COVID-19 – even in the presence of other viral respiratory viruses. Furthermore, trained scent dogs have been effectively used to directly sniff individuals to provide quick (seconds to minutes), non-intrusive, and accurate results in public settings including schools, airports, metros, and concerts."

Surprisingly, one of the peer-reviewed papers examined in the review claims that scent dog screening could be the new "gold standard" replacement to RT-PCR. "They… found that the sensitivity of their scent dog-based test was superior to the RT-PCR test. In addition, the specificity of the two testing methods were nearly identical. They concluded that the scent dog method, with its high sensitivity, short turn-around-time, low cost, less invasiveness, and ease of application 'lends itself as a better alternative to the RT-PCR in screening for COVID-19 in asymptomatic individuals,'" Dickey explains.

There are some caveats. More studies with an increased number of dogs is required to gain a greater understanding of their diagnostic abilities. "More work in developing target disease samples and research is needed in different public settings," says Dickey.

Dickey hopes that the buzz drawn by the review demonstrates a hunger for dog-assisted diagnostics. "...the work described in our recent COVID-19 scent dog review represents a major needed demonstration of how effective and practical trained scent dogs can be in clinical and even public settings."

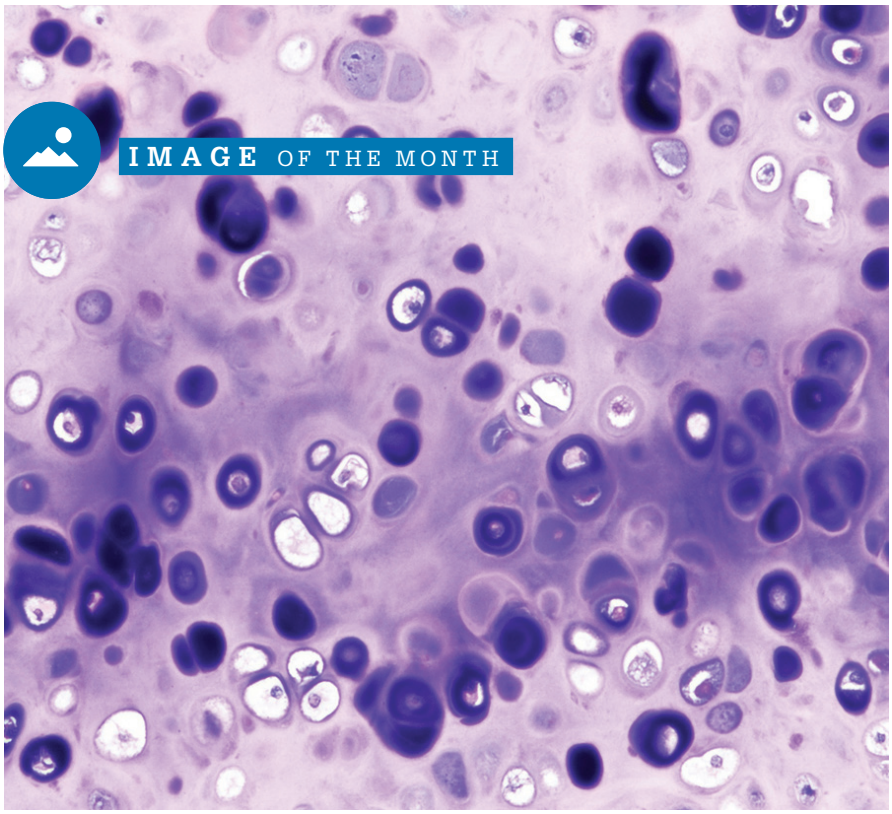
See references online at: tp.txp.to/1023/doggy-diagnostics

Parkinson's Progress

Could a new blood biomarker help with early Parkinson's diagnosis?

Researchers from Lund University have found a blood biomarker that proves promising in detecting Parkinsonian disorders in the preclinical stages. Blood samples were taken from a cohort of individuals from the Swedish BioFINDER 2 study and 2,943 proteins in the cerebrospinal fluid were identified using advanced proteomics. Out of the 428 individuals, 81 patients had Lewy Body disease (LBD) and the remaining were healthy controls. The test aimed to identify biomarkers that would indicate whether an individual with motor disturbances or cognitive impairment had damage to the dopamine system in the brain. Researchers found that individuals who had a dopamine-related disorder exhibited high levels of DOPA decarboxylase (DDC) in their CSF – regardless of the stage of disease. They hope that DDC can become a biomarker in the early detection of Parkinsonian disorders and predict future conversion to clinical LBD.

See references online at: tp.txp.to/1023/parkinsons-progress



Finding the Art in Cartilage

A photogenic (and purple!) stain of cartilage

Staining of cartilage, submitted by Craig Horbinski, Director of Neuropathology, Nervous System Tumor Bank, and Path Core at Northwestern University, IL, USA.

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

QUOTE of the month

As opposed to other medical fields, microbiology is one of the few areas where we know things will get worse over time – either through the emergence of novel pathogens or acquisition of antimicrobial resistance.

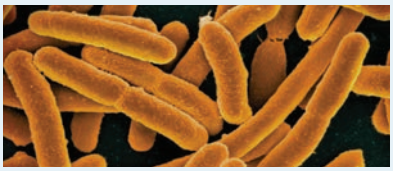
Salvador Almagro-Moreno, Associate Professor of Medicine at the Burnett School of Biomedical Sciences, University of Central Florida, Florida, USA

This quote was sourced from an article that originally appeared on our sister brand, The Medicine Maker.

Minmaxing Microbes

Genes resistant to antibiotics are optimizing their spread through careful fine-tuning

Researchers have explored how genes are evolving to maximize their effectiveness, despite efforts to reduce antibiotic consumption and bans of antibiotics, such as colistin, in agriculture.

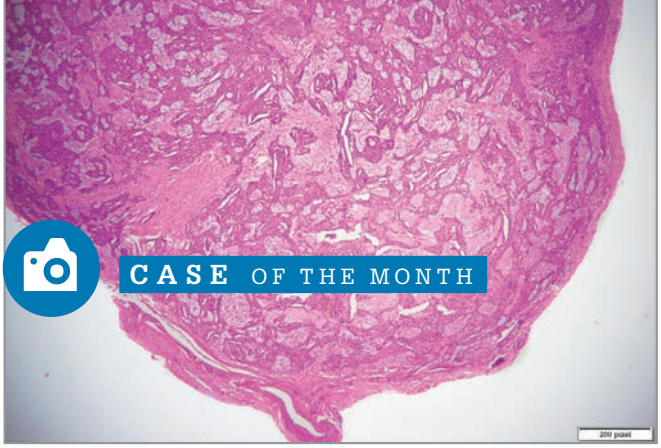


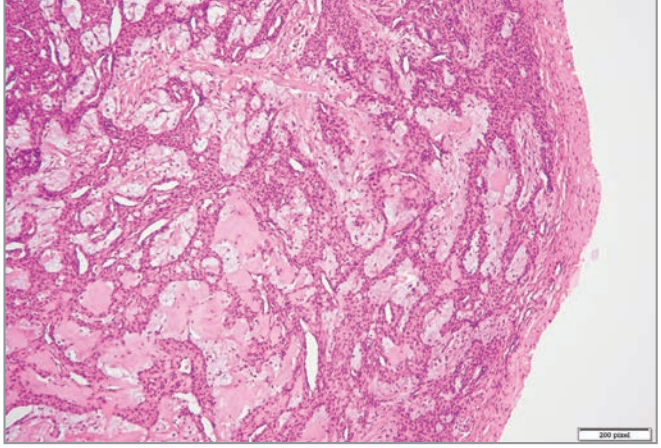
Credit: National Institute of Allergy and Infectious Diseases, National Institutes of Health

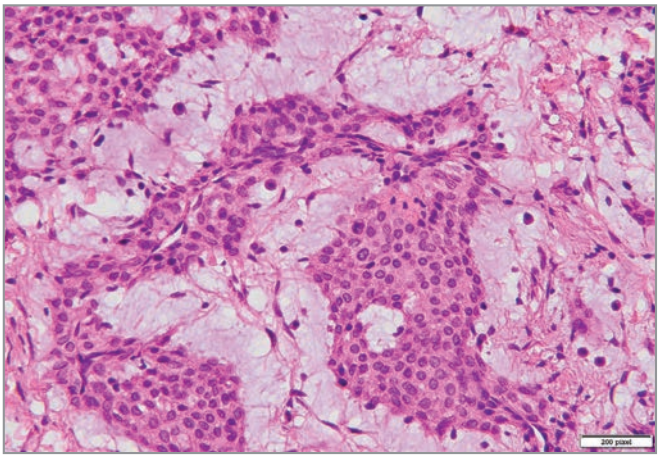
They found *MCR-1* has "fine-tuned" its expression levels in E.coli, minimizing any performance costs on the bacteria. "These new low cost, high resistance variants of *MCR-1* then spread across strains of E.coli that are associated with different ecological niches," explains corresponding author Craig MacLean from the University of Oxford. The team found that colistin's ban reduced *MCR-1* overall, but low cost, high resistance genes didn't drop so sharply.

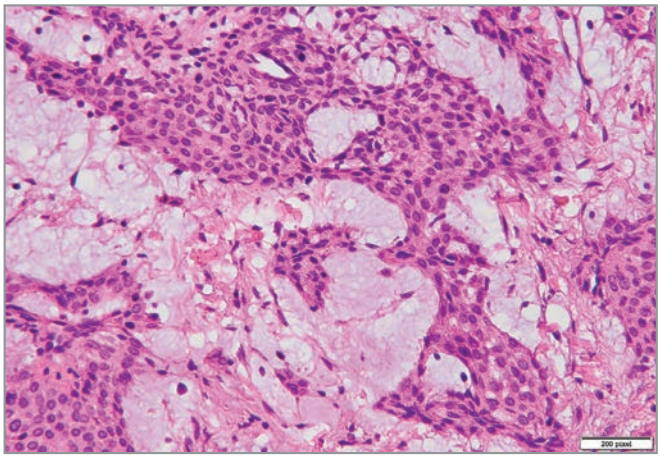
Surprisingly, the fine-tuned *MCR-1* genes were seen to actually boost colistin resistance. "We still don't fully understand why this is the case, but we think that it probably reflects the fact that high levels of *MCR-1* activity lead to changes in the cell membrane that make bacteria more sensitive to colistin; for example, by increasing membrane permeability."

See reference online at: tp.txp.to/1023/min-maxing









CASE OF THE MONTH

A 42-year-old female presented with a painful, slowly growing nodule on her hand. The histopathology is shown above (Figures 1-4).

Submitted by Muhammad Ahsan, Chughtai Institute of Pathology, Lahore, Pakistan, and Rida Noor, Faisalabad Medical University, Faisalabad, Pakistan.

Given the morphologic findings, what is the most appropriate diagnosis?

a) Chondroid syringoma
b) Glomus tumor
c) Eccrine hidradenoma
d) Myopericytoma
e) Mucinous carcinoma

Answer to last issue's Case of the Month…

d) *Treatment for dysphonia a decade prior to biopsy*

The laryngeal biopsy shows abundant polarizable crystalloid structures with associated granulomatous inflammation and foreign-body giant cells. This patient had a long-standing history of dysphonia and had undergone treatment with intralaryngeal Teflon injection ten years prior to biopsy. Historically used in the treatment of unilateral vocal cord paralysis, intralaryngeal Teflon injection has fallen out of favor due to frequent complications, including the exuberant granulomatous response illustrated by this case. This condition is known as a "Teflon granuloma."

Submitted by Megan C. Smith, Resident in Anatomic and Clinical Pathology, Vanderbilt University Medical Center, Department of Pathology, Microbiology, and Immunology, Nashville, TN, USA.

See reference online at: tp.txp.to/1023/case-of-the-month

To register your guess, please go to http://tp.txp.to/1023/case-of-the-month
We will reveal the answer in next month's issue!

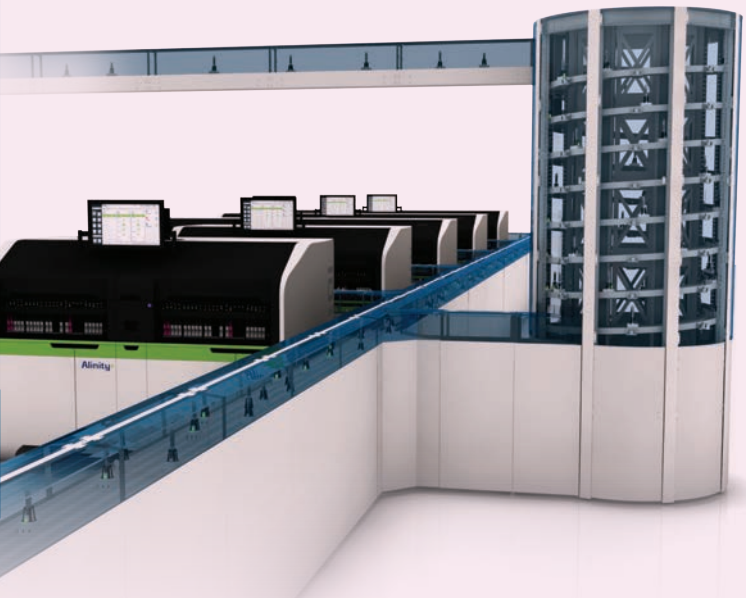
Case of the Month is curated by Anamarija M. Perry, University of Michigan, USA.

Transformation Through Automation

A case study in perfectly executed innovation from the Hospital Universitario y Politécnico La Fe in Valencia, Spain

In the dynamic landscape of contemporary healthcare, technology is reshaping traditional practices. A striking testament to this transformation is the remarkable journey undertaken by the Hospital Universitario y Politécnico La Fe in Valencia, Spain. Through the strategic adoption of cutting-edge automation systems, the institution has not only optimized its operational efficiency but has also established itself as a pioneer in the realm of laboratory medicine.

During the transition to a new facility, La Fe had two bold objectives: i) to minimize manual interventions across various phases of laboratory processes – from preanalytical to analytical and post-analytical – and ii) to create a streamlined pathway for managing STAT (short turnaround time) samples.



All efforts were geared towards ensuring swift and accurate diagnostic outcomes – an inarguably crucial factor in delivering effective patient care.

One important part of achieving its aim was the creation of a versatile system that could seamlessly process samples and data, while adhering to established indicators that are central to effective laboratory management. Notably, La Fe's samples originate from a diverse range of sources, including a broad spectrum of patients – from pediatric to adult – as well as inpatient units, primary care centers, and allied healthcare facilities spanning the region.

Impressively, the hospital's innovative approach goes beyond procedural optimization. By incorporating two dedicated "towers," our track design allows the test tubes running on the cars on the track to be elevated – therefore creating space for pathways and corridors under this elevated track area. The hospital was able to overcome architectural barriers and not only improve sample transport but also create a dedicated personnel corridor – exemplifying the hospital's commitment to efficient workflow management.

Abbott's Alinity systems played a pivotal role in La Fe's transformation. In fact, the hospital is currently equipped with four triple Alinity systems – three of which house dual biochemistry modules and one immunoassay module; the fourth houses 2 immunoassay modules and one biochemistry module. The integration of these systems has helped reimagine laboratory operations, seamlessly organizing centrifugation, decapping, aliquoting, and sample archiving with an unparalleled level of precision. Indeed, one major achievement is the estimated 40 percent reduction in aliquoting, which has helped further optimize resource utilization and streamline workflows.

The hospital also relies on AbbottLink – a performance evaluation tool that informs the expansion of its instrument portfolio, guided by predetermined parameters. AbbottLink is a system that creates seamless connectivity between Abbott instruments and allows for synergy between laboratory software, data files, and applications – all the while offering real-time troubleshooting and system monitoring of the lab.

Another essential ingredient in this success story is the meticulous sample traceability mechanism, which offers a comprehensive view of sample movement – enhancing transparency and accountability across the laboratory ecosystem. Of particular note is the inherent flexibility built into the track system, which allows for future equipment expansion and evolving diagnostic demands.

Beyond operational efficiency, the integration of automation has also resulted in increased safety enhancements and error mitigation. Reduced human intervention curtails the risk of human error, thus fostering a safer environment for laboratory professionals, as well as their patients. The shift in approach has also had an impact on the workspace itself; by eliminating compressors, the track system effectively mitigates noise and heat generation, creating a more congenial and efficient working environment for laboratory personnel.

In the contemporary realm of healthcare, where technology is increasingly becoming a major driving force, Hospital Universitario y Politécnico La Fe emerges as an example of perfectly executed innovation. By harnessing the transformative potential of automation, La Fe has not only redefined what laboratory medicine can be, but has also set a new standard of precision, efficiency, and patient-centric care.

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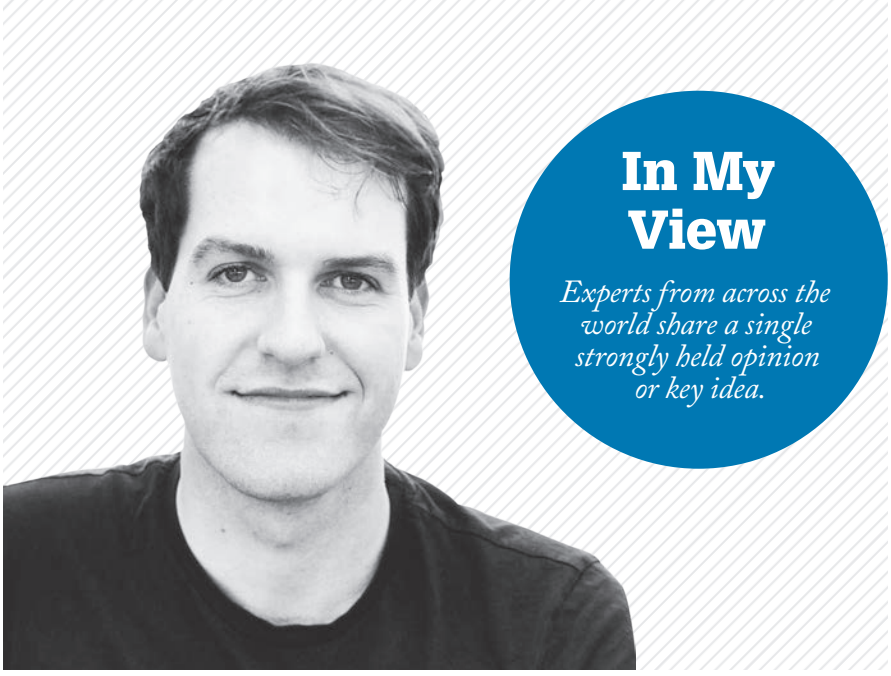

In My View

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

Unlocking Technological Potential

Why I advocate for a modular approach to digital pathology procurement

By Callum Arthurs, Digital pathology researcher at Imperial College London and co-founder of machine learning pathology company Compath

In recent years, digital pathology has witnessed remarkable advancements, offering laboratories unprecedented opportunities for efficiency, collaboration, and diagnostic accuracy – not to mention the mind-blowing power of machine learning. Despite this, the procurement process for digital pathology solutions across Europe has often fallen short for laboratories. Having personally visited numerous pathology labs and witnessed the challenges they face, I advocate for a modular procurement system that enables labs to select best-in-class solutions for each component of the digital pathology workflow.

The current procurement process often involves labs tendering for the complete package, including computer workstations, high throughput scanners, mega slide scanners, image management system (IMS), and cloud storage. Although this may initially appear logical, it unintentionally limits labs from selecting the most suitable solutions tailored to their unique requirements.

In these cases, labs are trusting the company leading the tender submission (the IMS provider in this example) to assemble the best possible solution. However, this practice frequently results in the IMS provider partnering with the cheapest scanner and storage providers to create a proposal that only appears to be cost-effective. It's important to note that to mitigate the risk of resorting to third-party solutions, there is often a 20–30 percent markup on price. As a consequence, labs often find themselves compromising and reluctantly accepting a combination of suboptimal solutions bundled together. For example, they may get a great IMS but this is almost worthless if the scanners producing the images have poor image quality.

A modular procurement approach allows labs to evaluate and procure each area of the digital pathology platform separately. I would go as far as separating out the lots for the different types of scanners that the lab requires, such as one tender for a high throughput scanner and one for a slower, Z-stacking, and mega slide scanner. By doing so, labs can choose the most advanced and tailored solutions for their specific needs. The modular approach empowers labs to select the best-in-class solution for each stage of the digital pathology workflow.

Here are five key benefits to the modular approach:

1. Flexibility. A modular procurement approach enables labs to customize their digital pathology platforms to suit their unique requirements.
2. Innovation. A modular approach allows labs to incorporate cutting-edge tools and methodologies as they become available, ensuring they stay at the forefront of technological advancements.
3. Scalability. Instead of being tied to an all-encompassing solution that may become obsolete or limit expansion, labs can seamlessly integrate new components into their existing platform.
4. Cost efficiency. By evaluating and procuring each component separately, labs can make informed decisions based on cost-effectiveness.
5. Interoperability and collaboration. Collaborative efforts often result in standardized data formats, interfaces, and communication protocols – all things that the community have been working on in recent years.

As digital pathology continues to revolutionize diagnostic practices, it is crucial for procurement processes to adapt and unlock its full potential. Granted, such a change will increase the timeframe and number of tenders that need to be managed by the laboratory workforce – a workforce that is already under-provisioned and overworked. But I believe that time savings down the line will likely outweigh this overhead. And who knows? Maybe it will also push NHS trusts and healthcare agencies to make a leaner tender process.

Blame Culture is Toxic

Tips to understanding and addressing errors in the pathology laboratory

Credit: Photographed by Carwa

By Bamidele Farinre, Pathology Quality Manager/Governance Lead (Chartered Scientist)

"How could you do that? You've released the wrong result! What a grave mistake…" says the manager.

"But I performed all processes according to the standard operating procedure," says the employee, trying to justify their approach.

"We will have to DATIX this as a serious incident," continues the employer. "And put you on a performance management plan."

"I'm not sure what went wrong…" cries the employee.

This dialogue may sound familiar to most professionals in the healthcare system. We all make mistakes from time to time. It's what makes us human. But no good comes from blaming and shaming each other for our imperfect nature. You benefited from learning from your mistakes, so allow others to do the same. A blame culture presents a serious threat to patient safety – especially, when blame sits on one person's shoulders to disguise a systemic problem or when people simply stop reporting mistakes.

Similarly, a blame culture also prevents you and your team from doing your best. And it can lead to several other detrimental outcomes, including reduced job satisfaction and morale, increased employee turnover, and reduced engagement and productivity.

It's true that errors in the lab can have serious consequences, potentially affecting patient diagnoses and treatment plans. However, it is crucial to approach the issue of errors with a focus on improvement rather than blame. Here, I'd like to shed light on the factors contributing to errors in the pathology laboratory and explore approaches to foster a blame-free culture that promotes learning, growth, and patient safety.

In a no-blame culture, employers encourage employees to report their mistakes and learn from them because they understand that errors can happen. A no-blame culture allows all employees – at all levels – to speak up and talk about mistakes without fear of being held solely responsible for the problem.

Pathology labs are complex. And they also operate within a larger healthcare infrastructure; sometimes errors can occur due to systemic issues or technological limitations. For instance, obsolete or malfunctioning equipment can contribute to incorrect results reporting. The blame for such errors should not fall solely on individuals but rather on a lack of investment in modernizing infrastructure. By providing state-of-the-art technology and promoting a culture of continuous improvement, organizations can proactively minimize errors caused by systemic factors. A no-blame culture can only have a positive impact on patient safety because it acknowledges "the ecosystem" in which people operate and creates an environment where individuals are supported in raising and resolving concerns, addressing incidents of unsafe care with empathy, respect, and firmness.

"It is crucial to approach the issue of errors with a focus on improvement rather than blame."

But how do we create this no-blame culture? Leaders must look to behavior modeling with self-awareness and self-efficacy. In the workplace, change starts from the top down. Leaders cannot effectively ask employees to take accountability and responsibility, if they refuse to do so themselves. We can easily change the way we address mistakes by treating them as learning opportunities rather than viewing them as setbacks. If you're a leader, seek out ways to turn your mistakes or wider failings into lessons from which the whole team can learn.

Even more pragmatically, we need to transition away from blame statements; for example:

"Who messed this up?"

"This is your fault!"

"Why on earth did you send out the wrong result?"

And we need to move towards accountability statements; for example:

"What is the root cause of this problem?"

"What changes can we make to ensure this doesn't happen again?"

"What can we all learn from this incident?"

One final note: empathy sits at the core of a no-blame culture. If we all start practicing and encouraging empathy, we'll more swiftly move in the right direction for increased patient safety, continual improvement, and a happier and more productive team.

The Power of Digital Pathology

How embracing telepathology and digital pathology has strengthened the laboratory

By E. Blair Holladay

When history books reflect on our current time period, what will they see? It's a challenge to pick just one thing. Cultures shifting. New discoveries being made at a rapid pace. A deeper understanding of the impact our past has on our present. Embracing technology to work smarter, not harder. Perhaps most important, they will see that this era is one that is solidly rooted in digital technology. Through our phones, computers, and social media, we are more connected now than ever before.

Historians will look back and see this as the time when digital pathology was embraced, with this revolutionary technology changing the way laboratories operate and significantly impacting patient care.

Digital pathology continues to empower pathologists and laboratory professionals to play a more visible and integral role in patient care, as well as in the broader healthcare team. As new technologies become more widely available, global health becomes local health, and the laboratory must be a leader in these endeavors. We are the experts. We have the knowledge. It is up to us to share and spread knowledge that benefits all patients. One of the greatest advantages of digital pathology is that it allows us to bring the laboratory's expertise to underserved regions, where pathology and laboratory services are often understaffed, and sometimes non-existent.

Almost a decade ago, when we launched our Partners for Cancer Diagnosis and Treatment in Sub-Saharan Africa to provide rapid cancer diagnosis, care, and treatment to underserved populations, we knew that telepathology would revolutionize care for these patients, and what's more, we knew that it was up to us to lead this drastically needed change.

In 2021, a collaborative effort of ASCP, Motic USA, and Memorial Sloane Kettering Cancer Center brought telepathology services to Nigeria, placing medical consultations on difficult cancer cases for millions of patients. We have partnered with Korle-Bu Teaching Hospital in Accra, Ghana, to install digital pathology equipment and train the pathologists at that hospital to use it.

And after a two-year delay because of COVID-19, ASCP brought telepathology to Haiti, and drastically reduced the turnaround time for histology and immunohistochemistry testing.

The power of digital pathology to change and enhance how the laboratory operates is undeniable. It has made our world smaller, but it has made the impact of the laboratory larger and stronger. The enhanced connectivity promotes a stronger multidisciplinary approach to healthcare as pathologists and laboratory professionals solidify their role as integral members of the care team. As this technology continues to evolve, pathologists and laboratory professionals can have a more prominent role in patient care. By embracing digital pathology, we can foster better collaboration, and continue to provide the high-quality care the laboratory is known for.

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The Clinical Benefits and ROI in Digital Pathology Start Here

How a fully digital and cost-effective lab is possible

Change can be painful. For medical laboratories, which are built to avoid any sort of deviation, it can be excruciating. It should not surprise us, then, that pathology's multi-decade flirtation with digital technology has been, so far, disappointingly non-transformative. Despite the hype and the billions invested, few anatomical pathology labs have made the "digital leap." Clearly, getting laboratories to go digital is harder than it seems. Economic circumstances haven't helped the situation, either. Lab managers, already stressed by reduced reimbursements and staff shortages, struggle with the added cost and complexity of digital technologies. In regards to digital transformation, they all seem to be asking the same question: "Where is the return on investment?" Under the circumstances, who can blame them for resisting change?

But what if I told you we found a better way? What if I told you that there is a way to go fully digital, simplify your workflow, all while reducing cost? Yes, it still involves change – lots of it – but if you're not afraid of the "c" word and read with an open mind, I'll share a few insights gained from my lab's journey into the digital realm.

This year marks 10 years since I stepped away from my role as Department Chair in a large health system medical center. Looking back, it was a crazy thing to do, but even though I loved my hospital-based practice, I was becoming increasingly uneasy as I contrasted the pace of tech-driven change outside the hospital, with the resistance to change within. Around that time, my older brother, Mike, analogized my situation to that of a beach-goer, hearing word of a major earthquake hundreds of miles away. He said: "When seismic shifts trigger a tsunami of change, people take one of three paths. Those deeply entrenched in their spot on the beach resist reality and perish in a flood of change. Most beach-goers watch to see what everyone else is doing. Those who pack up their beach chairs and move to high ground soon enough, may survive. Meanwhile, those who recognize the inevitable, and respond appropriately – they are the ones who prosper when the wave changes everything."

I was growing increasingly aware of the different ways that technologies were unleashing violent change in other fields. "Surely, it was only a matter of time," I thought, before the wave would hit us in the hospital laboratory. Tectonic shifts in IT were upending where and how people work. "Big data" and cross-modality analytics were everywhere, rippling into every corner of life. Finally, an explosion of computational power was beginning to enable new applications of machine learning that would clearly rock our world in ways we didn't understand. I realized that these seismic shifts in digital technologies were capable of triggering waves that could fundamentally alter what it means to be a pathologist. Sitting there at my microscope in the hospital, I figured I had a decision to make. My brother's voice rang out in my head: "Three paths: resist change, and you perish… wait for others, and maybe you survive… lead the change and prosper."

By virtue of the fact that I'm writing this story, it's probably not surprising that I chose to embrace the path of change. Thankfully, I haven't been alone on this journey. I convinced my pathologist partner, Jared Szymanski, to join me along the way. Our first foray into digital pathology began like many others' at the time – we went right out and bought a really expensive slide scanner. Since we couldn't convince our hospital administrators to shell out the money for the scanner, Jared and I sold our spouses on the idea that this would one day turn out to be a great investment. However, we quickly learned the same sad lesson so many others have since learned: glass was both faster and cheaper than digital. More disturbingly, we actually liked working with microscopes more than monitors. It was a tough, but important admission, and thankfully, both of our wives forgave us for our foolish investment.

The turning point

As our high-throughput digital-dinosaur sat gathering dust, we asked ourselves why the digital workflow was so inefficient for the lab and what made signing out digitally so unappealing for us as pathologists. Though painful to face those questions, it was a pivotal moment. We realized that a digital pathology workflow only makes sense economically if the entire process, whether patient to bedside, tissue to block, image-acquisition to diagnosis, report-building to ancillary-test-ordering – it all had to be digital pathology. Realizing that digital pathology transformation was more than just scanning and viewing slides on a monitor opened our eyes to the fact that histopathology as we knew it has been an innovation desert for decades. We realized that if we could integrate next-generation tissue handling technologies with digital imaging systems, we could vastly improve quality and efficiency and achieve the digital dream.

We pulled together a small team of engineers, software developers, and histotechnologists to reimagine how we might improve the entire workflow. Together, we designed a process that would eliminate paper requisitions, hand-labeled

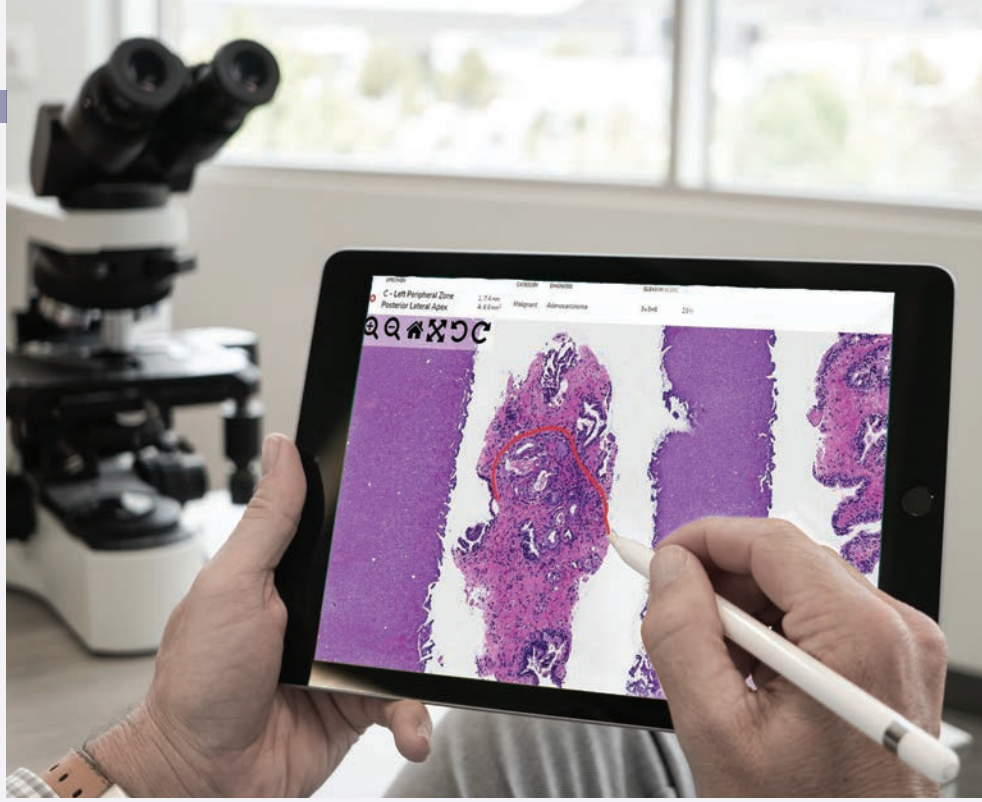
specimen jars, and the various inefficient ways of fishing tissue-flecks from formalin jars. Realizing that we lacked sufficient resources to redesign workflows for all specimen types, we decided to focus our efforts on one specimen type at a time. We started with prostate needle-core biopsies – we chose prostate because these biopsies are generally a pain for labs, and have significant variability in quality.

BxBoard

We started at the patient's bedside aiming to improve the quality of the tissue arriving in the lab, while improving ease of use for the clinic. The BxBoard, a replacement for formalin bottles, is a six-lane tissue transportation device that fixes tissue on a special formalin-soaked sponge. A surgeon or assistant carefully transfers tissue cores directly from the biopsy needle to the BxBoard. The Board's design establishes and maintains tissue orientation (without ink) and enables tissue to fix on an even geometric plane. Clinics love the efficiencies during the biopsy procedure, and labs have universally reported significant increases in tissue on the slide. Preservation of molecular biomarkers also appears to be enhanced as quantity not sufficient rates dramatically fell when compared to formalin jars.

BxChip

Once in the lab, the tissues are transferred from the BxBoard to corresponding lanes in the BxChip. The BxChip is a clinical tissue array holding up to six cores in a tissue-like matrix that processes and cuts just like tissue. The BxChip was invented by members of our Romanian research team led by Sorin Musat. The chip maintains tissue orientation, holds the tissue on an even plane, and significantly reduces slide and block count for labs. Labs who have used this technology have reported a 76 percent decrease in tech time per prostate biopsy, a 136 percent reduction in biohazard waste, an 83 percent reduction in cassettes and glass slides, and an 83 percent reduction in stain costs.



The power of standardizing pre-analytic workflow

But what does this all have to do with digital pathology? By standardizing the way specimens are transported, documented, processed, and embedded, we have been able to translate gains in physical lab efficiency into massive gains in digital workflow efficiency. Combining AI tissue detection with Lumea's artificial tissue fiducial has created massive efficiency gains for pathologists. The algorithms recognize and track each tissue in the different BxChip lanes, which enables the computer to accurately measure and keep track of each specimen. As the pathologist annotates digital slides, the system automatically calculates tumor size and percentage involvement, auto-filling the pathology report in real-time as they review the case. Lumea also partners with many different AI companies, enabling users to pick and choose from a list of vendors if they'd like to use AI for quality control checks or to automate other tasks.

We have seen a 50 percent reduction in diagnostic time per case for the pathologist. Among the many labs adopting the system, we have seen significant increases in biopsy core length, and, most notably, an increase in prostate cancer detection rates. It is rare to find anything that increases quality while improving efficiency. And yet, harmonizing standardized tissue handling with our digital imaging tools has achieved this remarkable improvement in value.

I'm very proud of what our multidisciplinary team has been able to create. Over the last 10 years, these tissue handling technologies have touched hundreds of thousands of patients all around the world. In many labs where digital transformation is not yet ripe for adoption, the tissue handling technologies stand by themselves. However, when the inevitable waves of change push every lab to make the digital leap, those labs that have already adopted these tissue handling tools will be able to seamlessly transition into a digital workflow with an actual return on investment.

It is my hope that other pathologists and labs who adopt these next generation tissue handling systems will not need to question the wisdom of their decision to go digital. Rather, for them, the seismic change brought about by digital technology should be totally evident.

Visit https://lumeadigital.com/request-a-demo/ to request a free demo.

Matthew O. Leavitt is Executive Director at DDx Foundation, Founder of PathNet Labs and Lumea Inc.

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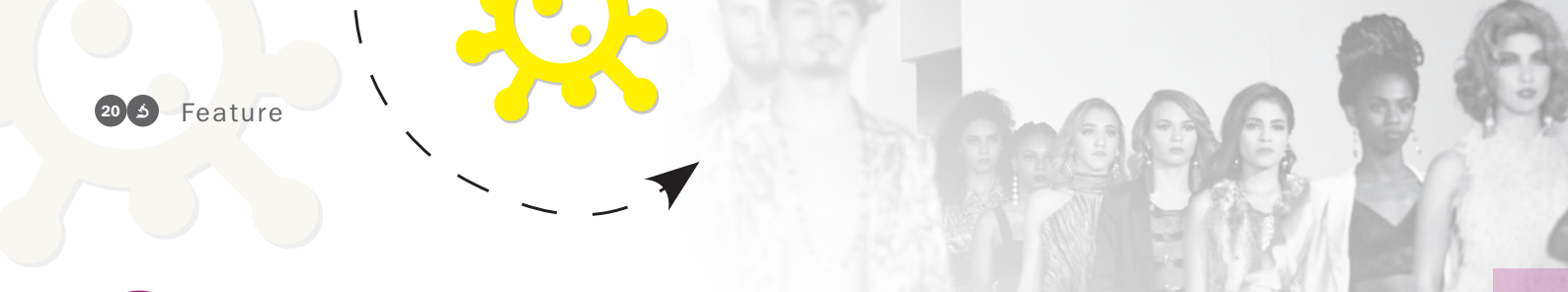
VIRUS in FURS

How fashion-fueled mink farms are the perfect petri dish for a future pandemic

By Georgia Hulme



Going once. Going twice. Gone. The gavel rattled out at the Finnish auction house – Saga Furs – where a fervent atmosphere gripped the room. Palomino, blue iris, and pearl cross – were just a few of the mink colors on offer in the hall, where 220 eager buyers had flocked to battle it out for premium pelts. The nine-day auction that took place in June this year sold 8.2 million euros worth of mink furs and brokerage sales peaked to 111 million euros (1). And while this great sum circulates the Finnish economy, scientists around the world are raising the alarm on the global health implications rooted at the very source of these raw materials: fur farms.

Zoonoses are infectious diseases that can jump from animals to humans. According to the US Centers for Disease Control and Prevention, it is estimated that 75 percent of emerging infectious diseases in humans are zoonotic (2). One only has to look at COVID-19 to see the profound effects of a pandemic of (likely) zoonotic origin. But many others have emerged over just the last few decades. The 2002 SARS outbreak infected over 8000 people and was thought to have emerged from an intermediary animal host – the palm civet (3); virological evidence for MERS-CoV, which was first identified in Saudi Arabia in 2012, suggests it may have started from contact with dromedary camels (4); and fruit bats are thought to be crucial to the spread of Ebola – which has killed over 15,000 since 1976.

Ninety percent of the fur sold to the fashion industry is sourced from animals raised on factory farms, which is sold in auction houses like the one detailed above (5). In 2000, the UK was the first European country to ban fur farming. Many followed by example, including Austria and Norway. More recently, bans have crossed the Atlantic, with California banning fur sales earlier this year. It is unsurprising, then, that the anti-fur movement has gained influence over fashion houses. Popular brands like Chanel, Alexander McQueen, and Gucci have cut ties with all animal pelts, and, in 2018, The British Fashion Council announced that London Fashion Week would no longer showcase animal fur.

However, according to data from 2021, demand remains high (6). Globally, China is the largest producer of mink and also the largest consumer of fur. Other notable producers include the US, which produced 1.4 million pelts in 2021, and Russia, which produced 1.2 million. These countries lack federal regulations compounded with little-to-no state regulations for fur production facilities. And though Kopenhagen Furs – the world's largest auction house for pelts – pledged to wind down their sales in 2020, a quick web search brings up auction dates to as far in the future as August 2024 (7). Not only is the practice of these fur farms deemed "inherently inhumane" by Humane Society International, but tight confinement of stressed mink in unsanitary conditions is a hotbed for potential zoonotic spillover (8).

So, let's turn our heads to the avian influenza threat brewing in mink fur farms. The level of alarm is so great that in July 2023, Thomas Peacock and Wendy Barclay – two leading virologists from Imperial College London's Department of Infectious Disease – published a paper that emphasized the severity of mink farming and its risk to public health (9). We were lucky enough to speak to Peacock, as well as Shely Bryan, fur free campaigner and senior advisor at Humane Society International, to investigate one crucial question. Is mink farming a ticking time bomb for a potential pandemic?

Why mink?

"Farmed mink are susceptible to Aleutian disease, which has zoonotic potential, and they can also contract human and avian influenza A viruses (AIVs)," says Bryan. "This raises concern that they could be 'mixing vessels' for reassortment of circulating influenza viruses. But by far the biggest focus right now is the susceptibility of mink to both SARS-CoV-2 and, most recently, to highly pathogenic avian influenza A (H5N1)."

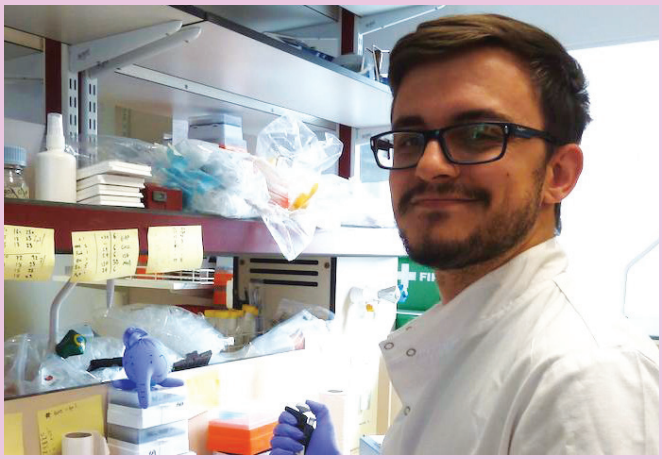
In 1996, H5N1 was first detected at a domestic waterfowl farm in Southern China. Between 2003 and 2005, wild birds spread H5N1 to poultry, who were affected in Africa, Europe, and the Middle East. And now, a new clade – 2.3.4.4b – has spread wider and faster than previous variants, ravaging poultry industries worldwide. In May 2023, the WHO released a statement on H5N1, stating: "Given the widespread circulation in birds and the constantly evolving nature of influenza viruses, WHO stresses the importance of global surveillance to detect virological, epidemiological, and clinical changes associated with circulating influenza viruses which may affect human (or animal) health (10)."

When I spoke with Peacock, I was eager to understand the zoonotic potential of avian influenza, and its risk to public health. "AIVs do not replicate very well in humans – they're restricted in a lot of ways," he tells me. "To infect a human, and for the virus to be passed on – the virus needs to change a number of its properties. There are a lot of factors that stop H5N1

THE EXPERTS

THOMAS PEACOCK

I'm a virologist, and I completed a PhD in virology about 10 years ago. I'm currently based at the Pirbright Institute, which is a big veterinary research institute in the UK. I also work at Imperial College London. These days, my research mostly revolves around avian influenza viruses and animal influenza viruses in general. Over the pandemic, I did quite a lot of work on SARS-CoV-2, as many virologists did. I've recently been involved with some big consortia in the UK that have been looking at the H5 influenza strain. The flu map consortium – led by the Animal and Plant Health Agency – is one that I have been deeply involved in. They do all the UK testing for H5 strains, along with Imperial, Pirbright, and the Roslin Institute in Edinburgh.



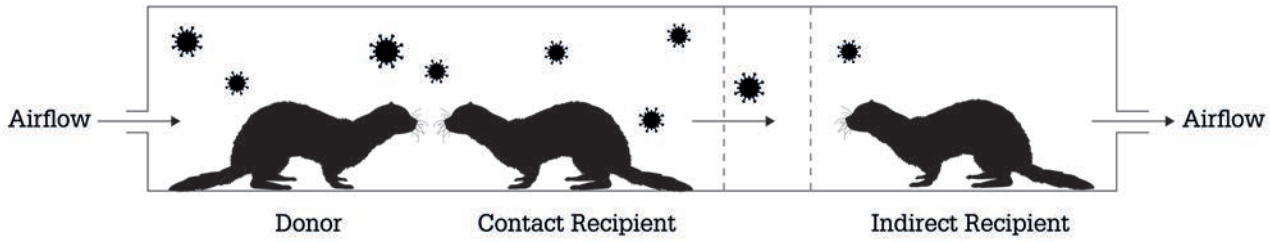
SHELY BRYAN

I've worked in the animal protection movement for three decades, with a particular interest in wild animals. I've also been a specialist on the fur trade for Humane Society International for many years, and I am particularly interested in the economic and public health aspects of the trade.

from infecting humans. But one way that a virus can find a way around this is by adapting to an intermediate species."

This information made me pause. So why is mink farming more of a concern than other forms of animal agriculture? Why are mink so susceptible to viral infections? "It's true that one of the biggest risks to humans in terms of H5N1 is through poultry," Peacock clarifies. "But the biggest difference? Sustained circulation of H5N1 within mink could drive the selection of a virus that could transmit by the airborne route. The virus does not adapt the same way in poultry."

Peacock went on to describe the "ferret model" of viral pathogenesis – the gold standard for understanding influenza airborne transmission. The model uses two cages where two ferrets are separated with a partition that allows airflow exchange – one ferret is infected with the virus, while the other is closely monitored to see if it gets infected. The ferret respiratory tract is widely considered to resemble that of humans. Not only do they share similar lung physiology and sialic acid (SA) receptor distribution, but upper respiratory symptoms of the flu – such as coughing and sneezing – are common in both ferrets and people (11). "Ferrets have some strange genetic quirks," says Peacock. "We think – though we



don't know for sure – that mink also have a respiratory tract that looks a little bit more human than, say, a cat or a dog." Similar to ferrets, the SA receptors SA-α-2,3-Gal and SA-α-2,6-Gal are both found in the respiratory tracts of mink (11).

A study published in 2019 found that mink could be infected by more subtypes of influenza A viruses than swine – a species that have long been considered the primary intermediate host for influenza strains after the emergence of pandemic H1N1 influenza virus in 2009 (12). It was also discovered that mink had the highest diversity, richness, and evenness of influenza subtypes – whereas pigs could only be infected with limited subtypes of IAV, and seemed to be resistant to H5N1. The researchers concluded that mink need to be taken "more seriously in influenza surveillance."

Fur farms

Fur farms are well-known to be cramped, squalid places, where thousands of caged animals are crammed together in low welfare conditions – not dissimilar to the ferret model of pathogenesis. Although these factors alone create an ideal recipe for viral transmission, mink are especially vulnerable to disease – not only because of their biological makeup, but also because wild mink are solitary, highly territorial creatures. They are also semi-aquatic – and their thick pelage and webbed feet allow them to hunt in a range of territories. In fur farms, the ability to express such natural behaviors are denied, which leads to a serious host of health implications, including self-mutilation, fighting, and immunocompromisation.

"In these farms, mink rarely get the opportunity to swim, which only exacerbates their stress," says Peacock. "If they are exposed to the virus, they're less likely to fight it off which will make it easier for the virus to spread to other mink – who are also stressed out. It's a vicious cycle – and just another factor at play here."

Bryan explains further: "Stress-induced hormonal changes, such as increased cortisol being released into the bloodstream, can impair the activity of immune cells like macrophages and neutrophils, which lessens an animal's chance of removing pathogens during the early stages of infection.

"Stress can also compromise the integrity of the gastrointestinal and respiratory mucosal barriers essential for preventing pathogens taking hold, and stress-induced changes in the gut environment can also lead to a weakening of the protective effects of the gut microbiota, making the animals more susceptible to infections and reducing their ability to digest and absorb nutrients properly."

Transmission is also facilitated by the animals' genetic diversity, which is low on farms in which a select few males are continuously sired. The mink are also exposed to a

plethora of viruses, brought in by farmers and contaminated poultry products, which increases the chances of the animals being introduced to human and avian influenza A viruses. In short, a hypothetical route to co-infection is easy to envisage, according to Peacock and Barclay. The potential for mink to act as hosts for genetic reassortment is high, particularly between H5 subtype avian influenza viruses and human-adapted variants.

This concoction of chronically stressful conditions, use of highly predisposed animal species, and poor hygiene greatly increase the likelihood of viral transmission. Fur farms truly are "the perfect petri dish for zoonotic disease," says an exasperated Bryan.

Recent outbreaks

The spread of COVID-19 in mink fur farms has been reported in multiple countries, including The Netherlands, Spain, Italy, and the US. In November 2020, Denmark made the unprecedented decision to cull their entire population of fur farmed mink after a mutated variant of SARS-CoV-2 was detected in the mammals; other measures – including biosecurity – proved inadequate to contain transmission (13).

At the end of 2022, however, the ban in Denmark was lifted. "The industry in Denmark is about one percent the size it was before the pandemic. It turns out that having a ban of two years made farmers move on and farm something else," says Peacock. "I believe fur farming in Denmark is very heavily regulated compared with how it was before."

Bryan agrees. "Overall, fur farming continues to decline globally with numbers of animals bred and killed tumbling across Europe, China, North America, and Russia." But she also makes it clear that – without more information – it is impossible to know if fur farmers have learnt from COVID-19 outbreaks. "We don't know how many countries continue to require regular testing for the virus on fur farms. What is clear is that animals continue to be confined to small cages, in large numbers, in close proximity to one another, and disease outbreaks continue to take place."

> "WE MUST FOCUS ON THE ROOT CAUSES OF ZOONOTIC DISEASE TO STOP VIRUSES BEFORE THEY SPILL OVER TO THE HUMAN POPULATION."

In October 2022, mink at a fur farm in Galia, Spain, were observed to have bloody snouts, tremors, hypersalivation, and a loss of appetite (14). Death of mink increased at an alarming rate. Mortality continued to rise weekly, before plateauing at the end of the month. Confident the culprit was SARS-CoV-2, veterinary professionals collected oropharyngeal swabs from two of the affected mammals. The tests came back negative. Instead, the mink tested positive for H5N1 – the first documented case of highly pathogenic avian influenza H5N1 clade 2.3.4.4b in fur farm mink in Europe. Although none of the farm workers were infected, the speed of transmission pointed towards evidence that H5N1 spread from mink to mink – an uncommon trait of H5N1, which is usually only passed on

Credit: Jo-Anne McArthur / Unsplash.com

Mink kits at a Swedish fur farm cuddle the body of their dead mother.

Photos taken on two fur farms in Finland as part of an investigation into the cruelty of fur farming with TOWIE's Pete Wicks, Humane Society International, and Finnish animal protection organisation Oikeutta Elaimille
Credit: Kristo Muurimaa/Oikeutta Elaimille

Photos from an investigation at a Finnish Fur Farm
Credit: Jay Akbar/Mail Online

Photos from an investigation at a Finnish Fur Farm
Credit: HSI

through infected birds. The researchers who sequenced the samples found the virus polymerase had a mutation, *T271A*, in the *PB2* gene – a major concern for global public health. "In all likelihood, we narrowly escaped a larger disaster, as the incident appears to have been contained," write Peacock and Barclay in their recent paper (9).

But now, it seems history is repeating itself. In July 2023, H5N1 was detected across 20 fur farms across the South and Central Ostrobothnia regions of Finland, where samples confirmed signs of mammal adaptation in the *PB2* genes *T271A* and *E627K* (15). Such mutations allow improved replication in mammalian cells, and may explain the reason for such rapid spread of disease. "I don't know the exact chance – but I think there is certainly a possibility of a H5 pandemic arising from fur farming," says Peacock. "It's an industry that doesn't really serve a huge purpose. It is also a dying industry. If we stop it early, it wouldn't be a bad thing – not only for the poor mink, but also for human pandemic preparedness."

And although Spain and Finland are the first two recorded H5N1 outbreaks in farmed mink, Peacock worries about the countries that have stayed silent on the epidemic. "We've heard very little about the situation in Polish mink farms. If there's H5N1 in Finnish mink farms, I wouldn't be surprised to find it in Polish farms. They are either not being looked at or not being detected. Or they have recognized it's an issue, but have not done anything about it. Currently, H5 is not a notifiable disease on mink farms. So, unlike poultry farms, mink farmers are not obliged to report a H5 outbreak to The World Organization for Animal Health. I hope this will be corrected because it seems absurd that you have to report it on a chicken farm, but you don't have to report it on a mink farm."

Protocols and regulations

Since the COVID-19 outbreaks on fur farms, precautions – such as increased biosecurity and active surveillance – have generally become more stringent. After the H5N1 outbreak in Finland, the Finnish Food Authority put steps into place to improve biosecurity at the farms. Culling sick animals, avoiding interactions with different livestock, and regular cleaning were just some of the protocols introduced (15).

Peacock emphasizes the importance of good biosecurity behavior. "If you're a pathologist working with respiratory aerosols, wearing appropriate PPE and conducting your work in well ventilated areas is key," he tells me. "And if you think samples may have H5N1, you need to make sure that you're conducting appropriate fixation or inactivation protocols."

However, the credibility of current biosecurity measures was questioned when they failed to contain the outbreak of SARS-CoV-2 in Danish mink farms. A study published in 2021 suggested how the very foundation of fur farming makes it hard to maintain a high level of biosecurity; the open-sided housing systems allow contact with wild birds that are potentially infected with avian influenza viruses (16).

Recent outbreaks of H5N1 have forced governing bodies to recognize fur farming as a public health threat. Earlier this year, the US made a decision to vaccinate California condor birds against H5N1 in a bid to contain transmission – but the challenge of unpredictable viral evolution and resistance remains (16). Most recently, the US introduced the Mink: Vectors for Infection Risk in the United States (VIRUS) Act, a bill that vows to ban mink farming in the

US. The bill would phase out the practice over one year and offer a grant program to help farmers transition out of the industry. The UK has also joined in on this anti-mink momentum, and in June this year Conservative MP Giles Watling headed a debate in Westminster Hall about banning the import and sale of fur: "We are importing cruelty, and we are facilitating a trade that could very well be the source of the next pandemic (17)."

The WHO has also lobbied for more asymptomatic and symptomatic testing of those who may have been exposed to H5N1. "The WHO are trying to get a picture of how likely it is that people are going to be infected if they breathe in dust or aerosols that have been contaminated," says Peacock. "So if you're someone who has been exposed to H5N1 – such as veterinary pathologists or people who have been involved in culls – you should get tested, not only for your health but to help us better understand the public health risk of these viruses."

The glaringly obvious solution would be to permanently stop fur farming – worldwide. The uncomfortable reality is that these dangerous and potentially devastating pathogenic breeding grounds exist for one reason: fashion. When more and more brands are choosing synthetic fur alternatives, it is these increasingly few holdovers – the companies so uncompromising to change – that threaten us all. H5N1 has yet to jump from mink to humans, but with disease so rife in these farms, it feels more a question of when than if. Like throwing darts in the dark, with enough tries – and time – you'll eventually hit a bullseye.

"We must focus on the root causes of zoonotic disease to stop viruses before they spill over to the human population. Where we know there are risky practices, we should take urgent action to close them down now," says Bryan.

Peacock and Bryan agree on what needs to be done. Fur farming should be in the same category of high-risk practices as the bushmeat trade and live animal markets. And they strongly urge governments to consider the mounting evidence pointing to the need to eliminate fur farming in the interest of pandemic preparedness.

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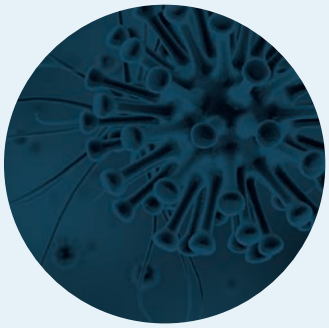


Agilent Technologies

DEMYSTIFYING TUMOR GENOMICS

Diving deep into the hidden depths of tumor genomic profiling with the SureSelect Cancer CGP assay

In the landscape of molecular profiling assays, the SureSelect Cancer CGP (Comprehensive Genomic Profiling) assay stands out as a tool that provides high performance. This state-of-the-art technology – built to unravel the genetic intricacies of solid tumor samples – is helping to unlock new realms of possibility to help advance precision oncology.

The SureSelect Cancer CGP assay possesses capabilities to detect a spectrum of clinically relevant somatic variants, from single nucleotide variants (SNVs) and copy number variations (CNVs) to insertions and deletions (indels), DNA translocations, as well as de novo gene fusions from RNA. It is also capable of diving deeper – setting sights on immuno-oncology biomarkers, such as tumor mutational burden (TMB) and microsatellite instability (MSI).

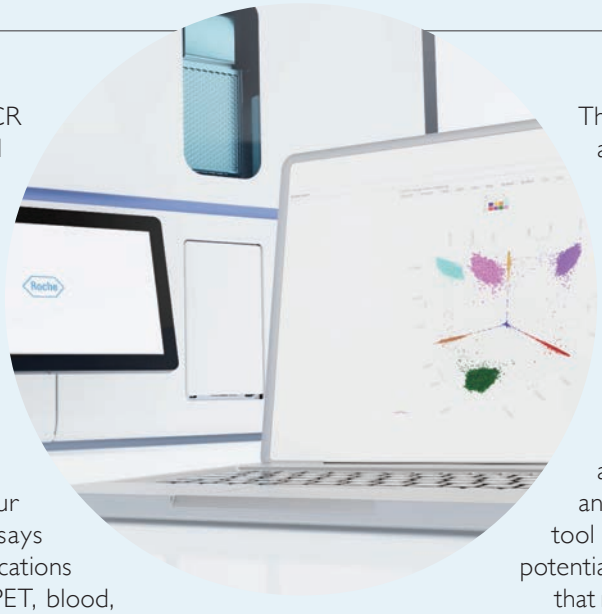
But what distinguishes the SureSelect Cancer CGP assay is its integration of assaying both DNA and RNA from a tumor sample. By allowing simultaneous sequencing of DNA from 679 genes and RNA from 80 genes – all within a single sequencing run – laboratory scientists are able to uncover key classes of somatic alterations at the molecular level.

At the heart of the assay lies SureSelect XT HS2 technology – a hybrid capture library preparation and target enrichment method that prioritizes efficiency and low sample input. The SureSelect Cancer CGP assay's seamless integration with the Agilent Magnis NGS Prep system provides much-needed practicality as well as automation – offering streamlined workflows and as little as 15 minutes of hands-on time. And with the ability to perform enzymatic fragmentation and bead clean-up, cumbersome physical shearing equipment is no longer required, further simplifying the process with automation. The technology takes just nine hours to generate NGS sequencing-ready libraries.

Inspired by the growing need for greater speed in cancer research, Agilent has created a powerful tool that combines efficiency, performance, and flexibility – empowering laboratories across the globe. The SureSelect Cancer CGP assay is for research use only and not for use in diagnostic procedures.

LIGHTING THE WAY FOR RESEARCH

How Roche's Digital LightCycler® dPCR System is illuminating the work of the lab



The Digital LightCycler® dPCR System is a powerful clinical research tool that integrates three clear needs: i) Sensitivity – quantifying more rare molecules (DNA or RNA) per run for each plasma sample. ii) Precision – achieving superior cluster tightness and data clarity that discriminates even small differences between samples. iii) Flexibility – expanding your menu of clinically viable assays across a greater variety of applications and sample types, including FFPET, blood, or plasma.

Advances in motion

Like some other systems, the Digital LightCycler® dPCR System uses nanoreactions and Poisson calculations to provide absolute quantification of target molecules (RNA or DNA). But what really sets the Digital LightCycler® dPCR System apart from the rest, making it a formidable clinical research ally, is the amalgamation of several key technical advancements and impressive features, including:

- Three different partitioning plate configurations with varying nanowell capacities – 20,000 partitions on the high sensitivity plate, 28,000 partitions on the universal plate, and 100,000 partitions on the high resolution plate
- Six separate optical channels and a separate control change, allowing for assay multiplexing
- Five-times concentrated master mixes, facilitating increased sample inclusion per reaction

The nanowell partitioning represents an easy-to-use dPCR setup, ensuring consistent sample partitioning. Meanwhile, the system's high throughput capabilities enable the simultaneous analysis of up to 12 plates, each with eight lanes, allowing the analysis of up to 96 samples to vastly enhance research efficiency.

In fact, the system was born of a deep desire to provide clinicians and researchers with a dependable tool to detect and quantify specific – potentially rare – molecules and variants that may evade other technologies. The impact of such accurate detection is hard to measure, as it could prevent misdiagnosis or missed diagnosis that would directly affect the lives of patients.

Importantly, the Digital LightCycler® can also be used to validate variants revealed by NGS – including investigating minimal residual disease (MRD) – and much more, including CNV analysis.

A light in the dark?

Roche is a renowned market leader in qPCR, with robust reagents and powerful instruments, so the development of advanced dPCR technology is a natural step forward in the company's overarching goal to deliver innovative tools that make a difference. But when members of the development

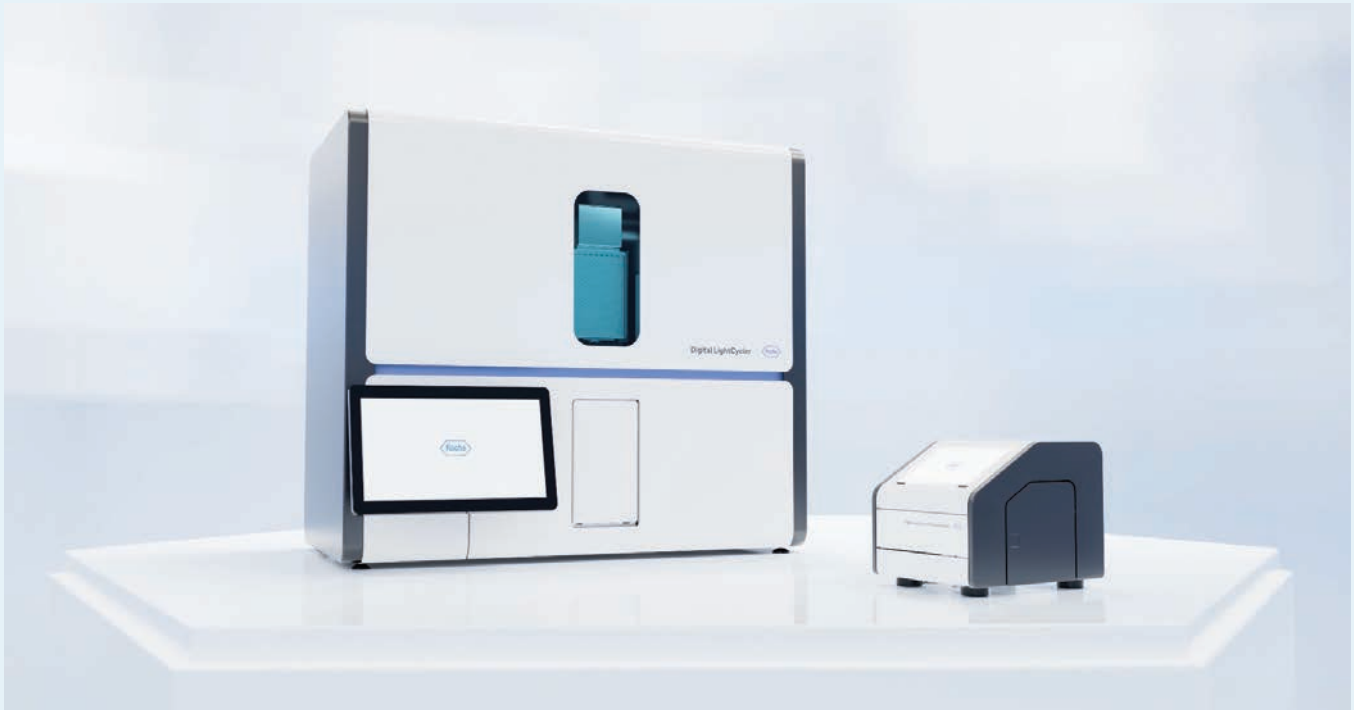
team stood back to review their approach to dPCR technology, they recognized a new milestone in sensitivity, precision, and flexibility – a powerful tool that empowers researchers to uncover rare molecules, detect variants, and ensure accuracy in diagnostics.

By offering a solution that helps overcome clear clinical research roadblocks and enabling clinical researchers to venture beyond the boundaries, Roche and its Digital LightCycler® dPCR System contribute to a deeper understanding of biomarkers, facilitating the discovery of novel therapies. Indeed, Roche's commitment to understanding and then meeting current and future patient needs sits at the core of its latest innovation.

With the Digital LightCycler®, Roche empowers researchers and clinicians to uncover answers that may otherwise lay hidden, ultimately paving the way for a brighter and healthier future.

Important Note: The Digital LightCycler® is a Class II US IVD instrument.

"...what really sets the Digital LightCycler® dPCR System apart from the rest, making it a formidable clinical research ally, is the amalgamation of several key technical advancements and impressive features..."



RANDOX

BALANCING CARE WITH QNOSTICS

How the Qnostics Control range tips the scales to benefit everyone in medicine

With the advent of personalized medicine and increased technological advancement, the demands of today's molecular diagnostic laboratories are high. Laboratory professionals must carefully balance standards, patient safeguarding, and quality of care – all while securing the best health outcomes.

Qnostics provides ballast for this difficult balancing act. With state-of-the-art quality control materials curated for the modern market, their solutions target an extensive range of infectious diseases, including respiratory diseases, transplant associated diseases, gastrointestinal diseases, sexually transmitted infections, central nervous system diseases and blood borne viruses – specifically for application with molecular methods.

Qnostics' controls are highly accessible and provide many benefits for end users working in IVD manufacture, clinical research organizations, and clinical molecular diagnostic laboratories. Importantly, they are whole-pathogen, meaning they contain the full organism genome and mimic the performance of patient samples. Moreover, the controls effectively monitor the performance of the entire testing process, including extraction, amplification, and detection.

Notably, the samples provided are inactivated by irradiation and heat treatment for safe handling, before being liquid frozen to limit sample preparation time and offer stability for two years. Finally, because the controls are truly third party, they can provide independent assessment of assay performance while helping meet ISO 15189:2012 regulatory requirements, which makes them stand out among first party controls.

Benefits in brief:

- Inactivated. Samples are irradiated and heat treated for safe handling.
- Liquid frozen. Convenient and easy to use – simply thaw and run on the analyzer
- Two-year stability.
- Consolidation. Qnostics and Randox offer a full range of molecular controls for infectious disease testing, enabling consolidation to a single supplier.
- Multi-analyte materials. Qnostics provide multi-analyte controls designed for use with multiplex assays, where appropriate.
- Fully traceable. Organisms traceable to WHO standards wherever possible.

Qnostics' Q Control range is designed to monitor molecular assay performance over time and can be applied for ongoing routine monitoring. Molecular Q Panels can be used to monitor the performance of quantitative assays, such as blood borne viruses and transplant related viral infections, across the clinical range. Analytical Q Panels and Evaluation Panels can be used for assay and instrument validation and verification, troubleshooting, and research and development.

Through the power of Qnostics, technicians are empowered to take control of the many variables in the lab – striking a better balance between precision and patient care.

Credit: Shutterstock

Foundation
Molecular Pathology

Interrogating the TME with AI

How standardizing the analysis of tumor microenvironments with artificial intelligence could advance understanding of cancer treatment and expedite drug development

The tumor microenvironment (TME) is the network of cells and extracellular matrix structures that surrounds, infiltrates, and interacts with tumor cells. The TME can include stromal components, such as fibroblasts, endothelial cells, and various immune cell subtypes, as well complex structures, such as fibrosis and/or lymphoid aggregates of varying degrees of maturity among many other elements (see Figure 1; 1). The TME plays a crucial role in promoting tumor growth, invasion, and metastasis by exerting its effects on the dysregulation of both the tumor-induced immune response as well as various cell growth and differentiation factors.

Modern oncologic drug development requires effective measurement methods to interrogate the TME. Such methods should provide a high degree of resolution of biological entities at the level of an individual patient and scale across large patient cohorts – within randomized control settings as well as real world conditions. The measurements should also be standardized with quantitative and reproducible outputs. Importantly, the native state of the tumor (representing the spatial dimension of cells and tissue) should be preserved such that these spatial relationships can be interrogated and related directly to the natural pathophysiology that defines the disease.

For example, a multinational group of researchers led by S Loi demonstrated the prognostic role of stromally-located tumor-infiltrating lymphocytes (TILs) in predicting patient survival following adjuvant chemotherapy (see Figure 2; 2). This and similar examples point to the opportunity for clinical integration of TILs as a biomarker for patients with early-stage cancers.

Current methods and their limitations

For over 100 years, the clinical diagnosis of solid tumors has been defined using H&E stained tissue; however, because of the subjective and labor-intensive nature of human interpretations, H&E based analysis is not scalable, quantitative, or reproducible enough to glean an in-depth understanding and novel insights about the TME. For example, though a pathologist can differentiate a lymphocyte from a tumor cell, they cannot accurately count the amount of lymphocytes or tumor cells, which could be well beyond hundreds of thousands of cells. Equally, they cannot reproducibly identify subtle differences in the maturity gradient of lymphoid aggregates or measure the amount of macrophages within 30 μm of the epi-stromal interface, and so on. Any one of these tasks could be an important biomarker to understand disease pathophysiology and link to other important markers. In short, it has not been possible to fully study the TME using standard manual microscopy-based pathology methods.

Other analytical methods such as proteomics, single cell genomics, and transcriptomics have recently been applied to understanding the TME with great success. However, these methods are costly and often require the disaggregation of the tumor, which prevents the spatial analysis inherent to fully understanding the TME. Methods that preserve spatial dimensions, such as multiplexed tissue-based immunofluorescence or nucleic acid-based spatial transcriptomics, are very powerful but also expensive, time consuming, and not easily scalable across large patient populations; thus, they cannot be applied to most real-world settings. These challenges mean that the generation of population level statistics is difficult, if not impossible. And because manual interpretation of H&E are neither quantitative nor reproducible to the same degree as contemporary "-omics" platforms, it's extremely difficult to apply sophisticated

analytics that can more clearly and routinely define and diagnose diseases.

Unlocking the power of AI

A new era of AI-based analysis is possible by imaging H&E slides and having pathologists manually and exhaustively annotate cells and tissues. These annotations are used as a source of "truth" to train neural networks, which can subsequently be deployed to identify the same aspects of the TME on previously unseen slides. Thus, deep learning models can identify each and every cell and their exact locations on a single H&E slide (see Figure 3).

Once cells and tissue features are accurately predicted, they can be used as a foundation to expand further into entirely novel measurements of pathological features otherwise impossible to calculate by humans. For example, the ratio of lymphocytes to fibroblasts within the area of 30 µm from the tumor boundary could be an important biological manifestation of immune dysregulation of which we were previously unaware (4). We can call this new set of AI-based pathological features as human interpretable features (HIFs) because they are rooted in the foundation of human annotations and thus provide a degree of biological "explainability."

A single slide could then output hundreds or thousands of HIFs in a scalable, reproducible, and standardized manner, lending themselves to analysis for individuals and mass cohorts. Importantly, HIFs can be directly related to genomic or transcriptomic data, providing a link between molecular underpinnings and pathological manifestations of disease. For example, aneuploidy, which can be measured by molecular methods, is universally linked to cancer progression. A collaboration between researchers at the Cleveland Clinic and Path AI has shown that AI-derived nuclear HIFs (for example, variations in the nuclear minor axis length), which would be impossible to measure manually, are a manifestation of aneuploidy that can be further used as a prognostic factor (5).

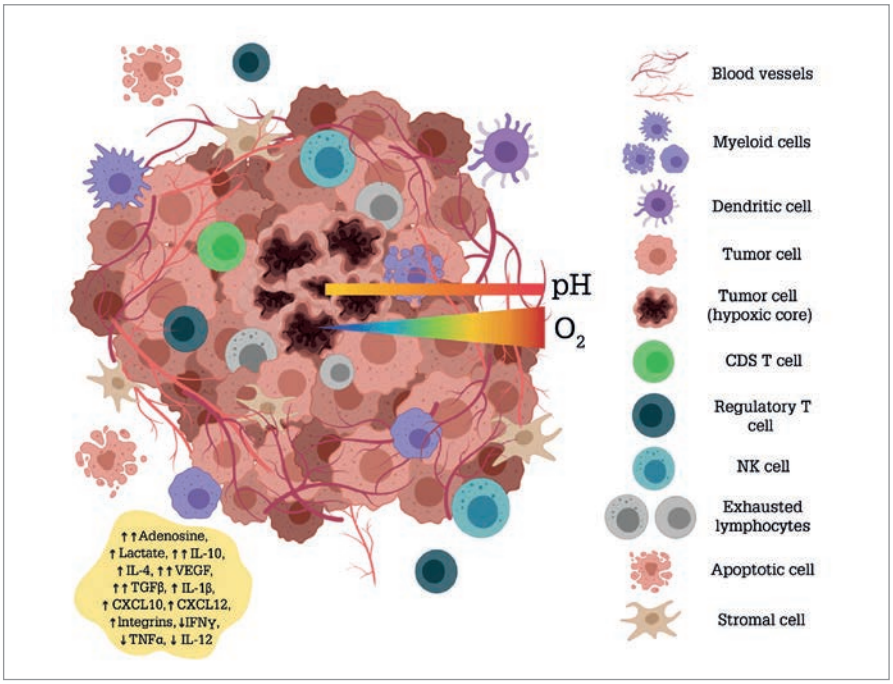


Figure 1. Components of the tumor microenvironment (1).
Credit: Fernández, Julián & Luddy, Kimberly & Harmon, Cathal & O'Farrelly, Cliona. (2019). Hepatic Tumor Microenvironments and Effects on NK Cell Phenotype and Function. International Journal of Molecular Sciences. 20. 4131. 10.3390/ijms20174131.

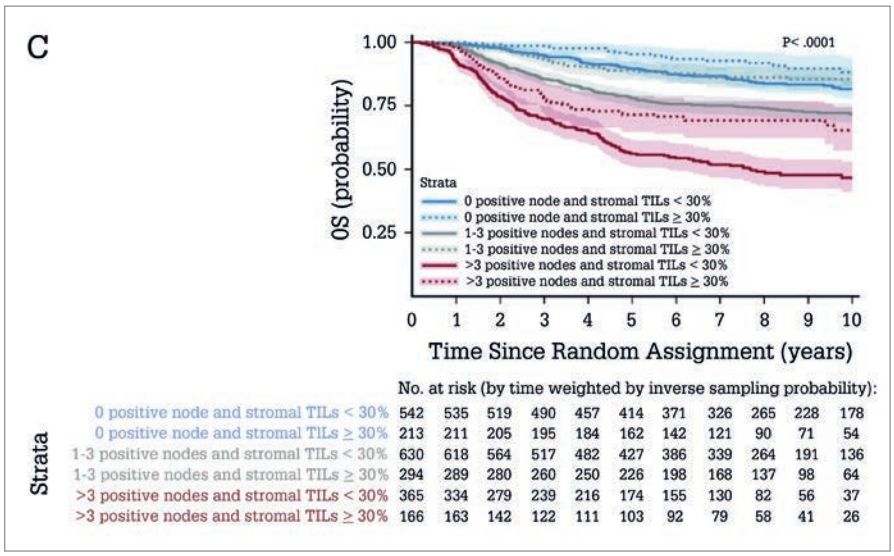


Figure 2. Multivariable survival analysis adjusted for stromal tumor-infiltrating lymphocytes, tumor size, number of positive nodes, histologic grade and treatment using a gamma frailty for study (3). OS represents overall survival.

A new tool for drug development – with potential for clinical use

HIF panels are a new and powerful tool that can augment existing analysis methods of the TME. HIFs can be used to predict the genomic profile of a tumor from H&E as a prescreening measure, allowing for confirmatory testing only for patients with a higher probability of genomic alterations. This approach has the potential to prevent

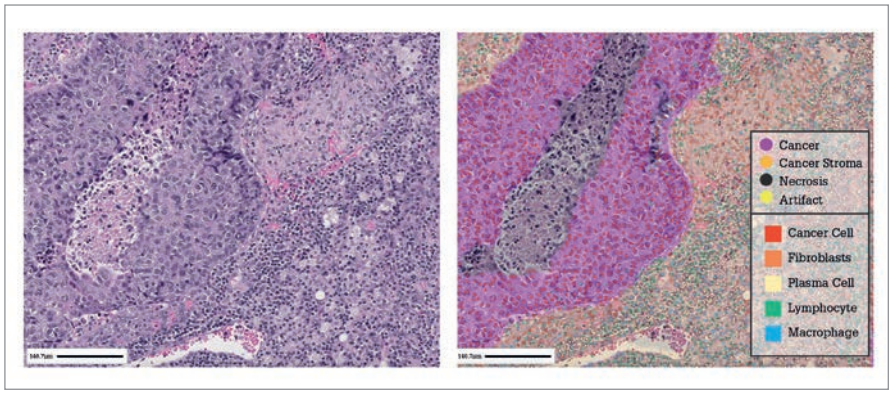


Figure 3. H&E-stained whole slide image of non-small cell lung cancer (left). AI-generated cell and tissue classification heatmaps and overlays on the same whole-slide image (right). (3)

unnecessary testing – making significant savings in the health care system – and more rapidly triage patients into appropriate treatments. In drug development, HIFs can be used to interrogate mechanisms of action or resistance and determine if changes pre- and post-experimental treatment are impacting the TME in a way that is consistent with a drug's hypothesized mechanism of action. With such information, pharmaceutical researchers and manufacturers could make quicker, more informed development decisions; for example, halting a drug development program where proof of concept is not demonstrated in early clinical trials.

The generation of HIFs using modern AI-based methods is a new but important biological measurement. HIFs provide an important degree of biological explainability that can be analyzed within individual patients, as well as across large clinical trials or real-world cohorts. I believe this powerful tool can augment existing analysis methods, offering great potential to unlock novel insights and expedite drug discovery and development.

Mike Montalto is Chief Scientific Officer at PathAI and was formerly the Vice President of Translational Research at Bristol Myers Squibb.

See references online at: tp.txp.to/1023/interrogating-the-tme

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Foundation

Infectious Disease

Flu-niversal Enrollment towards a Phase 1 trial for a universal influenza vaccine has started within the National Institutes of Health's Clinical Center in Bethesda, Maryland. Expected to involve 24 volunteers, the study will immunise the participants with two intramuscular injections, 16 weeks apart. Half of volunteers will be given a lower 60mcg dose, while the later half's vaccination will be 180mcg. After vaccination, the participants will partake in phone call interviews and examinations for 40 weeks. Samples of their blood will also be taken at the time to study immune response to the potentially universal flu vaccine (1).

Hella Klebsiella The pathogen responsible for a plethora of healthcare-associated infections – *Klebsiella pneumoniae* – should be considered as an under-appreciated zoonotic hazard, according to a new paper (2). A mix of new clades, as well as a lack of diagnostic processes, have key implications for the One Health approach. Due to the pathogen's abundance across human, animal, and environmental microbiomes, it is unsurprising to see an increase in its resistance to antibiotics, the authors explain. The paper recommends the adoption of a new approach to surveillance of *Klebsiella*, with particular consideration to how current systems might be upgraded.

Mpox on the mainland In the afterglow of the 2022–2023 mpox outbreak, new research has detailed the first local case of the disease in mainland China caused by an imported case (3). As other research highlights, secondary infection was primarily driven by sexual contact between men who have sex with men (MSM) population – a pattern also shared by the first local case. The specific mpox virus found in the cases cited by the paper were found to belong to the "B.1.3 branch of the West African lineage." The paper concludes that more is needed to combat the global threat of mpox spread.

Reservoir bods Anti-retroviral therapy is an important treatment for those living with HIV, but reemergence of diseased cells once treatment ends makes it problematic. A series of papers have revealed the mechanisms behind reservoirs of HIV-infected cells, specifically that a selection of them produce HIV RNA and proteins spontaneously. Previously believed to be dormant in the body, the studies established reservoir activity in human subjects – and how it may affect patient outcomes. The results of the two papers suggest that the reservoirs "maintain HIV-specific CD4+ and CD8+ T responses during suppressive ART," while preventing "their differentiation into functional cells," respectively (4,5).

See references online at: tp.txp.to/1023/in-other-news

IN OTHER NEWS

A flood of disease.
New analysis of flooding disasters over the last three decades has shown an increase of related infections and deaths in tropical disease and respiratory infections (6).

No more tears.
A genomic surveillance program in Pittsburgh was able to detect Pseudomonas aeruginosa cases linked to commercial tear drops – highlighting the system's potential for future outbreak monitoring (7).

Anti-social.
Analysis of Facebook's efforts to combat vaccine misinformation did not materially reduce engagement with anti-vax content on the platform (8).

Counting crossovers.
A fungus with the potential to cause fatal infections – Aspergillus fumigatu – has been shown to produce a record number of meiotic crossovers (9).

Intentional Infection

A study that infected patients with COVID-19 spurred some controversy, but what did it reveal?

By George Francis Lee

It was in October 2020 – in the throes of the COVID-19 pandemic – that a "first-of-its-kind" UK challenge trial was announced to some fanfare, as well as some furrowed brows (1). Seeking to understand the contagiousness of a suddenly infamous virus, the SARS-CoV-2 human challenge study planned to infect participants with a small dose of the virus. Today, nearly three years later, analyzed data from that trial have been published, offering "fascinating insights into contagiousness and transmission," including the role of so-called "supershedders" (2).

Anika Singanayagam and Jie Zhou – both from Imperial College London and joint first authors on the study – explained more about how the research came to pass and what it can teach us about COVID-19.

First, how did the research come to pass?

Singanayagam: We have had a longstanding interest in respiratory virus transmission. Through work on flu prior to the COVID-19 pandemic, we have been very aware that there are many unknowns about transmission and that transmission is difficult to study. We had already done a lot of prior work on techniques for sampling airborne viruses, mostly influenza, and so understood some of the challenges. At the onset of the pandemic, I was working at the UK Health Security Agency (then Public Health England) – and it was clear it was important to rapidly understand more about contagiousness and transmission because of the public health implications. Such understanding can help inform us on how we best implement non-pharmaceutical interventions, testing, and isolation. The idea of setting up a human challenge study for SARS-CoV-2 during the pandemic was discussed extensively via a consortium of experts in the UK, which included support from the government's Vaccines Task Force. Because of the unique and carefully controlled nature of this study, adding in a study component that involved measuring viral emissions was an ideal opportunity to learn more about contagiousness and transmission.

Zhou: Like Anika, I have been studying the transmission of respiratory viruses for many years. My PhD project was to define the smallest aerosol particles that can facilitate the transmission of influenza virus. This information can help design public health measures, such as physical distancing, use of masks, and ventilation. Since the COVID-19 pandemic, our team has conducted air and environmental sampling in many different settings, such as households, public transport, university campuses, student accommodation, and general hospitals. However, none of these studies were in real-world settings like the SARS-CoV-2 human challenge study, which allowed us to study its transmission in great detail.

In your own words, what did the study set out to do?

Singanayagam: The SARS-CoV2 human challenge study was the first in the world of its kind – healthy, young volunteers were deliberately given a very small dose of SARS-CoV-2 to induce mild infection and then monitored very closely in an inpatient hospital setting. In this type of study, we can perform intensive sampling right from the point that they are infected. This approach delivers information on those crucial, early time points after infection that are difficult to sample in other types of studies. We collected SARS-CoV-2 virus from the air, breath, and environmental surfaces from the study volunteers. The aim was to gain a really detailed understanding about peoples contagiousness – when it occurs, from where, and who is more infectious. We wanted to learn how contagiousness relates to symptoms, to viral load in the upper respiratory tract, and to testing with lateral flow antigen tests.

Zhou: The transmission of respiratory viruses, including SARS-CoV-2, is a complex process. There are multiple non-mutually exclusive modes of transmission, via direct contact, fomites, large aerosol particles (>100μm), and small aerosol particles (<100μm). To fully understand the transmission modes, we used different sampling strategies, such as sampling masks and ambient air sampling machines, to understand the airborne transmission in short and long (>1 meter) distances, respectively. We also swabbed large environmental surfaces to understand how much virus was deposited on them. Small and frequently touched surfaces, such as television remotes and

door handles, and participants' hands were sampled to understand the contribution of direct contact and fomite transmission.

What sort of challenges were involved in deliberately infecting participants with COVID-19?

Singanayagam: There were many challenges. In all stages – planning the study, setting it up, recruiting and screening volunteers – we had to ensure it was carried out in the safest way possible. Fortunately, there was a large group of experts working on the study, with a range of expertise, as well as extensive consultation with a wider group of independent people, such as ethicists and members of the public. Every step of the study had to be carefully considered, including how it would be conducted, how to minimize any risk to people involved – there was a great deal of planning that went into it. Of utmost importance was the safety of participants and ensuring they were well informed about any potential risks and uncertainties. Another challenge was that, due to the emergence of variants, introduction of vaccines, and the increasing scientific knowledge about the disease, the landscape for COVID-19 was rapidly changing.

Zhou: We were very lucky as well. I was directly involved in daily sampling and I can say that all participants were super friendly and cooperative. They participated in the study because they wanted to contribute to the medical effort and see research as a positive way forward through a pandemic.

What were the study's findings?

Singanayagam: We looked in detail at the 18 challenged volunteers who became infected. We found substantial amounts of virus in their emissions into the air and on the surfaces in their rooms. We saw a surprising amount of heterogeneity from person to person. So, despite them being inoculated in the same manner with the exact same virus and dose, the amount of virus they shed into the upper respiratory tract and then emitted was quite strikingly varied. We identified that there were a small number of participants who emitted a large amount of virus into the air. We found that the amount of virus emitted was not influenced by how symptomatic a person was – which is a common assumption about contagiousness that needs further research to understand. We also saw that viral emissions correlated more strongly with the viral load in the nose (more than the throat), which was interesting, as it suggests that more emitted virus was coming out through the nose. We found lots of the virus, including infectious virus, on surfaces, including those likely contaminated by hands and those more likely contaminated from depositing droplets. We saw that lateral flow antigen tests were very effective at picking up when people were contagious and actively emitting the virus into the air and environment.

Was there a particular result that surprised the team?

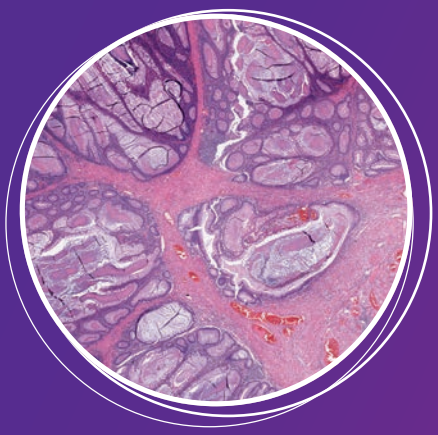
Singanayagam: We were surprised to see that most viral emissions occurred after the participants reported some symptoms. The idea of pre-symptomatic transmission of SARS-CoV-2 has been well described through epidemiological studies. Indeed, in line with this, we did see that around a third of emissions occurred before our participants developed the characteristic symptoms of COVID-19. We also found that using fever as a way of identifying infectious people was not very helpful! However, because the participants in this study were carefully noting even their mild symptoms, we could pinpoint with great accuracy how viral load and emissions correlated with the onset of early symptoms. Our data suggests that if you are aware of those mild early symptoms of a potential infection and take lateral flow antigen tests to confirm, you could capture a large amount of contagiousness.

Zhou: We were able to culture viable instances of SARS-CoV-2 from several environmental surfaces, such as television remotes, door handles, and tables. Previously, very few studies in real-world settings have found live viruses from surfaces, although SARS-CoV-2 has proved to be very stable in experimental settings. Although we cannot directly define onward direct or indirect contact transmission, our findings support the idea that measures such as hand washing and surface cleaning in close indoor settings are very important to reduce transmission risk.

Where could this research lead to in terms of public health planning?

Singanayagam: Because this is a study with a small sample size and highly selected participant group, it is important to interpret the findings in that context. The strengths of the study are that we can look in great detail and sample longitudinally, which gives us power to investigate and understand aspects of infection in a small cohort. The study has given us some really valuable insights into infection, which help us focus public health research to corroborate these findings – which can then guide policy. For example, our data indicate viral emissions could be coming from the nose, suggesting we should reinforce public messaging on covering the nose with face coverings. As mentioned above, the data from our study indicates we should not ignore those mild symptoms, but we should take rapid tests to confirm infection. If other research and cost effectiveness studies corroborate, it may be considered that deployment of lateral flow tests for use in paucisymptomatic illness would be a valuable alternative to asymptomatic screening. Our work also reminds us that viruses can be detected on the hands and surfaces around an infected person. Until we have further data to understand what this means for transmission, we should continue with measures like hand hygiene and surface cleaning, in addition to vital measures to combat airborne transmission.

See references online at:
tp.txp.to/1023/intentional-infection



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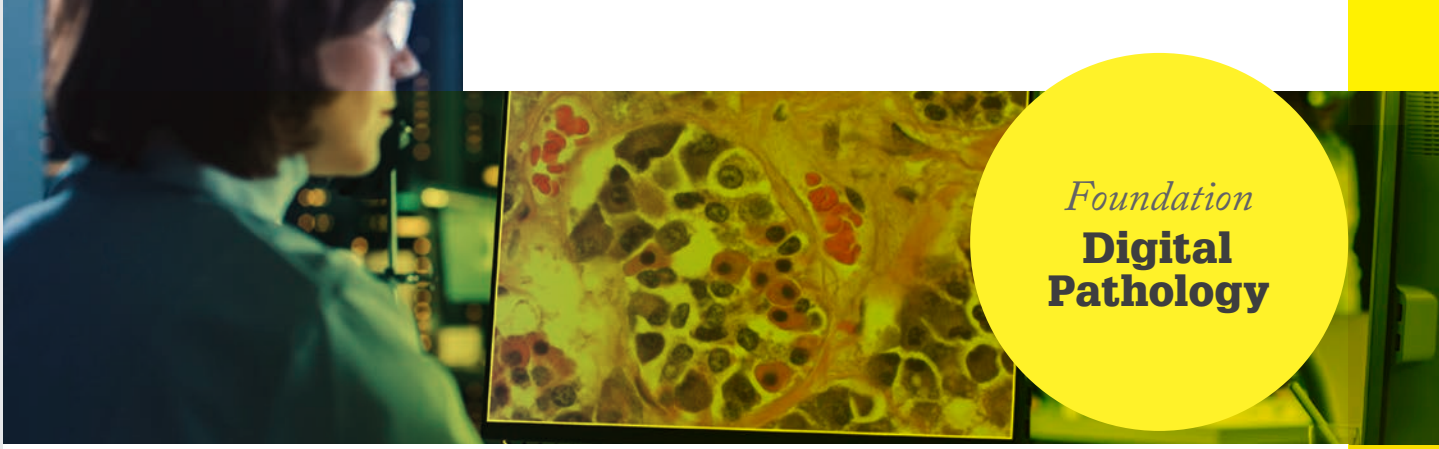


Credit: Shutterstock

Foundation
Digital Pathology

Flight Path

If we work together, we can stop all diagnoses falling under the radar

By Joseph Mossel

Between the years 2000 and 2010 – if you exclude September 11, 2001 – there were 250 airline fatalities in the US (1). And between 2010 and 2020 – there were only two (1). Evidently, the airline industry realized airline fatalities were unacceptable – and so damaging to the industry that relevant technology was needed to curb mortality. Interestingly, airline industries don't compete against each other. Safety is taken as a given.

Why is it considered acceptable that there are misdiagnoses in our industry? Everyone knows that it happens – and tolerates it. Consider this: the airline industry didn't set themselves a goal to reduce fatalities; they said zero fatalities. And I think the same kind of goal should be set for cancer diagnosis. With AI, we can reach zero diagnostic error. We have the technology, but that is not enough – we also need adoption within clinical practice. It will require an industry wide effort to achieve this goal.

We have direct access to misdiagnosis data because we deploy our algorithms in pathology labs where they're used on a day-to-day basis. The normal range of misdiagnosis ranges between two to three percent at excellent labs – but it can go as high as 10 percent (especially in labs that lack subspecialists). If your cancer is misdiagnosed, it's very likely to progress further and become more severe. The treatment is going to be more aggressive, mortality goes up, and the cost of the healthcare system also rises. We also need to understand that this is happening because of technological and resource limitations. It's not possible for pathology labs to have three pathologists investigating every case.

Our AI algorithms are trained by pathologists, for pathologists – and there are two ways you can deploy them in the lab. First, as a pathologists' assistant. The algorithm can act as a virtual fellow, where it can review the case in advance and fill out a draft of the report. This way, the chances of a pathologist missing anything is reduced. The algorithms are very objective and can conduct day-to-day tasks, such as measurements and quantifications without getting tired. Second, the algorithms can be used in places where it wouldn't be economical to have an actual human pathologist review the case. So, you can do triage of cases earlier on and make sure that the more urgent cases reach the top of the pile. You can preorder IHC staining to reduce turnaround time. In general, you can plug in the technology at different decision points in the slide preparation phase to make the process more efficient.

Our algorithms help reduce diagnostic error because they're extremely accurate – trained on huge datasets. Not only can they accurately detect cancer, but also help differentiate between different cancer subtypes. For example, the technology can tell the difference between invasive lobular carcinoma and invasive ductal carcinoma – or between high and low grade ductal carcinoma in situ. The algorithm can also help detect non-cancerous features, such as microcalcifications, breast biopsies, and perineural invasion. But perhaps the most exciting thing about these algorithms is the way they contribute to health equity; I can see the technology being deployed as part of standard practice in every pathology lab worldwide.

For this technology to actually become prevalent, it's critical that physicians and pathologists recognize the value and actively want to use it. Whenever we let pathologists play around with a new technology, they are almost always eager to deploy it in their labs. Regardless, there are still barriers. First of all, we need to acknowledge the importance of regulatory frameworks – and recognize that AI introduces new challenges for regulatory science. Agencies, the industry, and physicians need to work together to accelerate the deployment of this technology; we owe it to patients. The other piece of the puzzle is the economic model. How do we pay for this technology? Again, we need to have a big conversation with all stakeholders.

We need to see misdiagnosis as something that went terribly wrong – because we can prevent it from happening. Though I don't think it's something that is achievable overnight, within a decade I believe we can transform cancer diagnostics to achieve much higher levels of accuracy.

Joseph Mossel, Co-Founder and CEO of Ibex Medical Analytics, Tel Aviv, Israel.

See references online at: tp.txp.to/1023/flight-path

AI Driven Spatial Pathology: The Next NGS

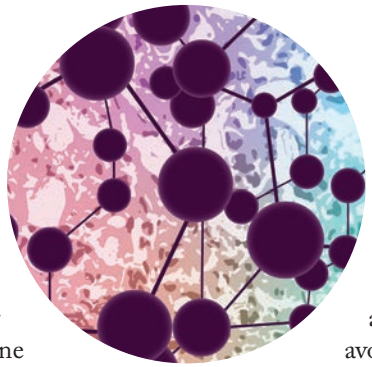
Emerging platforms are overcoming the limitations of next generation sequencing technologies

By Kenneth J Bloom

Prior to targeted therapies, the main customer of the pathologist was the surgeon. Surgery was the lynchpin of cancer therapy along with radiation and conventional chemotherapy. The pathologist's attention was focused on detailed assessment of tumor characteristics, such as tumor grade and differentiation, the completeness of surgical resection, the presence of lymphatic and/or vascular invasion and lymph node involvement. The benefits from targeted therapy changed that. Today, pathologists are asked to provide detailed information on a variety of biomarkers that are used to select the best therapy for patients.

The incorrect assessment of a biomarker can result in a patient receiving ineffective therapy. In this new world, the oncologist is now the main customer of the pathologist – and the details of the pathology report matter more than ever. This approach places new and greater responsibility on pathologists, and they have responded by developing and implementing new guidelines, technologies and proficiency tests to ensure accurate and reproducible biomarker results.

One new weapon in precision oncology is immunotherapy, which has resulted in durable responses and even complete remissions in a subset of patients. A variety of biomarkers have been developed to aid in the identification of patients most likely to respond to a common type of immunotherapy called checkpoint inhibition. These include *PD-L1* expression, tumor mutational burden, gene expression profiling, and tumor infiltrating lymphocytes. Unfortunately, even with these tests, it is difficult to reliably predict which patients will benefit from therapy.



Cancers are the result of an accumulation of genetic alterations that produce aberrant proteins, some of which are recognized as abnormal by a person's immune system. These are known as neoantigens. As neoantigens are released by the tumor, they are captured by dendritic cells for processing. Dendritic cells present the captured antigens to T cells in the lymph node, resulting in activation of CD8+ cytotoxic T cells and CD4+ helper cells. This process primes T cells to recognize and target cancer cells expressing these neoantigens. Activated T cells leave the lymph node and travel through the bloodstream to the tumor microenvironment where they infiltrate the tumor. Once there, activated T cells identify and bind to cancer cells that present the specific neoantigen they are primed against. Finally, CD8+ T cells release cytotoxic molecules resulting in cancer cell death.

Unfortunately, cancers employ multiple strategies to evade immune surveillance. These include the ability of cancer cells to downregulate antigen presentation, create an immunosuppressive microenvironment, and produce immunosuppressive factors. Additionally, prolonged exposure to neoantigens can result in the progressive loss of effector T cell function, known as T cell exhaustion.

Just as NGS interrogates the many potential molecular alterations that serve as biomarkers for targeted therapy, new technologies are needed to identify better biomarkers that allow the selection of patients who will benefit from immunotherapy. But cancers seem "smart," using every mechanism at their disposal to avoid immunosurveillance and thrive. To personalize immunotherapy, new spatial tools must identify the different types, states, amounts, and location of cells that make up the tumor and its microenvironment. Spatial biology tools are now being commonly employed in research, but they are slow, expensive, and require specialized equipment, which limits their adoption, especially for clinical use.

But spatial pathology platforms combined with deep learning algorithms, are now emerging to overcome these limitations. To do this, two main types of deep learning models are used. The first model takes a whole slide image as an input and uses various neural networks to predict tumor features, such as gene signatures, genomic abnormalities, and instability. The second model uses deep learning to classify the components of whole slide images into regions, like tumor and stroma, and then segment and classify every individual cell on the slide.

Deep learning models have traditionally been trained using pathologist's annotations but pathologists are limited in their ability to reliably classify cells. Next generation cell classification methods will use multiplexed immunofluorescence or transcriptomic profiling to train classifiers capable of reliably predicting cell types and cell states from H&E slides.

Immunotherapy and other emerging therapies, such as antibody-drug conjugates, could transform oncology care and improve patient outcomes – but only if we can identify biomarkers that can reliably select patients who derive benefit. Thankfully, advancements in digital pathology, high plex profiling, and deep learning have arrived.

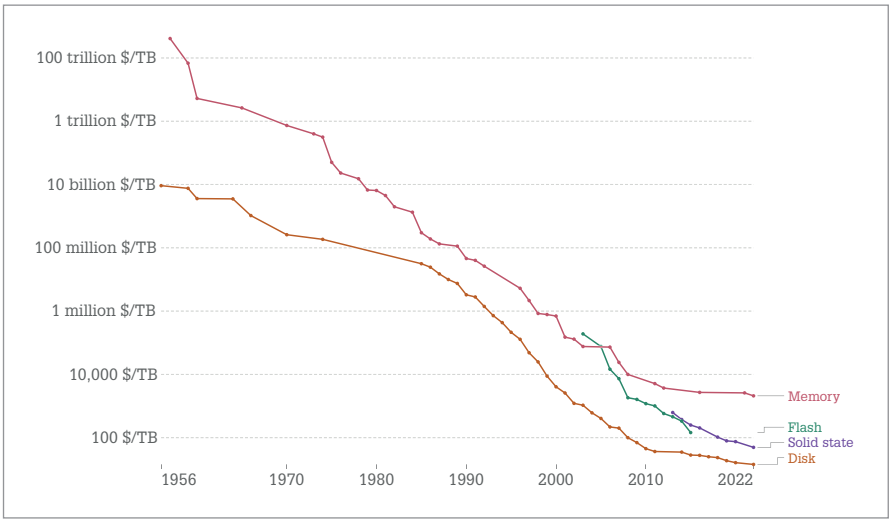
Kenneth J Bloom, MD, FCAP, Head of Pathology at Nucleai

Paving the Road with Existing Tech

The transition to digital pathology doesn't need to be a bumpy ride

By Asa Rubin

We don't need to hope that future technologies will solve all our problems, existing tech can already pave the way. Read how in part five of our "Barriers to Adopting Digital Pathology" series.



Historical cost of computer memory and storage
This data is expressed in US dollars per terabyte (TB). It is not adjusted for inflation.
For each year, the time series shows the cheapest historical price recorded until that year.
Credit: John C. McCallum (2022) | OurWorldInData.org/technological-change • CC BY

Pathologists are not known for being a technologically savvy bunch, which can make the road to digital pathology a rocky one. Many assume that digital pathology simply means getting a scanner, throwing in slides, and looking at them on a screen – only to discover there are a number of other questions that need to be considered. Where will images be stored? How can they be accessed quickly without crashing the system? How are they to be moved to the appropriate locations within the network?

These questions speak to the need for a robust infrastructure, but also create another impediment for departments wanting to convert to digital pathology. Beyond additional cost, they introduce numerous layers of novelty and complexity that could, to an ordinary pathologist, seemingly require equally novel and complex solutions.

It might surprise pathologists to learn that the majority of the components of a digital pathology infrastructure could be borrowed from pre-existing, common technologies. Take the storing of digital slides, for example. Most whole-slide images are between two and four gigabytes, akin to a full-length feature film in HD. Assuming 1,000 slides produced daily, that translates to an average of 3,000 gigabytes, or three terabytes, of new data each day. Over a year, this approaches a petabyte (1,000 terabytes) of data. It sounds gargantuan, but consider the graph below.

Two things become evident: the first is that the cost of data storage has been consistently falling since the fifties. The second, perhaps more important point, is that something drove this decrease in price – namely, demand. Commercial businesses, research labs, and internet sites, to name a few, all depend on mass data storage to function. This demand has not only led to better and cheaper hard drives but has spurred a revolution in data storage availability via cloud-based services. For digital pathology, the upshot is that, unlike slide scanners, which truly have had to be developed from scratch, data storage is a tried and tested technology easily converted to storing digital slides.

Another illustrative example is the methods that allow for fast viewing of whole-slide images. If a digital pathology department has even 10 pathologists working simultaneously, it could translate to a crushing amount of data running concurrently over a network. However, techniques such as "progressive" and "lazy" loading have been developed to load images only partially at any one time, making the data transfer demand significantly smaller. These techniques are widely used, with the quintessential example being Google Maps – a whole-slide image in its own right – that holds approximately 20 petabytes of data and is used simultaneously by millions.

Digital pathology infrastructure has to address numerous additional factors, including cybersecurity, computational power, and interfacing with the lab management system. But the two preceding examples demonstrate that well-established technologies already exist to solve most of these problems. Armed with this knowledge, pathologists will hopefully begin to see infrastructure not as a roadblock to going digital, but rather an opportunity to custom-build a system uniquely designed for their specific needs.

Asa Rubin is Medical Director at Pramana, Cambridge, Massachusetts, USA.

Profession

Your career
Your business
Your life

Peer-to-Peer, Featuring Aleš Ryška

Ivan Damjanov interviews Aleš Ryška about his career and experiences as President of the European Society of Pathology

Ivan Damjanov interviews Aleš Ryška

Credit: Aleš Ryška

Tell us a bit about the ESP…

Exactly 60 years ago, the ESP was founded as a professional society to represent pathologists throughout Europe. The founders established the group in Belgium, which is unsurprising considering they all heralded from Western Europe. We must take into account that the ESP was founded in a time of political division – and it was virtually unthinkable for pathologists from Central and Eastern Europe to participate in professional life within a society based in a "capitalist Europe." Since then, major developments have occurred – especially in the late 1980s and the millennium. Today, the ESP has more than 3500 members from 90 countries.

97 percent of our members are pathologists and three percent are allied health care professionals, such as molecular biologists and oncologists. Considering the multidisciplinary nature of modern pathology and the multilateral collaboration of pathologists with different clinical disciplines, I see a clear space for additional growth.

In 2019, our ESP strategy meeting set out a number of goals to achieve over the next 10 years. We emphasized the importance of developing the ESP, including both face-to-face and online education. We also prioritized the support of research development and set out to improve the quality of our journal, Virchows Archiv. It is difficult to describe the entire spectrum of ESP activities, but our general vision is: "Excellence in pathology for optimal patient care." We can summarize our agenda in three points:

1. High quality pathology diagnosis for all patients
2. Up-to-date education across Europe
3. Support cutting-edge research to understand diseases and translate science into clinical practice

When did it occur to you that you could become President of ESP? Was it a difficult process?

The ESP has a well-established mechanism for nominating new candidates for the presidency. A selection committee composed of all past presidents will usually first approach potential candidates. These candidates are then discussed within the ESP council and the final nominee is elected by the general assembly. When I was approached by Dina Tiniakos – who was the president in 2018 – I needed time to think through my decision. At that time, I was serving the society as the Chair of the Education Subcommittee and thought I had a clear idea of the presidential functions. In hindsight, the amount of activity that is outwardly visible is only a fraction of what the job entails. However, I have never regretted my decision to accept the nomination.

Did you propose a plan once you were President? What were your priorities?

The term of office for President is two years, which does not provide much room for revolutionary changes. Instead, we focus on fulfilling a long-term strategy that was set in action a decade before. Only history will judge the extent to which I have been successful. I think we have made considerable progress innovating our educational

activities. We have changed the concept of the long-established European School of Pathology course system; we have finally managed to make our educational portal functional; we have witnessed significant increase in interest for the annual Pathology Progress Test; and the first ever ESP masterclass was held at the end of last year. Our Giordano Fellowships – with several bursaries that financially support young pathologists who stay at ESP Advanced Training Centres throughout Europe – have been a huge success.

What did you learn from your time as President? Do you have any advice for your successor?

During my tenure, I have learned how important it is to have a well functioning team. I do not hold a graduate degree in management, so I had a lot to learn. I mastered how to delegate and coordinate several projects simultaneously relatively quickly, and I consider that as my greatest personal achievement during these two years of my presidency. My successor will be Peter Schirmacher, who is the director of a large university department in Heidelberg. With his qualifications and experience, I doubt that he will need my advice, although I am ready to assist if asked.

What is the future of pathology in Europe? And what about current needs?

Europe is an extremely heterogeneous continent comprising quite a number of rich and relatively poor countries. With English as the *lingua franca*, it is relatively easy for pathologists to communicate among themselves and also move from one country to another. Increased mobility of pathologists that currently exists in Europe has many advantages but also causes brain drainage as pathologists from poorer countries move to the more lucrative positions in the West. The reimbursement for pathology services varies considerably from one country to another and that contributes to inequality among the European countries. Furthermore, many modern techniques such as those of molecular biology are not available in poorer regions. The ESP is trying to level out these differences and we are helping pathologists globally – particularly in economically weaker regions – to obtain these expensive tests. Another important role of the ESP is the organization of external quality assurance programs in Europe. The ESP is the founding member of the umbrella organization called International Quality Network Pathology (IQNPath), which helps us coordinate the organization of European Quality Assurance (EQA) in pathology.

Opening ceremony of the ECP2023 in Basel. Discussion on stage with the chair of the Local Organizing Committee prof. Gieri Cathomas.

President's report during the ESP General Assembly. As can be seen, despite the serious matters discussed, the atmosphere can be quite relaxed.

Now, let's look at your career in more detail… How did your career in pathology start? Why did you choose to study in Hradec Králové? Wasn't the "real action" at that time in Prague, the capital of the Czech Republic?

My path to pathology was not a straightforward one – I became a pathologist by coincidence. During my senior medical school days, my pathology teacher asked me to help him out with fine needle aspiration cytology specimens. I accepted his invitation and thus FNA became my first practical encounter with diagnostic pathology. Gradually, I delved with ins and outs of real-world pathology, which I found very interesting. I was thereafter offered


Credit: Aleš Ryška

Regular meetings at the 16-head microscope are used both to discuss some challenging cases and to teach residents. The most challenging part of installing this instrument was designing a table shaped so that everyone could sit comfortably.

a residency in the pathology department. I stayed at the same workplace where I studied, which is also the answer to why I ended up in Hradec Králové – a city with only 100,000 inhabitants. Nevertheless, our University hospital contains 1,500 beds and is one of the largest medical facilities in the country. Also, our Institute of pathology is of comparable size as other institutes in Prague. The journey from Hradec Králové to Prague only takes one hour by car, so it is not surprising that we participate in several projects with other pathology institutes in Prague. Since we are centrally located we constantly interact with other pathology departments in the Czech Republic. We also participate in several national research projects involving other Czech pathology institutes.

Which aspects of pathology attracted you the most? Who are your role models?

In the old days, we visited clinical wards and performed fine needle aspirations (FNAs). This contact with clinical medicine was the reason why I never saw pathology as a purely laboratory discipline. Nowadays, we no do not perform FNA on the wards since we do not have enough staff to do it. Our pathologists participate in multidisciplinary team meetings and are seen as key players in the management of patients especially those suffering from cancer. During my pathology career, I have been very fortunate to have had several outstanding mentors – from Zoltan Kerekes, who actually lured me to pathology, to my former mentor Ivo Steiner – a true British gentleman. Major European pathologists such as Manuel Sobrinho-Simoes and Fatima Carneiro of Porto, Portugal have also been great inspiration and introduced me to the challenges of international pathology.

How important was subspecialty training for you? Do you encourage your junior colleagues to choose a subspecialty? Do you believe that one could still remain a general pathologist in your country?

This is a very interesting question. As far as the standard diagnostic service is concerned, I believe that a pathologist in a department of our type should be able to interpret lesions from several if not all organ systems. However, the situation is completely different when it comes to expert analysis or research. Here, sub-specialization is necessary. When I became chairman of our institute, the consultants all specialized only in one particular field, which had its advantages in terms of high expertise, but, in their absence, it caused considerable problems.

Now, each of us specialize in two specific areas, not only diagnostically, but also in terms of research. By covering several areas (for example, I am involved in the diagnosis of breast and thyroid tumors), there is an overlap and redundancy in the event of absence. In the case of controversial or diagnostically difficult lesions, we always have the option of consulting someone who specializes in that area. This system also creates greater flexibility; for example, if someone decides to change their workplace, the narrow sub-specialization is not a limiting factor.

How many pathologists work in your department? Do you have problems in recruiting young people into pathology?

Currently, there are a total of 14 consultants working in our department. Our team is relatively young; at 52 years of age, I am the second oldest consultant in my Institute. We have four residents at various stages of their specialty

training. When recruiting, we try to rely on graduates who have volunteered for research activities during their undergraduate studies. This approach has proven extremely effective.

How do you organize common tasks required from your department by the hospital or the dean and other leaders of the medical school? In the medical school curriculum, does teaching pathology weigh as much as it used to 50 years ago?

Covering routine diagnostics, teaching, and research remains a major challenge. Our medical school has four parallel undergraduate programs that include pathology. Namely, we teach pathology to regular students of medicine and dentistry, as well to those who take these courses in English. This means that every day there are six, sometimes nine, hours of practical classes, plus three to six hours of lectures. Such a large teaching load requires active involvement of the entire staff and that includes everyone in the department – from the residents to the head of the institute. Students are required to take two semesters of pathology, culminating in a final oral examination. We use this method of testing to ensure that our students truly understand pathology, and did not not just memorize facts from the lectures and textbooks to pass the final exam.

Routine diagnostic services consume a lot of our time since we must take care of a huge number of cases arriving from the clinical departments. For the teaching we use a syllabus which is handed out at the beginning of the school year and accordingly these two activities of the department are well planned ahead of time. The research is less programmed but it also takes considerable time. Too many medical students and young doctors all these responsibilities seem often to be overwhelming and many of them choose, what they perceive to be, an easier life. The numbers of young physicians interested in full time daily diagnostic service and research seem to be waning. Unfortunately, this trend has been apparently noticed in many other countries and is not unique to the Czech Republic. The focus of our students on a more manageable work-life balance is a reality we must respect, but let us hope that some of them will still join our ranks.

Has your career in pathology been a satisfying experience? What are you most proud of?

I have never regretted – not even for a single moment – my decision to pursue pathology as a career. For me, pathology is the only medical discipline able to integrate basic medical sciences, morphology and pathophysiology and understanding of disease, with cutting-edge research while also contributing significantly to patient care. Pathology is an evidence-based specialty and it relies heavily on facts despite certain subjectivity included in the microscopic evaluation of slides in our daily practice. For me, this aspect of pathology exemplifies the saying that medicine is, at the same time, a science and also an "art."

My greatest professional joy stems from the fact that I was given the opportunity to lead one of the most modern institutes of pathology in my own country. Heading a team that provides state-of-the-art diagnostic services to our patients and at the same time is recognized by our peers as a major referral center serving as a national consultation center has been a major goal that my collaborators and I have jointly achieved. Finally we are given credit for participating in the training of hundreds of medical students every year and teaching them pathology "as the basis of their future clinical practice" in Czech or the English language. And finally, with all these daily duties we have found the time and motivation to conduct research to the best of our potential and financial conditions. I still have a couple of years of active life in front of me and all these activities can be maintained for some time. I will retire (in a few years) with the feeling that I have not wasted my time as chairman.

Serving ESP as president has been a great honor and a privilege for which I would like to thank all my colleagues who have voted for me. I will be leaving my position at the ESP in September 2023 – shortly after the European Congress in Dublin. Although being President is extremely interesting and gratifying, I am looking forward to handing over the imaginary presidential torch to my successor, with my best wishes for an exciting period of life that is opening for him.

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

In Practice

Technologies and techniques
Quality and compliance
Workflow

Chemical Sourcing, Streamlined

Navigating the challenges of sourcing chemicals in the lab

By Dave Haase

In the day-to-day operation of a laboratory, the sourcing of chemicals plays an integral role. Chemicals form the backbone of tests, experiments, and procedures. Moreover, the quality, availability, and timely procurement of these substances can significantly impact laboratory outcomes. The process of chemical sourcing is riddled with complexities, including regulatory compliance, logistics, and their impact on laboratory work.

Understanding the challenges

Pathology labs face an uphill climb as they navigate through the twists and turns of sourcing chemicals. They must grapple with complex laws and stringent guidelines, while also ensuring efficient inventory management and reliable logistics.

1. Regulatory compliance

For laboratory operations, regulatory compliance is a pervasive challenge. Navigating the regulations that govern the sourcing, handling, storage, and disposal of chemicals can be a daunting task.

Various regulatory bodies enforce rules that, while essential for safety and environmental protection, can be complex and multifaceted. These regulations vary locally and internationally, adding another layer of complexity. Non-compliance can result in severe penalties including heavy fines, reputational damage, and cessation of operations.

2. Logistical issues

Logistical challenges are the next major hurdle in lab chemical sourcing. Inventory management is a fine balancing act. Labs must constantly strive for a balance between overstocking, which can lead to wastage and increased storage costs, and understocking, which can disrupt the flow of laboratory procedures due to the unavailability of necessary chemicals.

The process of moving chemicals from the source to the laboratory, and then storing them correctly, comes with its own set of problems:

- Delays in delivery can halt progress on critical projects, leading to missed deadlines and financial losses.
- Unstable storage conditions can degrade the quality of certain chemicals, thereby affecting the accuracy of lab procedures.
- Specialized storage and transport facilities that ensure the safety and stability of chemicals often come with a high price tag, leading to increased operational costs.
- Certain chemicals, particularly rare or restricted ones, can be challenging to source, and this can limit the scope of research and diagnostic work in the laboratory.

The importance of timely and safe delivery of chemicals cannot be overstated: it is a critical factor of lab operations that can determine the success of sensitive diagnostics and research.

3. The impact on laboratory work

Challenges in chemical sourcing can significantly impact the efficiency, cost-effectiveness, and quality of laboratory work. As noted, delays in the delivery of chemicals can halt research and diagnostic procedures, leading to a ripple effect of missed deadlines and inefficiencies. The cost of sourcing, particularly when dealing with regulatory compliance, storage, and transportation, can substantially add to the lab's operational costs.

Quality and safety are cornerstones of laboratory work. If the chemicals sourced are of inferior quality due to improper handling or storage, it can compromise the safety of lab personnel and the quality of lab procedures.

What may appear to be minor hurdles can collectively result in a significant decline in lab productivity and efficiency. Pathology labs might find themselves spending more time, resources, and energy on managing challenges than focusing on the core tasks of research and diagnostics.

The role of technology

Technology has a vital role to play in solving some of the most pressing challenges in lab chemical sourcing. In regulatory compliance, automated tracking and reporting tools have simplified maintaining compliance and minimized human error (see Box: Software and Systems).

The role of technology extends to tackling logistical issues. The Internet of Things (IoT) is revolutionizing inventory management in pathology labs. IoT devices can provide real-time data on stock levels, expiry dates, and usage rates of chemicals – data that can be used to optimize reordering processes, reducing the chances of overstocking or running out of essential chemicals.

There are also technological innovations that enhance the transportation and storage of chemicals. For example, advanced temperature and humidity control systems can ensure that chemicals are stored in optimal conditions. Similarly, developments in secure and safe transportation methods can ensure the integrity of chemicals during transit. Such innovations can help labs overcome some of the critical challenges in chemical sourcing.

The power of collaboration

The challenges of chemical sourcing demand collaboration between many stakeholders, including manufacturers, suppliers, transporters, laboratory personnel, and regulatory bodies. By pooling resources and expertise, these stakeholders can create robust, efficient, and safe systems for sourcing, handling, storing, and disposing of lab chemicals.

Effective collaboration hinges on open communication, mutual trust, and shared objectives. Regular meetings, shared digital platforms, and cooperative planning can help. But understanding and respecting each other's roles, responsibilities, and challenges is a prerequisite for working together and creating more streamlined sourcing systems.

One great example of collaboration is the partnership between the Massachusetts Institute of Technology (MIT) and global healthcare company Novartis. In 2018, these two organizations partnered to create a supply chain for specific lab chemicals required for their joint research projects. The resulting customized delivery schedules ensured that necessary chemicals were always available when needed.

Another example of collaboration in action is the use of the CDD (Collaborative Drug Discovery) Vault Collaborative Platform in 2020. Several diagnostic labs, including global giants like Novartis and Pfizer, began using this shared digital platform for managing and sharing Safety Data Sheets. This initiative enables the participating entities to remain compliant and improve safety – and it presents a practical illustration of the power of digital collaboration in chemical sourcing.

Future trends and strategies for streamlined sourcing

As we look towards the future, four key trends promise to reshape the landscape of lab chemical sourcing:

1. Increased digitization.
   We can anticipate further digitization of sourcing processes, including expanded use of digital marketplaces for sourcing, tracking, managing, and disposing of chemicals, and greater reliance on AI for tasks such as demand forecasting and regulatory compliance.
2. Greener sourcing.
   The push for sustainability is felt in all business sectors. We can expect to see more emphasis on sourcing chemicals that are environmentally friendly, accompanied by greener methods of transportation and disposal.
3. Decentralized sourcing.
   Other technologies enable labs to produce some of their chemicals in-house, reducing the need for transportation and storage and allowing for greater customization.
4. Increased collaboration.
   Collaboration is key to efficient sourcing; in the future, we can expect more collaboration both within organizations (between different labs) and between different organizations (for example, shared digital platforms for managing SDS).

But these trends also pose challenges that labs will need to prepare for; for example, the need for new skills and systems to manage digitization; new criteria for selecting suppliers; new equipment for the in-house production of chemicals; and new strategies for collaboration. By anticipating trends and preparing for them, pathology labs can be ready to take full advantage of the opportunities that the future holds for streamlined sourcing.

Dave Haase has been a leader for nearly 20 years in consumer products and pharmaceuticals and now runs ChemDirect, a consumer marketplace for chemicals.

The Place Maker

Sitting Down With… Aleksandra Zuraw, Veterinary Pathologist at Charles River Laboratories, Fairfield, Pennsylvania, and founder of The Digital Pathology Place

Please introduce yourself!

My name is Aleksandra Zuraw and I'm a Veterinary Pathologist who specializes in digital pathology. I am originally from Poland but now reside in the US. I founded The Digital Pathology Place – a digital platform that brings digital pathology solutions in front of the right people through educational videos and audio content. The website has grown into a podcast, a blog, a Youtube channel, and – somewhere along the way – I started helping digital pathology businesses reach their target audiences.

What led you to your career in veterinary science? And why did you pick pathology specifically?

When I was young, I read the book "All Creatures Great and Small" by James Herriot. The story was a defining moment in my life, and – from that point onwards – I knew I was going to be a vet. Everything was dictated by this book. After vet school, I practiced for three years. For the first year, I was a large animal vet, but soon realized the onslaught of emergency calls in cold conditions were not suited to me! I originally enrolled for a PhD program in Poland, but knew I wanted to do my residency at the same time. So, I found a university in Berlin, Germany, and was accepted for an externship program for 12 weeks. To be honest, I chose pathology through a process of elimination – I discarded poultry medicine, herd management, internal medicine, and was left with horse medicine and pathology. I was curious! I started the externship in the pathology department and never looked back.

Can you share your most interesting experience as a veterinary pathologist?

I'd say my role as a veterinary pathologist who supports drug development is very interesting in general. My little contribution – evaluating pathology slides – helps bring drugs to market. And that's exactly the kind of relevance that motivated me to enter the pathology field in the first place. Every FDA approved drug has had a veterinary pathologist look at its preclinical development – I don't think many people are aware of this. After all, the more prestigious part of development is when the drug actually makes it to clinical trials. But, before this happens, there are hundreds of drug candidates being tested in animals – and evaluated by a veterinary pathologist.

How did you become interested in digital pathology?

I started my post-PhD career at a digital pathology company. I worked with computer and tissue image analysis scientists to develop algorithms for the analysis and quantification of immune cells – with the aim of supporting pharma companies' immuno-oncology portfolios. I was not really looking at animal tissues. I was looking at digital images of human tissue and supporting biomarker discovery in the pharmaceutical industry. I loved that I could contribute to the quality of the data and to the insights generated by this technology. And I very much enjoyed the collaborative experience. Straight out of residency, I didn't look at any glass slides, I was viewing everything digitally. A lot of people wait a long time for their institutions to become digitized, but I entered this world instantaneously and didn't want to leave.

How did your blog – the Digital Pathology Place – get started?

I started the blog because I realized that the digital pathology pipeline contains many people with different areas of expertise and educational backgrounds. I call my group "The Digital Pathology Trailblazers," these are the people involved in sharing knowledge and bridging the gap between specialties. Everybody in the digital pathology ecosystem, including pathologists, computer scientists, regulatory experts, vendors, and sales representatives, all need to learn something that is new to them to communicate with the other players in the pipeline. We all need to speak the same "language" to produce the most seamless results! In 2021, I incorporated as a company to help digital pathology businesses reach the right audiences through informative content.

How important is social media as an educational platform for young pathologists?

I think social media is a means to reach a broader audience. But it's not a magic formula for success. The content you provide will only ever resonate with a fraction of the people. Social media merely acts as a net to draw in the people who are actually interested – the people who are willing to click on a video, and the people who actively engage with the content. For me, when someone engages with my videos, I invite them into my digital pathology community – the real value is when direct conversation can be established!

What is the biggest lesson you've learned throughout your career?

A pathologist is not always right! During education, there is always somebody to look up to in your niche, but when you step out of this circle and into full-time work, you are regarded as the expert. I was the only full-time pathologist at the first company I worked at. Going from the lowest to the highest step of the ladder was a fantastic feeling, but I soon realized that I was not familiar with the digital pathology and image analysis pipeline – for example, the technological aspects or the computer vision parts. At the start of my career, I was not giving the best pathology advice or approaching the problem from the best angle. Once I filled my knowledge gap about digital pathology as a whole, things became a lot easier.

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