JANUARY / FEBRUARY 2024 # 94

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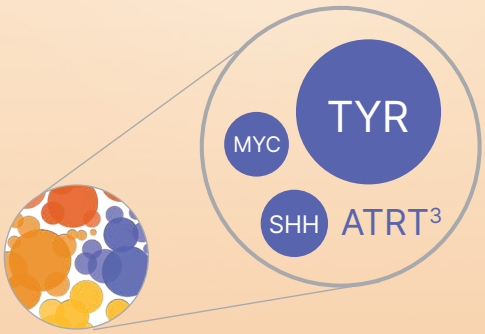

Learn more

1. https://www.molecularneuropathology.org/mnp/classifier/1
2. CNS Tumor Categories map to WHO Guideline entities
3. Ho B, Johann PD, Grabovska Y, et al. Molecular subgrouping of atypical teratoid/rhabdoid tumors-a reinvestigation and current consensus. Neuro Oncol. 2020;22(5):613-624. doi:10.1093/neuonc/noz235

M-AMR-01087

One Decade On

We're feeling reflective as we celebrate 10 years of The Pathologist – how about you?

It's anniversary time. The Pathologist is 10 years old! Yes, our first edition hit your doormats in 2014 – the year of the ebola epidemic in West Africa and the mysterious disappearance of Malaysian Airlines flight 370. Also in 2014, the Rosetta mission successfully landed Philae on a moving comet, President Obama announced the re-establishment of diplomatic relations with Cuba after more than 50 years, and Scotland voted "yes" to stay in the UK. And, on a lighter note, we were all dancing Gangnam style, thanks to South Korea's Psy and the power of YouTube.

I peeked through (OK – scrutinized!) that very first print edition to ascertain the hot topics in pathology at the time. Not surprisingly, ebola genome sequencing featured heavily in our news roundup. We also reported the FDA's plans to regulate laboratory developed tests – a topic which we revisited at the end of last year, via the Association of Molecular Pathology's response to the proposal. Human proteome maps and real-time tumor type identification were introduced as cutting edge "NextGen" topics. And our cover feature? A piece on "Facing the Digital Future of Pathology," examining the benefits and challenges of implementing "this inevitable technology." One of the contributors to the piece, Marcial Garcia Rojo of the Hospital de Jerez de la Frontera in Spain, predicted it would "take longer than 10 years to see digital pathology fully embraced across Europe."

A study published in 2023 confirmed that Garcia Rojo was right (1). Of 75 European pathology labs surveyed, 57 percent had no digital pathology capability. Europe was noticeably lagging behind Asia in this study, where 73 percent of labs had an established digital pathology workflow. Even in Asia, it appears that "fully embraced" is quite some way off.

We will be running some 10-year reflection pieces throughout the year, so keep your eyes peeled for those. But, back to the present day, we predict a hot topic this year might be climate change and its effects on the spread of tropical disease. This issue was certainly a concern at the recent COP28 meeting, where the United Nations included a dedicated "Health Day" for the first time. Our feature in this issue explores this theme, with a discussion of the increasing spread of Lassa fever and dengue fever (amongst others) by two experts in the field.

Our sincere thanks for supporting The Pathologist for the last decade, and here's to the next 10 years!

Helen Bristow
Editor

Reference

1. *D G Pinto, et al., Lab Invest, 103, 12, (2023). PMID:37839634*

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Looking for Lasting AML

Introducing a new droplet digital polymerase chain reaction (ddPCR) assay for the detection of acute myeloid leukemia residual disease

In the treatment of leukemia, monitoring of residual disease is key to assessing treatment response and guiding clinical decisions. Oncogenic fusions are often disease defining, presenting a unique marker of leukemic cells that are not usually present in healthy cells. However, for KMT2A fusions – major oncogenic drivers of therapy-related acute myeloid leukemia – sensitive detection has been precluded by the wide spectrum of KMT2A fusion-partners.

Current testing options include bone marrow morphology (which offers limited sensitivity) and flow cytometry (which lacks convenience and standardization). Keen to offer an alternative, researchers from the Washington University School of Medicine in St. Louis have developed a droplet digital polymerase chain reaction (ddPCR) assay to detect the most common oncogenic KMT2A fusions (1).

"The aim of the study was to design and benchmark a pooled assay that would enable the simultaneous detection of multiple different fusions across the KMT2A locus," explains corresponding author Grant A. Challen. "The assay detects these fusions by partitioning complementary DNA molecules into microfluidic droplets that are assayed with primers and probes that only produce a positive signal when fusion transcripts are present."

According to the team, targeting these fusions broadly was previously difficult because of technical challenges and the rarity of some of these fusions. "This assay is easy to scale and validate, making it possible to expand it to cover additional fusions," says Challen. "The assay is also inexpensive to run, enabling us to track disease trajectory more granularly during treatment, which may improve treatment decision-making in the future."

In the study, the assay detected KMT2A fusions in patient samples known to harbor KMT2A fusions without producing false-positive signals in samples from healthy individuals.

Initially, the assay will be assessed for measurement of residual disease in clinical trials of targeted therapies for KMT2A-driven leukemia. "Long-term we plan to offer this assay diagnostically as a laboratory developed test for fusion-specific measurable residual disease detection," concludes Challen. "This is a robust new tool for sensitive KMT2A fusion detection that is directly applicable for disease detection in patients with leukemia driven by these fusions."

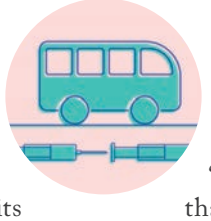
Reference

1. *AL Young et al,. J Mol Diagn, 25, 12 (2023). PMID: 37813299.*

An Injection of Infection

Research shines a light on the molecular "syringes" of certain bacteria

A team from the Max Planck Institute for Terrestrial Microbiology, Germany, has uncovered the molecular details that enable the type-III secretion (T3SS) system used by some bacteria, including *Salmonella*, *Shigella*, and *Yersinia*, to inject and then manipulate eukaryotic cells (1).



"Although we know a lot about this system, especially its evocative syringe-like structure, the key question of how the system recruits its effectors was unknown," says Andreas Diepold, Research Group Leader of the study.

The researchers used new methods to observe the T3SS – or injectisome – in situ, including proximity labeling and single molecule localization microscopy, leading them to discover a "shuttle service" that ensures that the required proteins are delivered from the bacterial cytosol to the injectisome at the correct moment.

It's hoped this knowledge could one day lead to new targets for anti-virulence drugs.

See references online

RESEARCH ROUNDUP

From spatial transcriptomics to AI diagnosis, we bring you the latest news in pathology and laboratory medicine

iSTAR of the show

Researchers at the University of Pennsylvania have developed a novel imaging technique – named iStar – that uses spatial transcriptomics data and high resolution histology to provide detailed analysis of individual cells and forecast spatial gene expression. iStar could help physicians detect more obscure cancer cells and help determine if safe margins are achieved following surgery (1).

More research needed…

A recent article published by *Nature* has highlighted how the dearth of research into long COVID-19 has affected low- to middle-income countries (2). The paper emphasized the importance of including study participants with diverse genetic backgrounds so that researchers can see what cellular pathways are involved and how they might vary from person to person.

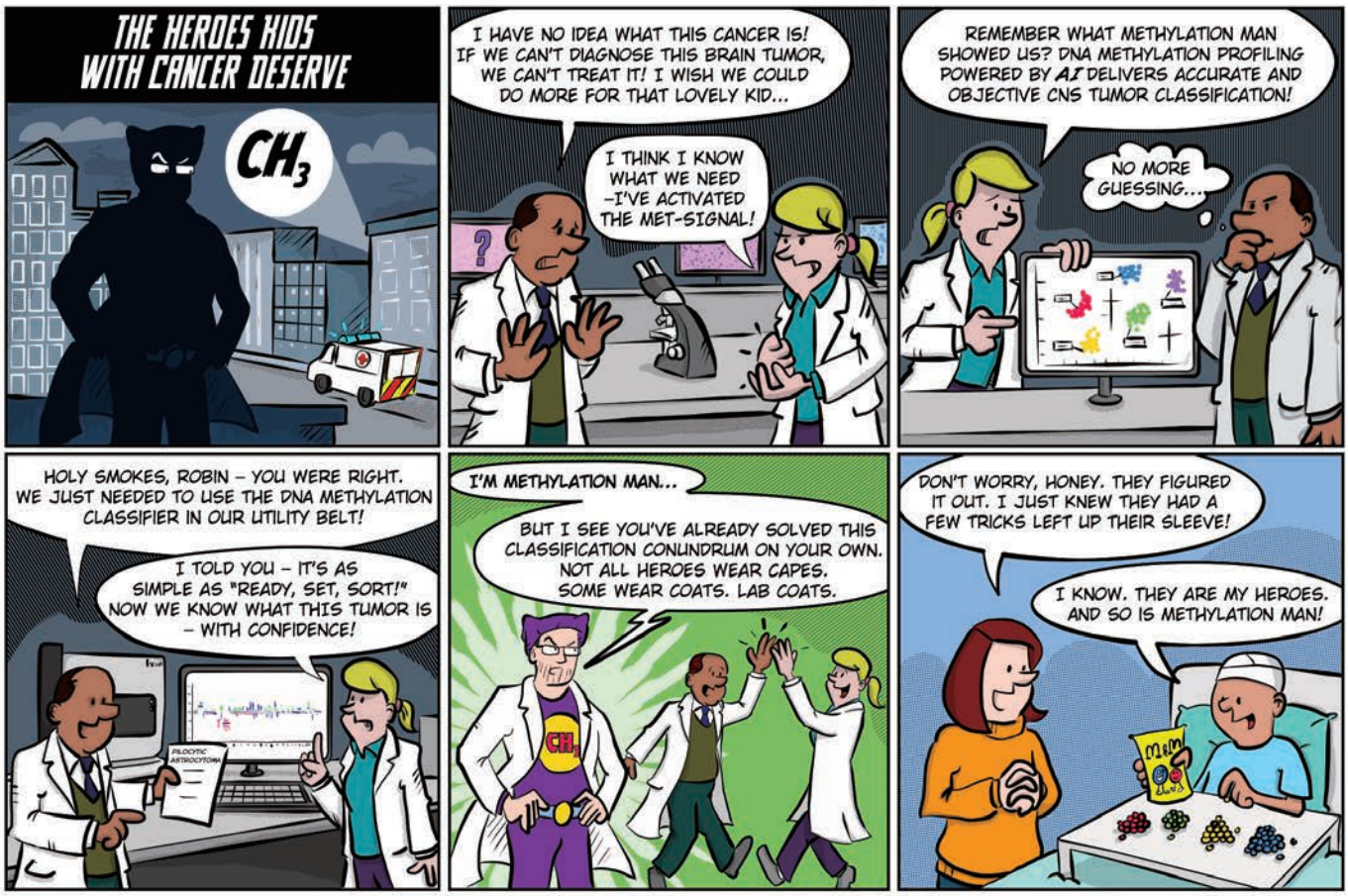
Screening sensation

Danish researchers have designed a new genetic screening test, desNIPT, that requires a simple blood sample from expectant mothers to make a comprehensive analysis of the fetus' genes (3). The method successfully identified 11 pathogenic gene variants in the unborn babies of 36 women.

X-ceptional Diagnosis? Part 1

PCR is the gold-standard method to diagnose COVID-19; however, there are limitations, such as high cost and lengthy turnaround times. To offer a potential alternative, researchers have developed a deep learning-based method called custom-CNN to diagnose COVID-19 infection in chest X-rays (4). The AI-model proved to have a 98 percent accuracy rate.

See references online



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Shake off the Nerves

Researchers investigate the molecular pathways involved in nerve-tumor communication

It is well known that perineural invasion (PNI) – the invasion of cancer to the space surrounding the nerves – can occur in solid tumors. Recently, it has been discovered that blocking nerve–tumor communication could improve patient outcomes, but what promotes this communication – and could we block it? Researchers are interrogating this possibility by looking into the genes and molecules responsible for the interaction between different cancers and nerves (1).

"Research has shown that tumor nerves, in different ways, 'strengthen' the tumor," says Sara Wilson, Associate Professor at the Department of Integrative Medical Biology at Umeå University, Sweden. Cancer animal models have shown the potential advantages of using chemicals to interrupt nerve signals to the diseased organ, Wilson explains. The improvements differed depending on the cancer type and nerve but, overall, blocking the nerves either with chemicals or surgery reduced the likelihood of tumors forming in the first place, reduced tumor growth and recurrence, mitigated metastasis, and gave a better response to chemotherapy (2). Further, scientists noticed that, in patients with gastric cancer, the chance of recurrence was reduced when the vagus nerve was cut (3). Although this is promising, Wilson notes that "organs need nerves for normal function – so the therapy would need to be selective."

Wilson and her team used bioinformatics to analyze genes of different cancers with a high density of tumor nerves and PNI, including head and neck, breast, prostate, pancreatic, and cholangiocarcinoma cancers. The most important finding was that the tumor and tumor microenvironments could be important sources of signals for nerve–tumor interactions including PNI, nerve plasticity, and neural tropism in a wide range of solid tumors throughout the body. "Interestingly, we also found that a group of genes which normally instruct nerves to develop during embryonic development – neurodevelopmental genes – were abnormal in the cancers analyzed," says Wilson. "It's as if the tumors reactivate the system normally used by embryonic neurons to develop and hijack it to provoke abnormal growth of the organ's nerves during cancer."

At the moment, the research is still at the preclinical stage. "The next phase will be about understanding if and how the genes we found are regulating nerve–tumor communication and finding ways to block them with chemical compounds," states Wilson. "We then want to investigate if these chemicals will slow down cancer in animal models."

References

1. *L M González-Castrillón et al., Front Genet (2023). PMID: 37719704.*
2. *AH Zahalka, PS Frenette,Nat Rev Cancer, 20, 143 (2020). Available from: http://www.nature.com/articles/s41568-019-0237-2*
3. *CM Zhao et al., Sci Transl Med, 6 (2014). PMID: 25143365*

CRC Biomarkers in the Microbiome?

A new study points to bacteria in the gut for signs of colorectal cancer

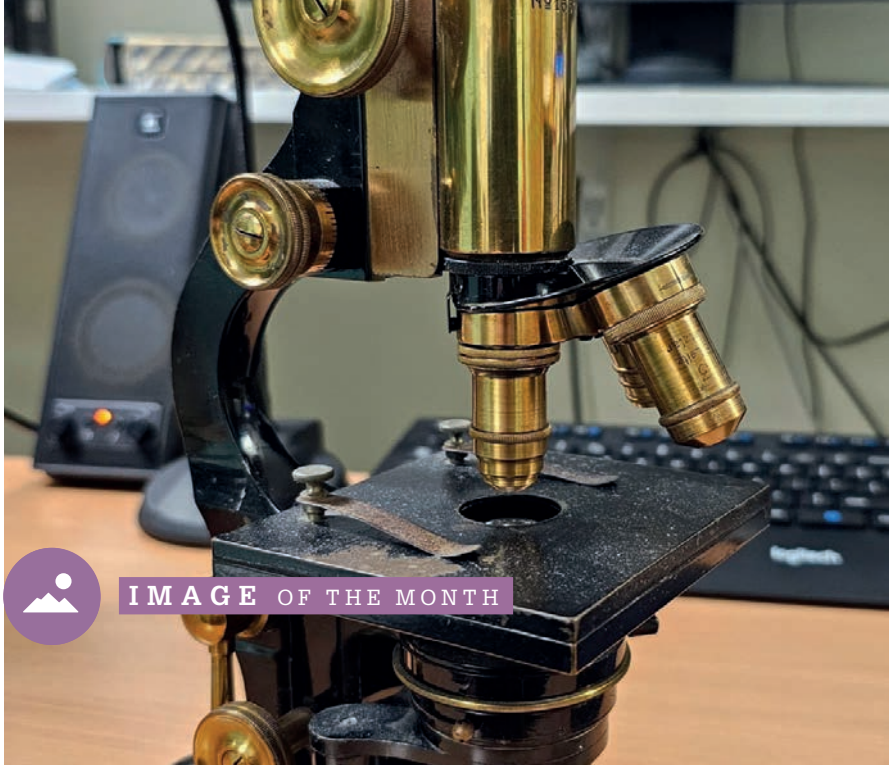
A recent study has investigated the association between the human microbiome and colorectal cancer (CRC) (1).

Ranko Gacesa, researcher at the University Medical Center Groningen, the Netherlands, explains: "Pre-existing pathologies – especially CRC – were linked to reduced microbiome diversity, a decrease in beneficial commensals such as butyrate-producing *Faecalibacterium*, and an increase in pathobionts, including bacteria previously shown to cause cancer in mice."

According to Gacesa, novel associations between the microbiome and pre-cancerous lesions were similar to those found in cancer, albeit with a lower effect size – implying that changes in the gut microbiome may be caused by cancerous and pre-cancerous pathologies.

The bacteria *Alistipes finegoldii* had a notable increase in individuals who had colorectal cancer within the last five years, though with no difference versus healthy controls in individuals who had pre-cancerous polyps or who developed polyps or cancer in the future.

See references online



Oldie, But a Goldie

The first Image of the Month for 2023 comes from Joe via X (formerly known as Twitter). He wrote: "I love this old microscope! Still works perfectly. #Leitz #Pathology #PathTwitter"

You can find Joe at @MBBS_Pathology

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

QUOTE of the month

"Lack of patient interaction is a leading reason to disregard pathology, but low awareness is an important issue for one-third of graduates and should be addressed by the professional community."

Artyom Borba, Tatiana Novikova, and Maxim Yaroslavtsev, Department of Pathology, Russian State Research Center–Burnazyan Federal Medical Biophysical Center of the Federal Medical Biological Agency, Moscow, Russia
Andrey Bychkov, Department of Pathology, Kameda Medical Center, Kamogawa, Japan

Reference

1. *A Borbat et al., "Not choosing pathology: An essay-based survey of first-year clinical residents," Am J Clin Pathol, 160, 593 (2023). PMID: 37536277.*

Keeping It in the Family

Research establishes a new protein family with links to bacterial pathogenicity

Gram-negative bacteria are known to create long-chain carbohydrates known as osmo-regulated periplasmic glucans (OPGs). These OPGs were once thought to be a by-product of low-solute concentrations, but new research suggests that they play a greater role in terms of bacterial pathogenicity – albeit with unclear explanations as to how and why.

Notably, knockout of OPG-associated genes is now known to hamper the pathogenicity of *Xanthomonas campestris*, *Agrobacterium tumefaciens*, and *Salmonella enterica serovar Typhimuriu* (1).

Researchers from the Tokyo University of Science shed even more light on the matter through structural and functional analyses of OPG-related genes in *E. coli* (1). The team established that the proteins EcOpgG and EcOpgD are β-1,2-glucanases and, according to the paper, these proteins showed different kinds of behavior from one another, pointing to a previously unknown glycoside hydrolase family: GH186.

Reference

1. *S Motouch et al., "Identification of enzymatic functions of osmo-regulated periplasmic glucan biosynthesis proteins from Escherichia coli reveals a novel glycoside hydrolase family," Commun Biol, 6, 961 (2023). PMID: 37735577.*

The Viral Frontier

The latest on the UK COVID-19 inquiry

On December 5, 2023, former health secretary Matt Hancock faced a barrage of inquiries regarding the UK government's pandemic response – providing a real insight into pivotal issues, such as timing of the lockdown, care home policies, and communication with regional leaders.

Amid the questioning, a haunting theme lingered: could an earlier implementation of the lockdown have prevented over 90 percent of the deaths in the first wave? The question is cloaked with "enormous uncertainty," and has stirred debates about the pandemic timeline (1).

During the investigation, epidemiologist Maria Rodriguez highlighted the oversight in care home policies. "The most vulnerable population was left at substantial risk due to the inadequate tailoring of policies concerning care homes," Rodriguez stated. Hancock's strategy for protecting these establishments and the people residing there at the height of the emergency was scrutinized. He was quizzed on how the regulations were created and whether they effectively safeguarded our weaker and elderly citizens.

Another line of questioning concerned Hancock's interactions with local authorities. Amidst allegations from leaders of three major UK cities that they were blocked from attending emergency response meetings, Hancock insisted he did hold discussions about social restrictions with some regional leaders.

The integrity of the COVID-19 testing system was another contentious item during the investigation. Asked to consider the testing capabilities of the UK, Hancock stated that, from mid-March 2020, the UK was able to increase its test capacity, although it moved "slower than it should have." He agreed that the government had good reason to intervene.

The British public now await the conclusions of this investigation. Not only will they be historically significant, but they will also provide essential guidance for handling future crises.

Reference

1. G Lacobucci, BMJ (2023). PMID: 38052467.

Cracking Colon Cancer

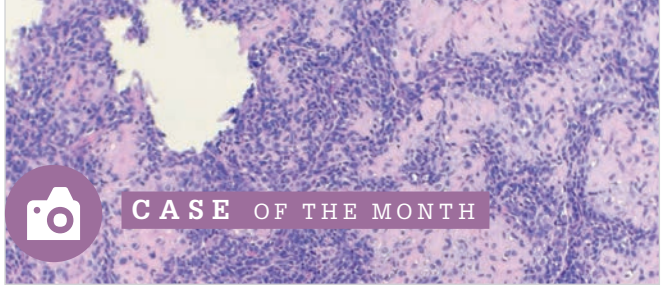
How a new clinically approved AI-based tool enables rapid microsatellite instability detection

Microsatellite Instability (MSI) – a tumor genotype characterized by mismatch errors of repetitive DNA – is found in 15 percent of colorectal cancer (CRC) patients and plays an important role in diagnostic, prognostic, and therapeutic outcomes. Universal screening of CRC patients for MSI is highly recommended, so a team of researchers from biotech company Owkin has recently developed MSIntuit – an artificial intelligence based pre-screening tool for rapid MSI detection from H&E stained slides (1).

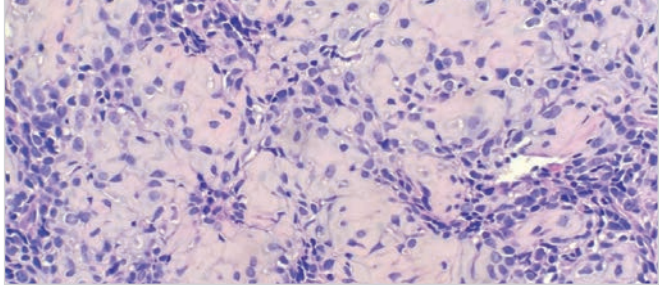
"Conventionally, MSI is diagnosed with immunohistochemistry or polymerase chain reaction," says Charlie Saillard, lead data scientist at Owkin. "These tests contribute to an ever-increasing workload for pathologists and technicians."

In the study, researchers trained MSIntuit on samples from the Cancer Genome Atlas. A blind validation was then performed on an independent dataset of 600 consecutive CRC patients. The AI model outputs "MSS-AI" (no further testing needed) or "undetermined," where a standard MSI test is then required. MSIntuit yielded a sensitivity of 96 percent and a specificity of 46 percent – rivaling gold standard techniques.

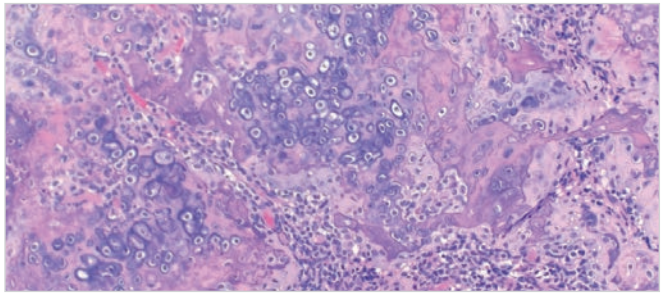
See references online



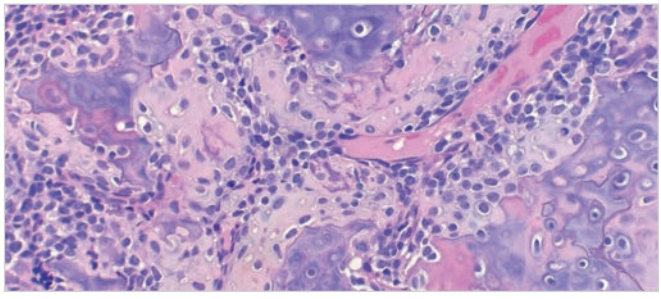
20x, hematoxylin and eosin, small round-to-oval blue cells with interspersed islands of eosinophilic cells



40x, hematoxylin and eosin, small weaving between areas of immature chondroid material



20x, hematoxylin and eosin, biphasic proliferation of small round blue cells and well-differentiated cartilage



40x, hematoxylin and eosin, biphasic proliferation of small round blue cells and well-differentiated cartilage

A 24-year-old woman presents with a mass of the pelvic soft tissue. Histologic images are shown. What is the most common genetic finding in this distinctive tumor?

a) IRF2BP2–CDX1 fusion
b) EWSR1–FLI1 fusion
c) t(11;12)(q24;q12)
d) HEY1–NCOA2 fusion

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

Answer to last issue's Case of the Month…

d) vaginal adenosis

Histologically, the vagina is made up of stratified squamous epithelium, lamina propria, a smooth muscle layer, and adventitia which connects with bladder (anteriorly) and rectum (posteriorly). The lamina propria should not have any glands, unlike this case that has simple cuboidal, endocervical-type glands, consistent with vaginal adenosis. On colposcopy, vaginal adenosis can appear as red, granular mosaic patches but fails to stain with iodine solution (1). Vaginal adenosis may arise de novo or due to prenatal diethylstilbestrol (DES) exposure in pregnant mothers who were prescribed this synthetic estrogen during the mid-20th century to prevent miscarriage (2). An estimated 5–10 million US citizens have received DES either during pregnancy or in utero (3). When women less than 30 years old were diagnosed with vaginal and cervical clear cell adenocarcinoma (CCA), a link was made with this rare carcinoma and DES exposure (4). Vaginal adenosis is considered a non-obligate precursor of vaginal and cervical CCA affecting between 34–88 percent of DES-exposed women (4, 5, 6, 7).

The differential diagnosis of vaginal adenosis includes endometriosis of the vaginal wall (a CD10 or IFITM immunohistochemical marker) may help in staining the endometrial stroma. Another differential includes a vaginal inclusion cyst, although the more superficial location and clinical physical examination can help differentiate it from vaginal adenosis, which occurs predominantly in the upper third of the vagina (1). A third differential includes CCA, which presents with necrosis, greater architectural complexity – such as papillary structures – and cytologic atypia with prominent nucleoli, increased mitotic activity, and hobnailing (4, 8).

Submitted by Jay Hwang and Cole Biehl, Department of Pathology and Laboratory Services, Brooke Army Medical Center, San Antonio, Texas, USA.

See references online

To register your guess, please go to http://tp.txp.to/0224/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.

TOWARDS A WORLD WHERE NGS-BASED COMPANION DIAGNOSTICS ARE AVAILABLE, IN HOUSE, FOR EVERY NEW CANCER THERAPY AND EVERY PATIENT

By Luca Quagliata, Vice-President, Medical Affairs, Clinical Next-Generation Sequencing Division, Genetic Sciences Group, Thermo Fisher Scientific

In the oncology space, as more and more targeted therapies are approved, it is all the more imperative that genetic testing technologies are available to connect patients with these treatments.

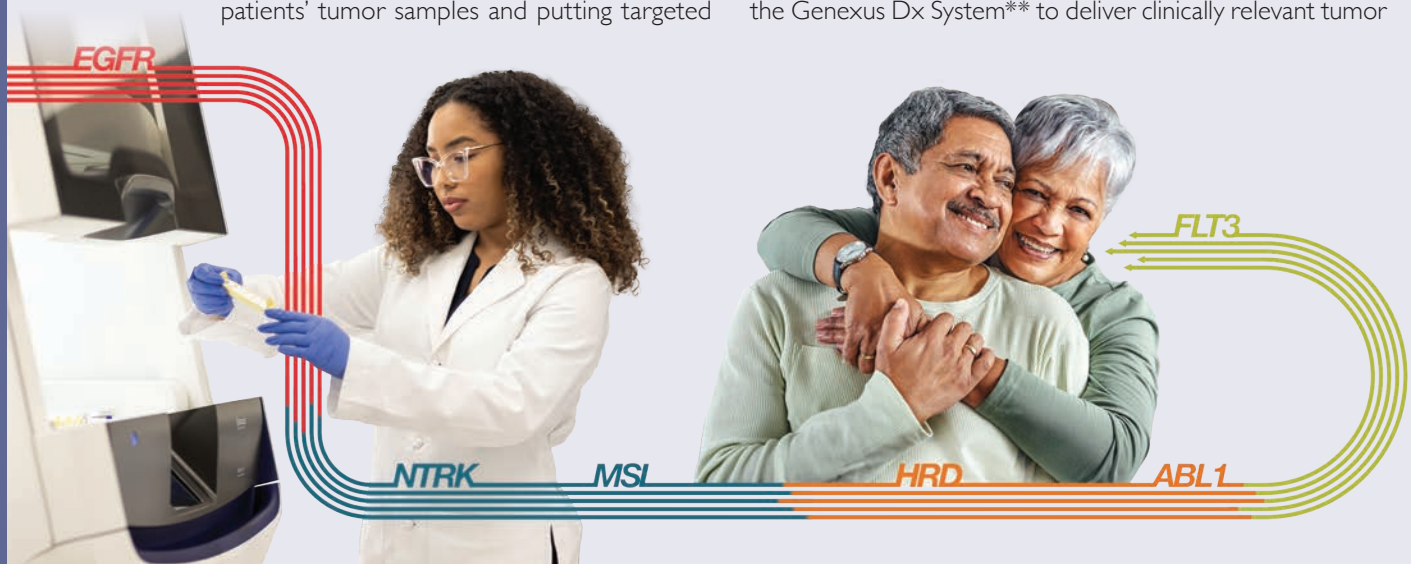
Collaborative companion diagnostics

Thermo Fisher Scientific is committed to helping expand the reach of precision medicine via close collaboration with biopharmaceutical partners to develop companion diagnostic (CDx) tests for their treatments. The co-development of CDx tests is designed to support the simultaneous regulatory submission of a therapeutic and a corresponding diagnostic. This process was designed to help ensure that a test is available to match patients with the new therapy as soon as it's approved.

Reliable and rapid access to CDx for new therapies allows clinicians to quickly begin testing patients' tumor samples and putting targeted therapies to use, which can be life-changing for patients who are a match.

Since 2017, when we launched Oncomine Dx Target Test*, the first next-generation sequencing (NGS)-based companion diagnostic approved by the US FDA, we have been focusing on expanding the indications and access to the testing worldwide. We have received regulatory approvals for nine CDx biomarkers for 17 therapies on label, for non-small cell lung cancer as well as thyroid cancer and cholangiocarcinoma. The test, with different indications per local regulatory approval, is now available in 18 countries across the globe. And we continue expanding further, working with both current and new pharma partners – in precision oncology it is all about the two industries working closely together.

Last year we launched the Oncomine Dx Express Test in Europe. This in vitro diagnostic CE marked test is used with the Genexus Dx System** to deliver clinically relevant tumor



ThermoFisher SCIENTIFIC

mutation profiling in as little as 24 hours. It utilizes a highly automated workflow from both formalin-fixed, paraffin-embedded tissue and plasma samples.

Bringing NGS in house, close to the patients

When test results are available early enough to inform a patient's care, this can help to prevent the patient from being placed on a harsh and potentially ineffective treatment and instead help them be matched with the appropriate targeted therapy. Thermo Fisher Scientific and Integra Connect recently collaborated on a real-world study, presented during the 2023 American Society of Clinical Oncology Annual Meeting, which reiterated the importance of rapid genomic testing (1). The study, like others recently published, found that when genomic testing results were available early enough to inform a patient's care, this had a positive impact on outcomes overall. With this in mind, we are continuously driven by the need to expand access to these testing technologies so more patients can benefit.

In the routine clinical world, targeted oncology treatments are guided by local multi-disciplinary teams. This is another reason to enable in-house access to genetic testing technology. However, the technologies used must be up to the challenge. The Genexus Dx Sequencer and Oncomine Dx Express Test rely on simple workflows so that minimal training is required to run tests, allowing this technology to be implemented in a broader spectrum of laboratories, with historically minimum resources for an NGS test.

Supporting precision medicine research

In precision oncology research, a broad spectrum of oncomine assays*** allows researchers to tailor their studies to the needs of specific labs and samples. With the fast turnaround times of these technologies, NGS results can be delivered at the same time as other single-gene testing methods. Thermo Fisher Scientific's Ion Torrent Genexus system is the first NGS solution to automate the specimen-to-report workflow and delivers testing results in 24 hours.

Thermo Fisher Scientific is also committed to supporting and encouraging independent researchers who are working to expand the reach of precision medicine through the Oncomine Clinical Research Grant Program. In 2020, we launched this global initiative to support research projects investigating unmet diagnostic needs for next-generation sequencing-based testing. To date, the program has awarded 22 research proposals working across areas including solid tumors, hematology-oncology, immune-oncology and pediatric oncology. Awardees have spanned 14 countries on 5 continents.

Thermo Fisher Scientific is a world leader in serving sciences who support customers who are accelerating life sciences research, solving complex analytic challenges, increasing productivity in their laboratories, and improving patient health through diagnostics or the development and manufacture of life-changing therapies.

The company has more than 100,000 employees worldwide through trusted brands which fall under the Thermo Fisher Scientific umbrella, including: Applied Biosystems, Invitrogen, Fisher Scientific, Unity Lab Services, Patheon and PPD.

In our clinical sequencing division through our Oncomine product line, our goal is to provide simple and fast next-generation sequencing-based solutions for clinical research and routine patient testing that will help accelerate science, empower local care teams and bring the benefits of precision medicine to more patients.

**For in vitro diagnostics use.*
***For in-house diagnostics use. CE IVD according to IVDD. Not available in all countries, including the United States.*
****For research use only. Not for use in diagnostic procedures.*

Reference

1. *J Scott, et al., JCO Oncology Practice, OP2200611 (2023). PMID: 37556776.*

In My View

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

Breathing New Life into Diagnostics

Jonathan Edgeworth on how metagenomics could transform testing for respiratory infections

By Jonathan Edgeworth, Professor of Clinical Infectious Diseases at King's College London, Consultant Microbiologist at Guy's and St. Thomas' NHS Foundation Trust, and Vice President of Medical Affairs at Oxford Nanopore Technologies.

Credit: Internal Communications team at Guy's & St. Thomas' Hospital

The healthcare community has always taken respiratory infections seriously – but the COVID-19 pandemic underscored just how central these infections are to clinical care in general. Respiratory infections are a leading cause of sepsis and, in many healthcare systems, the largest driver of antibiotic use. They are also the infection type most likely to cause a pandemic.

With so many ramifications for patients, it is imperative that clinical laboratories deploy the best possible tools for testing samples associated with respiratory infections. Today, laboratorians use a broad range of technologies – from cultures and singleplex PCR tests to syndromic molecular panels, and from low-throughput, sample-to-answer systems to high-throughput, industrial-scale operations. Each new pathogen that must be detected can mean implementing a broader panel test, adding a pathogen-specific kit, or even bringing in an entirely new diagnostic platform.

In the future, there may be a more straightforward approach that would have the inherent ability to detect all pathogens without requiring any new kits or equipment. Metagenomic testing is a sequencing-based alternative that can detect all organisms in a patient sample. And because no prior hypothesis is needed about the causal pathogen, metagenomics offers an unbiased view that can catch co-infections, hidden causes of infection, and other clinically relevant information missed by conventional diagnostic approaches. In addition, it can detect genetic markers of antimicrobial resistance to inform treatment selection.

The age-old approach

Even with the growing popularity of PCR-based diagnostic tools, the go-to test for respiratory infections hasn't changed in nearly a century. Culture-based testing is cheap and easy, with widely available consumables and well-established methods for preparing the test and for reading results. Indeed, cultures are still regarded as the diagnostic gold standard; unfortunately, they take days to generate results, and there are many slow-growing or even unculturable organisms that can cause respiratory infections.

Beyond pathogen identification, it takes even longer for culture-based tests to produce information about antimicrobial resistance. In healthcare systems where respiratory infection testing is based solely on cultures, there is no opportunity to adjust a patient's treatment – such as to de-escalate antibiotic treatment when the pathogen is found to be a virus or to shift a patient from a broad-spectrum antibiotic to a targeted antibiotic in a clinically relevant time frame. Not only does it lead to poorer patient outcomes, but it also contributes to the growing epidemic of antibiotic resistance.

Many clinical laboratories have adopted molecular diagnostic platforms to reliably identify pathogens faster and provide patients with the right treatment as soon as possible. But these tests also have their disadvantages. Labs have a set menu of tests – even when send-out tests

are included, which means that only the usual pathogens can be detected; in other words, rare, novel, or emerging pathogens are missed by these tests. To manage costs, most labs run these tests serially. If the causal pathogen is the very last on a long list of suspects, it could take just as long to get the answer as it would with a culture-based test. In addition, most molecular assays focus on pathogen identification and do not profile antimicrobial resistance markers.

The metagenomic era

The idea of turning to sequencing-based metagenomics to identify all viruses, bacteria, and fungi in a community is not new — scientists have been using this approach for years to characterize microbial communities in soil, deep ocean vents, biofilms, and more. But metagenomics can just as effectively be deployed to look within ourselves.

In recent years, clinical metagenomics has been evaluated for various types of patient samples and has proven an efficient and useful technique for detecting microbes found in and on humans. Until now, though, there have been good reasons not to roll this method out more broadly. For example, most studies relied on short-read sequencing technologies. The short snippets of DNA produced by these tools can be challenging to align for an accurate pathogen identification, and they are not amenable to connecting genetic markers of resistance back to their microbial hosts. In some countries, reimbursement issues have arisen when metagenomics workflows report all organisms found in a sample rather than just the one or ones most likely to be responsible for infection.

A different technology and an altered approach may be what's needed to make metagenomics a valuable component of the respiratory testing toolbox. Long-read sequencing platforms can help address the alignment challenges associated with short-read data; they can also fully resolve more complex genomes, such as those characteristic of fungal pathogens. With long-read data, it is also possible to link resistance-carrying plasmids to their host genomes.

Nanopore-based sequencing, which can be used to generate long or short reads as needed, can also produce data very quickly. In a recent pilot project at the Guy's and St. Thomas' Hospital NHS Foundation Trust in London, a clinical laboratory team evaluated nanopore sequencing to support a rapid respiratory metagenomics workflow (1). They tested nearly 130 samples from more than 85 individuals with lower respiratory infections, setting detection thresholds equivalent to culture-based testing to avoid reporting microbes that were unlikely to be clinically relevant. For most samples, results were reported to the clinical care team on the same day the sample was collected. Interestingly, nearly half of the results led to shifts in antimicrobial selection (in some cases escalating and in others de-escalating the initial treatment choice). Several unexpected organisms and cases of co-infections were reported; these would not have been found with conventional tests.

On trial

Clearly, further investigation is warranted to determine whether rapid metagenomics could be a useful alternative to standard respiratory testing approaches in clinical laboratories. Clinical trials will be helpful in understanding whether the treatment-selection benefits seen in this pilot project will translate to other laboratories and broader patient populations. As these evaluations occur, there will need to be assessments of the ideal reporting thresholds to ensure that causal pathogens are included in results and that most other microbes are not. If rapid metagenomics realizes its promise, technology developers will have to do their part to facilitate widespread adoption by automating sample preparation, analysis, and reporting.

"Rapid metagenomics could identify a hidden burden of infections that are clinically significant but cannot be detected with current tools."

If these initial successes with rapid metagenomics for respiratory testing hold up in larger trials, it could be a much-needed solution to growing challenges in healthcare. With more respiratory pathogens circulating in the general population, the old approach of testing for one microbe at a time becomes less feasible. With the rise of antimicrobial resistance, it is more important than ever to adopt rapid tests that can inform responsible treatment selection in a matter of hours. Rapid metagenomics could also identify a hidden burden of infections that are clinically significant but cannot be detected with current tools.

Overall, rapid metagenomics has the potential to serve as a one-and-done test for respiratory infections to ease the testing burden on clinical laboratories and help physicians deliver better outcomes for their patients.

Reference

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The Transformative Power of Patient Advocacy

Michele Mitchell shares her personal journey into patient advocacy

By Michele Mitchell, Patient Adviser and Co-Chair of the University of Michigan Department of Pathology's Patient and Family Advisory Council, Ann Arbor, Michigan, USA.

I believe patient advocacy transcends professional achievements; it's a personal odyssey molded by impactful experiences. A considerable portion of my life centered around my IT career at Blue Cross Blue Shield of Michigan. However, life is multifaceted, and I embraced roles beyond my profession – a devoted wife, stepmother, and grandmother. This journey, intertwined with a life-altering encounter with breast cancer, was further complicated when I started caring for numerous family and friends, many struggling with similar health challenges. Retirement was a shift towards advocating for others navigating comparable trials.

My passion for patient advocacy was sparked when I underwent cancer treatment at the University of Michigan Health System, where I received exceptional care. The center wanted to support patients, and I became a patient advisor and co-chair in various advisory councils, including the Department of Pathology Patient and Family Advisory Council. These volunteer opportunities gave me a platform and empowered me to push for improved patient outcomes within my healthcare system.

My commitment extended to volunteering at the American Cancer Society's Reach to Recovery Program, supporting newly diagnosed breast cancer patients and advocating for cancer screening on various platforms. Additionally, my involvement with the American Society for Clinical Pathologists (ASCP) as a patient champion allowed me to emphasize the importance of patient–pathologist interactions through speeches and educational discussions.

As an author, I've shared diverse insights, from discussing the impacts of the 21st CURES Act on the healthcare experience to highlighting the significance of patients meeting with the pathologist who diagnosed their disease. The transformative experience of reviewing my pathology reports with a pathologist, years after my diagnosis, fueled my dedication to expand access to such opportunities universally.

Most recently, I investigated the possibilities of what generative AI could offer patients and further delved into the realm of harnessing the potential of the AI movement, particularly focusing on exploring the possibilities and obstacles in leveraging generative AI and natural language processing. If managed properly, AI can provide individuals with insights into their medical conditions as they struggle to decipher the implications of their ailments. This integration can offer patients a comprehensive understanding of their health status, paving the way for informed decisions regarding their wellbeing.

"For me, patient advocacy reaches far beyond mere recognition; it involves reshaping healthcare environments to center around each person's needs and elevate their voices."

Though recognitions like the 2020 ASCP Patient Champion of the Year and the 2023 Michigan Cancer Consortium Inspiration Award are gratifying, true fulfillment lies in driving tangible policy changes and making real transformations in healthcare. My true passion is championing patient-centered care and advocating for a multidisciplinary approach to healthcare for all.

For me, patient advocacy reaches far beyond mere recognition; it involves reshaping healthcare environments to center around each person's needs and elevate their voices. My dedication lies in fostering fair systems that authentically cater to and honor patients. Taking on this self-appointed role is a privilege, and I approach it earnestly, striving to inform, embolden, and effect substantial changes in healthcare policies and safety measures.

As my journey in patient advocacy progresses, I am driven by a profound sense of duty and respect for this responsibility.

Creating Blueprints for Our Future

The road ahead is paved with planning

By E. Blair Holladay

In recent years we've witnessed a transformation – sometimes subtle, sometimes more overt – of the medical laboratory. We are no longer content with being contained solely within the laboratory, and instead, pathologists and medical laboratory scientists are stepping out from behind the laboratory walls and into the forefront of patient care.

Becoming a more patient-facing profession is critical to patient outcomes and to increasing visibility. We are responsible for so much of a patient's healthcare journey (we're all familiar with the 70 percent statistic) and it is only prudent that our patients can put a face with a name, and vice versa. On top of this shift, we've seen the broader implementation of artificial intelligence (AI), and a rise in telepathology that has allowed us to treat patients not only in our own institutions, but institutions in otherwise underserved parts of the world.

These evolutions don't happen overnight, and they all come with a learning curve. As we move through the processes, we are developing models for success as we go, learning from our experiences and adapting to ever-changing demands on the laboratory, and of healthcare overall. These models allow us to not only share knowledge internally but also to contribute to a broader collaborative ecosystem and foster a culture of continuous learning and growth. ASCP continues to advance progress in healthcare with the establishment of innovative and necessary tools like the National Pathology Quality Registry, for example, which takes large amounts of transactional laboratory data and converts it into actionable, customizable, real-time benchmarking dashboards laboratories can use to make informed, strategic decisions on quality improvement, business analytics, and test utilization.

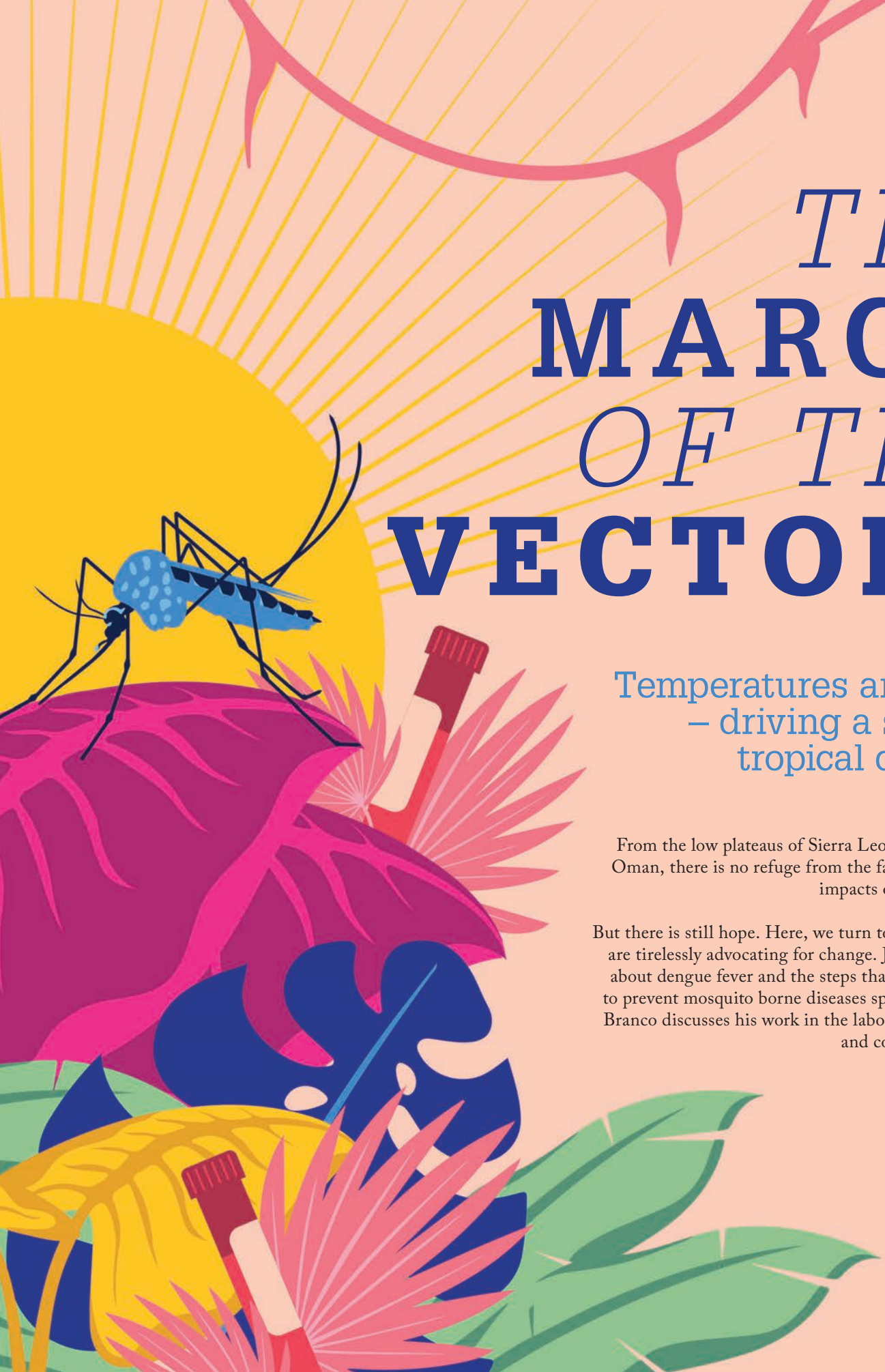
What's more, these models are applicable to many initiatives in and out of the laboratory. The fact of the matter is that if we want to see significant change not only in the laboratory but in healthcare, we must be the ones to implement it. We must be the ones to foster change. We must be the ones to lead. We must be the ones to show others not only how to do it, but why it is necessary.

Knowledge supports growth

We cannot have progress without knowledge, and for that knowledge to take hold, it must be disseminated across institutions. Models, blueprints, strategies for change – these all serve as tangible representations of accumulated knowledge and provide us with structure to help transfer knowledge from one individual or one group to another. These representations shine a light on the successes and yes, the failures. But it's important to note that both are something even more valuable: opportunities. Whether we succeed or we fail, we have seen an opportunity where we can grow, and the outcome, good or bad, serves as a guide for future decision making and problem solving.

I think what is most exciting about the period of laboratory evolution – or perhaps laboratory revolution is a better term, in light of the great innovation emanating from laboratories – is that this isn't a static exercise. Creating the models and blueprints we need to affect change is a dynamic endeavor that encourages continuously improving upon outcomes. That translates to the understanding that our strategies must continually evolve, through the incorporation of new insights, technologies, and methodologies.

Every institution is unique and has its own set of challenges and goals. In committing to building the models, strategies, or blueprints we need to overcome those challenges and meet those goals. We not only embrace change, but we also strengthen the future where the laboratory is the preeminent leader for patients.



THE MARCH OF THE VECTORS

Temperatures are rising – driving a surge in tropical diseases

From the low plateaus of Sierra Leone to the wadis of Oman, there is no refuge from the far-reaching health impacts of climate change.

But there is still hope. Here, we turn to two experts who are tirelessly advocating for change. Jorge Abarca talks about dengue fever and the steps that need to be taken to prevent mosquito borne diseases spreading; and Luis Branco discusses his work in the laboratory to diagnose and combat Lassa fever.

DON'T EAT THE OYSTERS!

Infectious disease consultant Jorge Abarca on how climate change is accelerating the spread of vectors

In Singapore, a watchful eye is kept on stagnant water. Ground puddles, water containers, clogged drains, toilet bowls, and discarded pails are all carefully monitored by the Government. But why? These sites create favorable conditions for mosquitoes to breed, mosquitoes that carry around dengue fever – a viral infection that has no cure, and in rare occasions, is fatal. The Singapore dengue control programme is committed to clamping down on the issue with a focus on removal of water containers from in and around homes, solid waste management, and limited use of insecticides (1). But they are fighting against an external factor that can not be overcome without global collaboration: climate change.

Warmer temperatures are speeding up the replication of dengue fever virus. And Oman is just one of the countries that has felt the effects of climate change on vector spread in recent years. We spoke with Jorge Abarca, an infectious disease consultant working in Oman, to discuss the importance of international collaboration in combating the spread of infectious disease, future innovations in dengue disease management, and how we can take a leaf out of Singapore's book.

In simple terms, how does climate change contribute to the spread of infectious disease?

Climate change is a contributor to the expansion and dissemination of vector-borne diseases. A combination of rising temperatures, altered rainfall patterns, and an increase in humidity create ideal breeding conditions for disease vectors. Increased rainfall also creates more breeding sites for mosquitoes – especially in urban areas.

In your presentation at RCPath 2023, you said cases of dengue fever have gone up in Oman – why is this the case? And why is this particular disease such a concern?

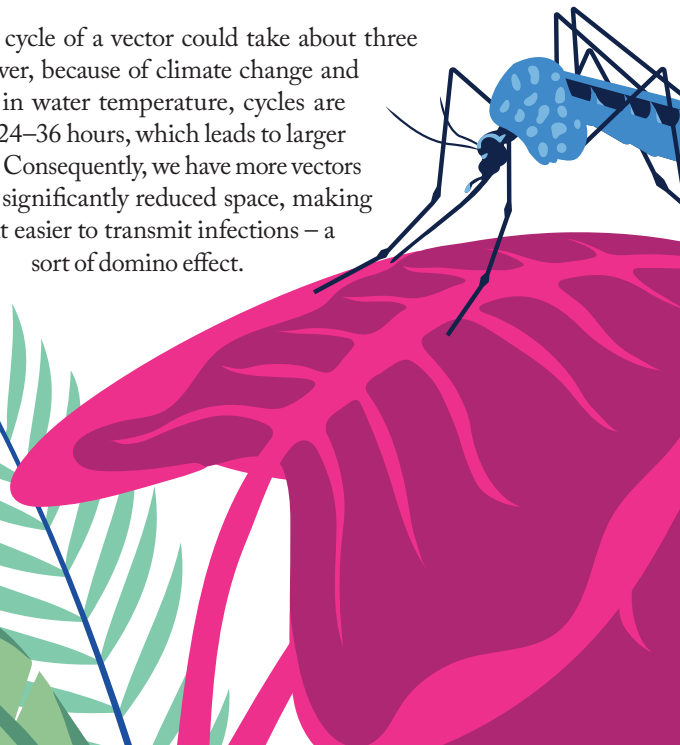
Well, I'm concerned about all infectious diseases! But yes, the spread of dengue fever is particularly alarming. In previous years, dengue fever has not been endemic to Oman. But recently, I was given the official numbers from Oman's Minister of Health. In 2020, there were 300 cases; in 2021, there were 24 cases; and in 2023, there were 1989 cases of dengue fever. So the number of cases drastically increased. What happened?

During these years – although the COVID-19 pandemic wasn't at its highest level – other diseases were effectively put on the back burner. They were not being monitored as closely, and it's likely that many positive cases were not properly diagnosed during this time. When COVID-19 cases decreased, and people started coming out of isolation – that's when the cases drastically increased. A similar pattern can be observed with influenza. The WHO showed how common flu cases decreased during the pandemic. This is because everybody isolated, so it was spread less, but also because many cases remained undiagnosed.

But there is the case of climate change, too. In 2022, the temperatures exceeded 40 °C in Oman, and seasonal monsoons (Khareef) brought heavy rains and cooler temperatures, especially in the Dhofar region. Oman lacks a proper drainage system, so flooding is usually extreme. This, of course, increases the water deposits that mosquitoes are attracted to. From a governmental perspective, there was not a proper implementation of programs for awareness, education, and detection of dengue fever. Healthcare workers were solely focused on COVID-19, so the increase in cases came as a surprise to everyone.

Vector cycles are shortening – what could this mean for disease spread?

The normal cycle of a vector could take about three days. However, because of climate change and an increase in water temperature, cycles are taking only 24–36 hours, which leads to larger populations. Consequently, we have more vectors in a significantly reduced space, making it easier to transmit infections – a sort of domino effect.



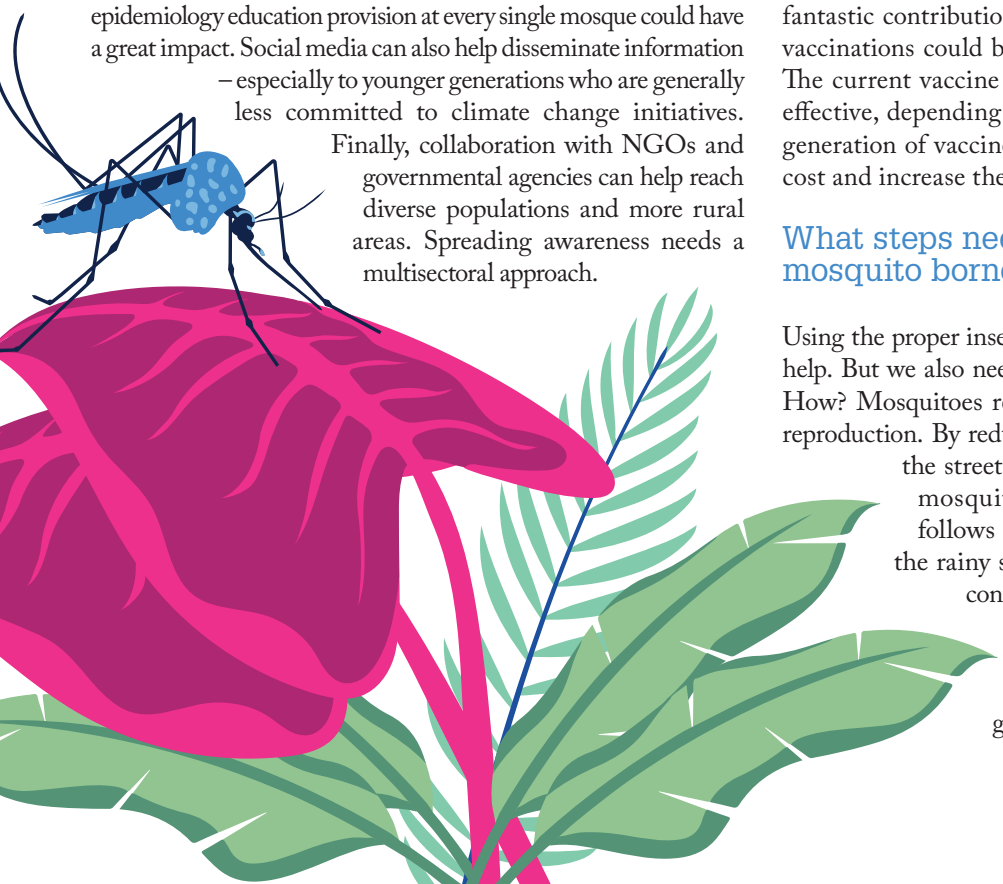
Considering the global nature of climate change, how important is international collaboration in combating the spread of infectious disease?

International collaboration is indispensable in addressing the global impact of climate change on infectious disease. We need a collaborative effort to facilitate the sharing of research findings, resources, and expertise.

Local organizations can also contribute by raising awareness and providing proper education and information. We learnt so much from COVID-19 – the general population was amazing. The fact that everybody – given the proper information – isolated for months is no small feat. If we applied this effort and commitment to climate change action, the impact would be huge. Margaret Mead once said, "Never doubt that a small group of thoughtful, committed citizens can change the world; indeed, it's the only thing that ever has." It couldn't be more true!

What more could be done to raise awareness of neglected tropical diseases risk?

We need more educational campaigns involving healthcare professionals – primary care physicians and GPs can all play a role. Given that Oman is a Muslim country, health care and epidemiology education provision at every single mosque could have a great impact. Social media can also help disseminate information – especially to younger generations who are generally less committed to climate change initiatives. Finally, collaboration with NGOs and governmental agencies can help reach diverse populations and more rural areas. Spreading awareness needs a multisectoral approach.



"Vibrio bacteria like to accumulate in oysters and the higher the coastalwater temperature, the higher the risk. It almost goes without saying that there is nothing aphrodisiacal about vibriosis."

What future innovations can we expect to see in dengue disease management?

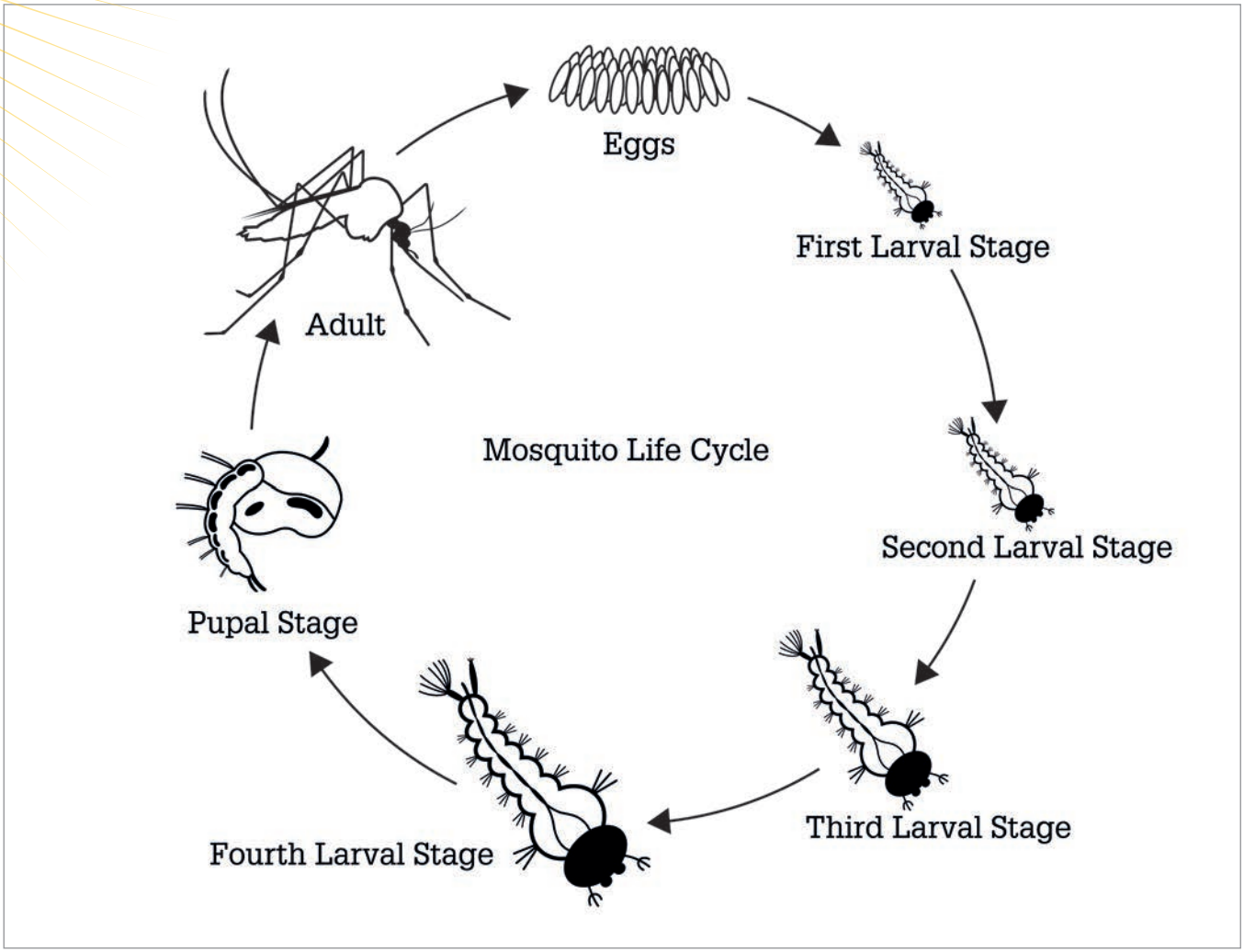
Right now, artificial intelligence (AI) is a hot topic everywhere. In the realm of disease management, we can, for example, design algorithms to combine different aspects of climate change – humidity, rainfall, and high temperature data – to predict by how much vectors could increase.

We also need continuous monitoring and surveillance. For instance, integrating satellite imaging to monitor environmental changes and predict potential dengue fever hotspots. This activity should be supplemented with community-based surveillance, which helps foster a proactive approach to outbreak prevention.

Future innovations in the pharmaceutical sector could be a fantastic contribution. COVID-19 showed us how effective vaccinations could be developed in a short amount of time. The current vaccine for dengue fever is only 40–70 percent effective, depending on very specific serotypes. But the next generation of vaccines can be better. We need to reduce the cost and increase the coverage – especially in endemic areas.

What steps need to be taken to prevent mosquito borne diseases spreading?

Using the proper insecticides and biological control agents will help. But we also need to tackle the problem as a community. How? Mosquitoes require water and high temperatures for reproduction. By reducing the number of water containers on the streets or outside our homes, we can decrease mosquito breeding. Singapore, for instance, follows a stringent protocol, especially during the rainy season, where fines are imposed if water containers outside houses are not controlled. The government consistently encourages public awareness. Collaboration between the general population and the government can lead to significant progress.



What policy recommendations do you think are essential at both national and international levels to address the rising threat of neglected tropical diseases in Europe?

First, there needs to be global acceptance that climate change is real. Currently, we have some big nations who are in complete denial. It is an undeniable situation in our world. All the big nations and their health departments need to act – and fast. We need to increase research, increase funding, and increase education. We also need to implement proper policies for recycling and trash removal. All this may sound easy, but it is very complicated; everybody needs to be involved – at every level of society. Politicians need to be convinced. We need to create funds. As I have highlighted before, a multisectoral approach is paramount!

The risks of failing to act are very real. It's not only dengue fever that is exacerbated by climate change; there is also Zika virus, Chikungunya virus, and many other mosquito-borne diseases. But it's not just viruses we have to worry about. In the US, Lyme disease is increasing because of climate change. And if you like raw oysters, I can offer a final example; Vibrio bacteria like to accumulate in oysters and the higher the coastal water temperature, the higher the risk. It almost goes without saying that there is nothing aphrodisiacal about vibriosis.

Reference

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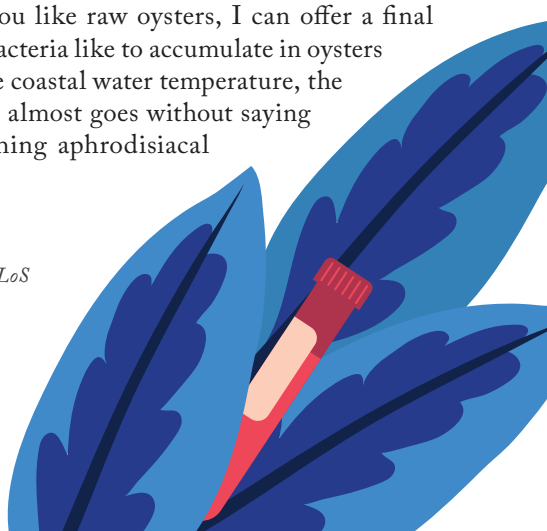
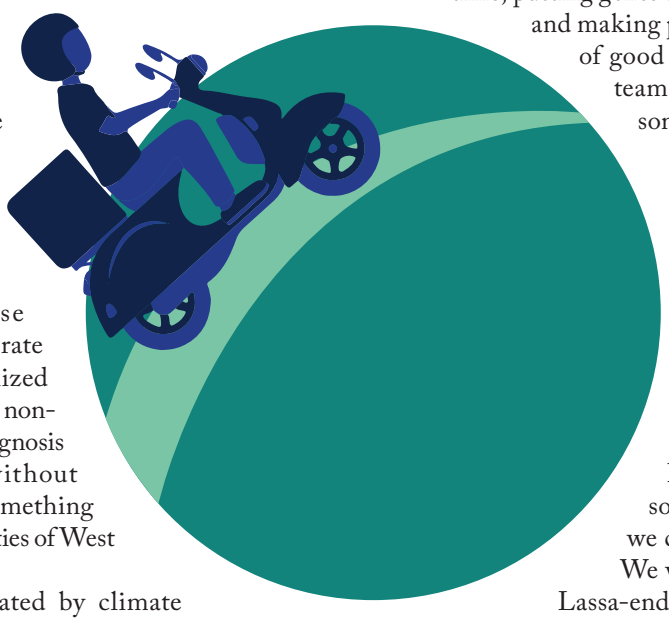


I TEST THE PAINS DOWN IN AFRICA

How rats are helping to migrate a neglected tropical disease across West Africa – and how the labs are battling to diagnose it

On the rural roads of Kenema, Sierra Leone, a lone rider blazes a trail with a special parcel in tow. It weighs less than a handful of pennies, but it's worth ten times its weight in gold. The motorcyclist has a long way to travel – possibly 200 miles – but getting there could mean life or death. That's because someone is waiting for a Lassa fever test, and speeding along the dusty tracks is the only way to get it to them on time.



Lassa fever is a zoonotic disease endemic to West Africa. Although often symptomless, the disease has a 15 percent fatality rate in those who are hospitalized due to infection. Vague or non-existent symptoms make diagnosis practically impossible without laboratory testing – not something that the poor rural communities of West Africa have much access to.

The problem is exacerbated by climate change. The virus is spread through human–rat interaction, and increasing extreme weather events are leading rodents to make haste into populated areas (1), boosting the chances of infection and potential death. What's more, the disease is spreading outside of its traditional endemic locale.

But all is not lost. Though the issue has been growing, so have efforts to quash it. The WHO, the CDC, and a plethora of other groups have been working to bring testing to the region, including Zalgen Labs, which played a fundamental role in creating a reliable test. The company now has its sights set on a vaccine.

We spoke with Luis Branco, Managing Director and co-founder of Zalgen on how it launched laboratories in Sierra Leone and how exactly its two-wheeled diagnostic delivery service came into existence.

How did you get involved in Lassa fever testing?

The story dates back to 2004, when I was collaborating with some colleagues who worked on high-containment pathogens. I was introduced to Robert Gary out of Tulane University, who had a long-standing presence in the world of virology. Robert was interested in exploring opportunities in the viral hemorrhagic fevers space – where Lassa and others like Ebola belong. The aim was to identify pathogens that were largely neglected but could have a very high potential for a natural pandemic. He wanted people on the team who had different skills. I was something of a gene jockey at the time, putting genes together, cutting and pasting them, and making proteins out of them – all that kind of good stuff. So I was brought onto that team and we got going with the help of some NIH funding.

We aimed to develop new-age recombinant-based diagnostics for these diseases. Very little had been done throughout the years and there really weren't any good diagnostics. The ones that existed required extensive safety testing and needed high containment BSL-4 labs, so they couldn't be commercialized. Instead, our idea was to develop some solid, rapid, bedside tests that we could use in the field.

We wanted to give medical facilities in Lassa-endemic countries the chance to save lives through diagnosis. So, we started looking at other aspects of Lassa fever to aid our understanding of the disease itself, including the ecology, the interaction between rodents and humans, human and rodent genetics, how people respond to infection, and so on.

One of the funding sources from the NIH was keen to understand how people develop Lassa antibodies. Out of that emerged the largest-known collection of human-derived antibodies against Lassa fever. We went to individuals who

had been lucky enough to survive the disease and asked them for a sample of their blood so we could mine it for antibodies that had potential to develop into a therapeutic. I should note that my whole career prior to becoming part of this program was antibody based – I was involved in a number of programs that were aimed at driving antibodies against viral agents. With Lassa, we looked at our collection of antibodies and thought, "We may have a therapeutic here." We ran some preliminary studies that showed that these antibodies were protective in animal models of the disease, which opened the door for funding opportunities. So, Gary and I decided to found Zalgen. We have stayed very active in the space of diagnostics while continuing to develop therapeutic drugs for Lassa.

When did you start working in situ in Africa?

We put boots on the ground from day one. We developed diagnostics by doing work stateside in our laboratories here and then we took trips – sometimes several a year – to areas like Sierra Leone and Nigeria, where we helped develop laboratory infrastructure that would permit us to actually evaluate these diagnostics on-site. Obviously, this was where the disease and the patients are located, so we needed access to relevant samples in situ.

CEPI is the Coalition for Epidemic Preparedness Innovations, which was created to create vaccines for pathogens with some of the highest pandemic potential – one of which was Lassa.

Once the tests had a certain level of extensive validation, we started distributing them to other entities that worked on Lassa fever; CEPI and the WHO came along to give legs to these initiatives. Throughout the years, people had worked on Lassa vaccines, but none had proceeded to licensure. Yet people had put out platforms, so CEPI funded a number of initiatives on a competitive basis, and we got an award from CEPI to provide all the diagnostics that were necessary to conduct those studies.

The diagnostics are important to understand the prevalence of Lassa in the region and to measure the potential immune response to a vaccine. These diagnostics identify active Lassa infections, but also determine whether or not a person had been previously infected with the virus. CEPI also funded a study called the Enable Lassa research program – the largest surveillance program to date (2), which, among other things, aims to answer a key question: how far and wide is Lassa fever present in that region? Again, we supply the diagnostics for that.

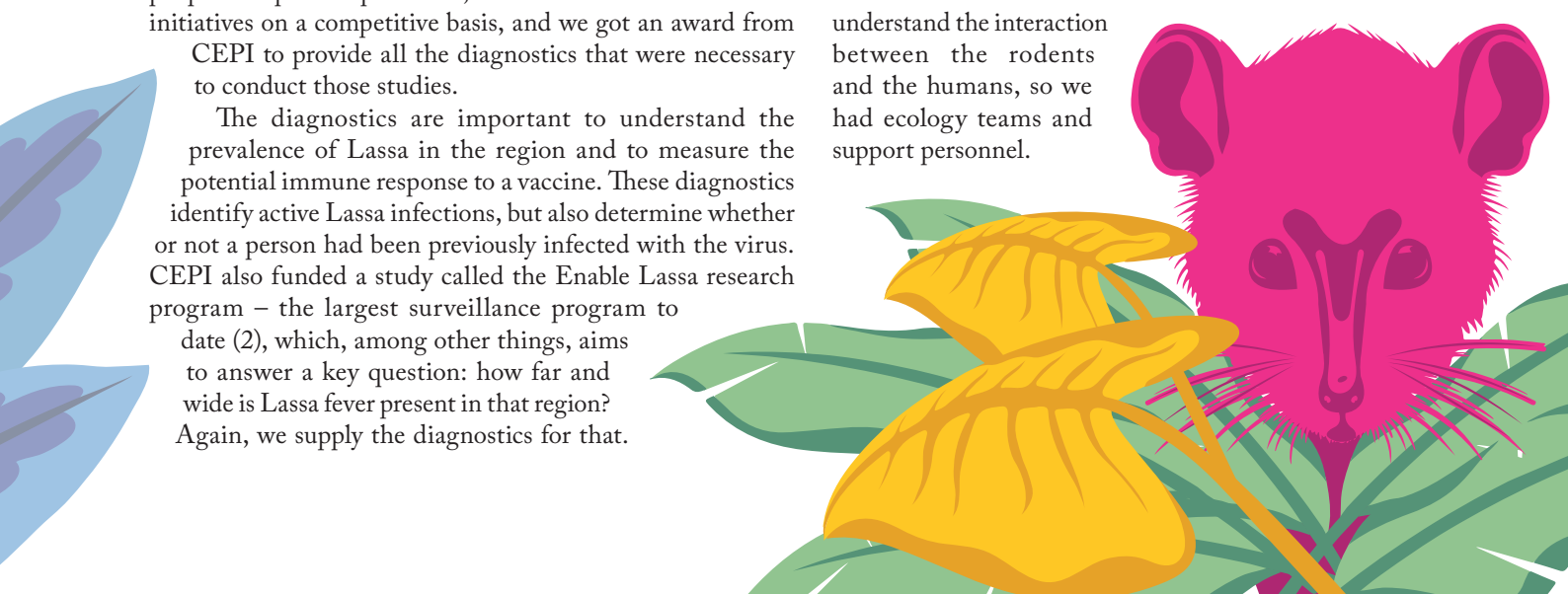
"These diagnostics identify active Lassa infections, but also determine whether or not a person had been previously infected with the virus."

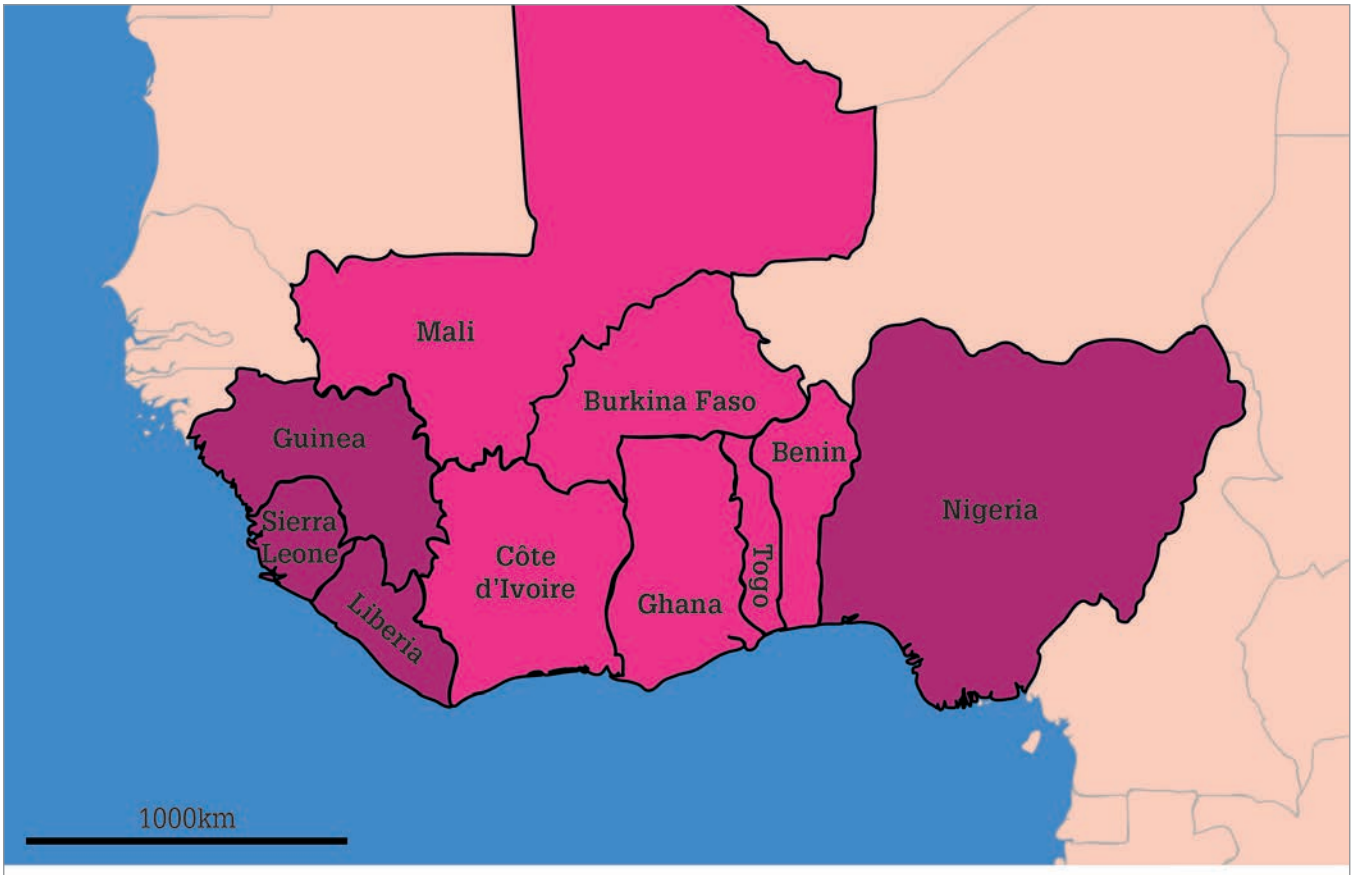
The program has multiple sites throughout West Africa that collect a lot of samples – they bring them in, they test them, they derive the data, and then put a picture together.

Once completed, it gives us a sense of how widespread the disease is, while setting the scene for vaccine studies. Obviously, you need to have naive populations – people that have never been exposed – so you can see what kind of immunity they develop from vaccine exposure and not from viral exposure. And that's why this study is still ongoing, so we can understand where the hot spots are and where they have the best population centers to choose for future clinical trials.

What was it like going to do field work?

I have a lot of stamps on my passport! And those are the moments that really define a career, right? It was not just about going in and having access to samples and to a patient population, we put in a lot of work. We're talking about hammer and nail type of approaches, where infrastructure was built; brick and mortar facilities with sustainable resources, like water and electricity and proper cooling so that we could have laboratories with equipment that needed certain temperatures to operate. There was also lots of community building. We needed drivers who could take us around the country and personnel who could bridge the gap between cultures and social norms. We needed to understand the interaction between the rodents and the humans, so we had ecology teams and support personnel.





Lassa Fever Distribution Map

Countries reporting endemic disease and substantial outbreaks of Lassa Fever

Countries reporting few cases, periodic isolation of virus, or serologic evidence of Lassa virus infection

Lassa fever status unknown

Source: Centers for Disease Control and Prevention / https://www.cdc.gov/vhf/lassa/outbreaks/index.html

How and where did you start setting up facilities?

Our first location of interest was Kenema in eastern Sierra Leone. It's one of the hotspots for Lassa fever. The WHO and the CDC did have a presence there for a long time until the civil war broke out in the early 1990s and they had to leave the country for safety reasons. That set the stage for us returning to Kenema down the line.

Many of those first few trips in early 2005 were on unpaved roads. It would take about 10 to 12 hours to reach Kenema – today it takes about three and a half. The infrastructure was lacking and the facilities really were very poor. For a long time, we operated on tiny amounts of small-town-supplied power for water and electricity – it was very sporadic. We ran some operations by just burning fuel; we had these old UN generators to power the facilities and part of the hospital. There was a lot of adapting to circumstances.

Later on, we installed large arrays of solar panels that provided a good amount of energy all day long while recharging batteries, which allowed us to continue work the next day. We also built a brand new Lassa ward – a wing of the hospital that was specifically designed to accept infected patients on one side, have them treated, and allow them to recover on the other side. Things have improved dramatically since then. Huge investment in Sierra Leone means that there's regular access to power and fiber optics for high speed internet, for example, the "good old days" of us trying to figure out how to supply power for an experiment are gone.

When it comes to Lassa fever, we've learned more in the last 10 years than in the previous 50 combined. These viral and hemorrhagic fevers, especially Lassa and Ebola, have seen a tremendous boost not just in knowledge, but also in countermeasures.

Why is Lassa considered difficult to diagnose?

It was difficult because diagnostics were not available. Everybody learned about PCR during the pandemic, right? You could go to your local testing center, have a swab up your nose and then run a test. But that kind of technology requires complex instruments and the people with the knowledge to run them properly. For example, you need a lab that can maintain room temperature, which was just not possible or sustainable in places like Sierra Leone.

And that's why we developed and continued to sustain the use of rapid tests – the kind that people can get from a pharmacy and run themselves. There might be better infrastructure in places like Kenema and other places throughout West Africa, but there are still huge distances for people to travel. Imagine if you were in London but you had to go to Liverpool to get tested. Imagine making your way there in difficult conditions without a car or public transport.

Our solution is networks of medical personnel that know Kenema well. These days, a medical officer can place a call to Kenema and say, "I have a patient here we suspect has Lassa." We have a team member who gets on a motorbike with a little packet and rides out to them. If it is Lassa fever, they'll call for an ambulance to bring them to Kenema to be treated on the Lassa ward. It's an incredibly valid and appropriate way to diagnose. Once at the ward, we can confirm the Lassa fever diagnosis in the lab with other tests like PCR.

Just as we all know how powerful it was for the general population to be able to go to a pharmacy and get the SARS-CoV-2 rapid tests, it's equally powerful for the community living with Lassa to get diagnoses this way.

> "When it comes to Lassa fever, we've learned more in the last 10 years than in the previous 50 combined."

It's no longer difficult to diagnose Lassa, but there are still many obstacles in distributing diagnostics. The countries in which Lassa is endemic – Sierra Leone, Liberia, Guinea, Burkina Faso, Ghana, and even all the way out to Nigeria – are some of the lowest GDP countries in the world. They really don't have the resources to procure and then sell these types of diagnostics in-house. One aspect that we always highlight is the fact that none of these countries have ever bought a single diagnostic from us. And to be clear, when I say we commercialize these tests, we sell them to vaccine developers, NGOs, and organizations who can provide financial support. Everything that lands in these countries is free for the people that need and use them.

How is the changing climate affecting the spread and distribution of Lassa?

I know that not everybody believes in climate change and its impact, but, if I take a completely neutral stance, we cannot negate the fact that the rodent reservoir is expanding. We know that even from 15 years ago when we started going to Sierra Leone and Nigeria; we have seen a dramatic expansion in exposure to the virus and the numbers of people getting sick. There are many more reported cases, and rodents and humans are certainly coming into contact a lot more. When we started over a decade ago, we knew that Lassa fever was prevalent in Sierra Leone, Guinea, and Liberia. On the other side of that belt, in places like Nigeria, there was evidence for zero prevalence. You could go there and test some people who might have antibodies against the virus, possibly because of someone who traveled through. Today, we've got significant expansion of Lassa fever; there are people succumbing to it throughout all of Nigeria and now Togo and Benin. In fact, there are new strains that have emerged from Benin and Togo, so we know there has been expansion.

How do you adapt tests for these new strains?

A fantastic question! We're constantly chasing that problem. When we started this whole program, our focus was to simply get it up and running. To that end, we focused on the prevalent Sierra Leone lineage of the virus, which is called lineage four. We developed all of our platforms around lineage four, but when we brought our tests to Nigeria the tests didn't perform very well.

And that's because two different lineages are more prevalent in Nigeria: lineages two and three.

We realized that we needed to develop what we call a pan platform – something that was going to be applicable to just about every lineage of Lassa that we knew about or could imagine. We're now at the point where we have largely discontinued our first-generation product. It works well in Sierra Leone, but we're not taking any chances.

When the Togo and Benin strains emerged, we immediately jumped on them. It's a living, breathing platform.

We scientists are sometimes labeled as fanatics because we have these "crazy" ideas about great pandemics that could wipe out the world. But every now and then, nature shows us that these things do happen.

It's up to us in worldwide public health to make sure we have the tools to tackle the problem. It's the worst thing in the world to say we could have solutions, but we didn't work on it when we had the chance; we didn't pay attention to it and now we are months or years away from a countermeasure. Just look at COVID-19 to see how many people succumbed to the disease simply because we weren't prepared. We're trying to build countermeasures for Lassa now – before it's too late.

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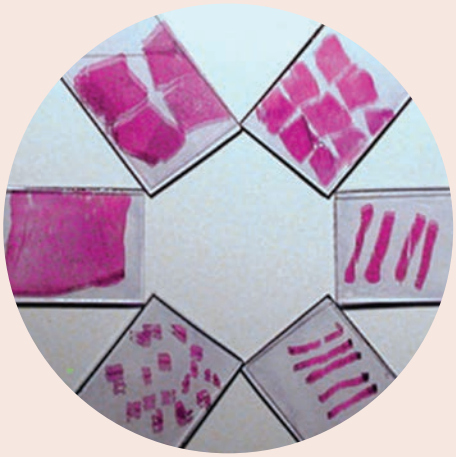

INNOVATION IN PRECISION CRYOEMBEDDING

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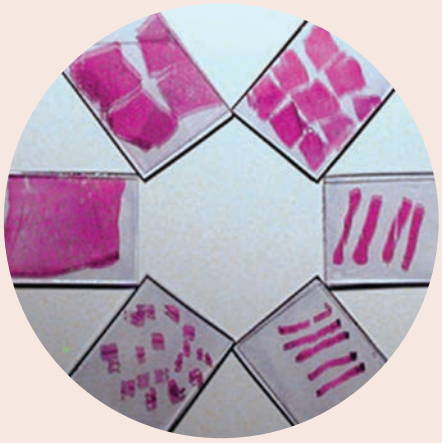
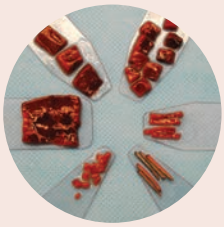
INNOVATION IN PRECISION CRYOEMBEDDING

Addressing the need for speed and precision when processing high volumes of frozen sections





The faster and more efficiently a user can execute a frozen section, whilst minimizing artifacts, the faster they can respond with a diagnosis, leading to better patient outcomes. The Peters Precision Cryoembedding System, by Pathology Innovations, is a combination of simple techniques and an apparatus for embedding tissues for frozen sections. Used by thousands of laboratory medicine professionals globally, it allows a level of control and predictability that can surpass even formalin-fixed, paraffin-embedded tissue.

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- Face down cryoembedding – Rather than standing tissue in solidifying paraffin, tissue is adhered flat to the base of a freezing well. The adhesive property of freezing steel allows precise positioning of tissues, as shown in the meticulously laid sesame seeds and flower petals to the right.
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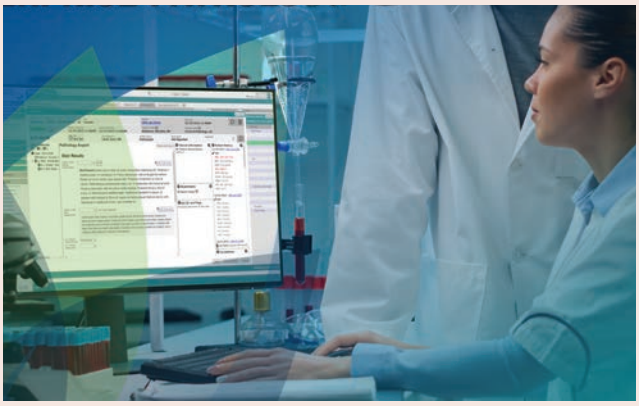
"Interfacing our cassette and slide printers eliminates the potential for data entry errors and has improved efficiency. Orchard Enterprise Pathology has eliminated the need for so many of the manual processes that we were performing previously." Kelley Durden, Pathology Supervisor, Flagler Hospital.



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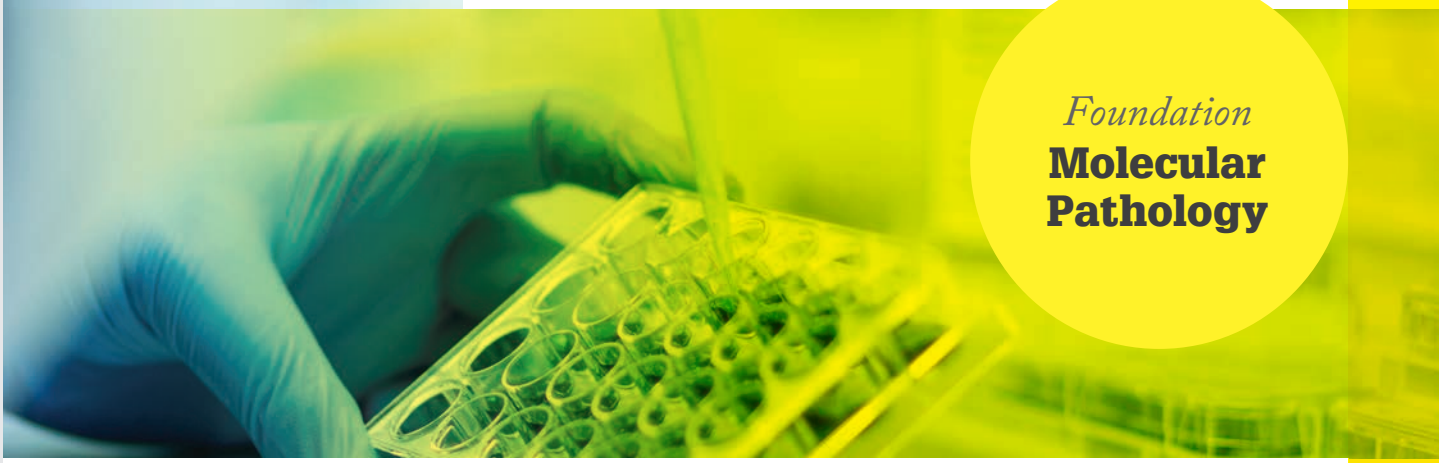

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Foundation

Molecular Pathology

Brain food A link between the gut microbiome and neurodegenerative disorders has been well established. But is there a link between gut bacteria and typical neurological development? Researchers have compared gut microbial taxa, cognitive function and brain structure in 381 children in the States (PMID: 38134274). The study, which used advanced learning models, showed that certain microbial species were markedly more or less prevalent in children with higher cognitive function. Correlations between taxa and size of different brain areas were also found. The report states, "These findings provide potential biomarkers of neurocognitive development and may enable development of targets for early detection and intervention."

Pre-empting pre-eclampsia Micro RNA (miRNA) on the surface of blood cells collected from pregnant patients has been found to differentiate those with pre-eclampsia – and even to predict its severity. The study, published in Science Advances (PMID: 38117879), discovered three relevant miRMA biomarkers using small RNA sequencing and an iterative machine learning method. Combining the miRNA biomarker information with results of an existing protein biomarker test resulted in increased sensitivity and specificity. Following validation of the three candidate biomarkers, the authors believe they will "allow for better clinical resource allocation, prevent low-risk patients from unnecessary admission and procedures, and increase understanding of their roles in pre-eclampsia disease pathogenesis."

Financial pressures Researchers in Australia have discovered a way to predict patients' response to blood pressure medication – and they say it could save the Government billions of dollars. The study interrogated real-world data for links between a sodium-dependent genetic predisposition to hypertension, blood sodium levels, and blood pressure (PMID: 38131187). The findings could be used to predict a patient's response to treatment that reduces sodium or another treatment targeted to their genetic risk profile. Murray J. Cairns, who led the research, claimed in a statement that one in three Australian adults has hypertension, adding that a "25 percent reduction in the prevalence of hypertension could save the Australian Government $34 billion per year."

A measly sum With measles vaccination rates on the decline, and cases increasing, the risk of disease from a mutated form of the virus that spreads through the brain is also on the up. A team at Mayo Clinic have been able to map the progress of subacute sclerosing panencephalitis (SSPE) across the brain of an adult patient who caught measles in childhood (PMID: 38127684). Through genetic sequencing of the viral RNA from 15 areas of the diseased brain they tracked viral mutations and spread over time. "This horrible disease can be prevented by vaccination. But now we are in the position to study SSPE with modern, genetic sequencing technology and learn more about it," said co-author Iris Yousaf.

IN OTHER NEWS

Beat it
A new classification system for coronary microvascular diseases has been proposed by a Chinese expert consensus; four major types and nine subtypes are detailed.

Bad air days
Inhalation of particulate matter containing cadmium can lead to respiratory damage, say researchers in the States. The findings will aid our understanding of how air pollution drives morphological changes.

All aquiver
Japanese jellyfish study reveals the creatures' ability to regenerate damaged tentacles is due to blastema formation by repair-specific proliferative cells. Findings may inform studies into human regenerative abilities.

Dementia–cholesterol link
Elderly people with very high levels of HDL-C – or good cholesterol – have an increased risk of dementia, according to a study; the risk increased by 42 percent for those over 75 years old with HDL-C levels >80 mg/dL.

See references online

Milk Monitor

How DNA sequencing of breast milk can replace tissue imaging for early diagnosis of breast cancer in pregnant and lactating women

By Markella Loi

Approximately 1 in 3,000 women will be diagnosed with breast cancer during pregnancy (PrBC) or postpartum period (PPBC), making it the most prevalent malignancy in this demographic (1).

The lack of reliable, sensitive, and non-invasive diagnostic and prognostic tests for early-stage breast cancer in these patients prompted researchers in Barcelona, Spain, to assess the potential of breast milk DNA sequencing (2).

To explore the research, we spoke with Cristina Saura, principal author of the paper and Head of the Breast Cancer Unit, Service of Medical Oncology, Vall d'Hebron University Hospital and Vall d'Hebron Institute of Oncology (VHIO).

Why did you focus on breast milk analysis?

Our starting point was a breast cancer patient diagnosed while pregnant with her third daughter. She was concerned that she had passed the tumor through her breast milk (BM) to her second daughter during breastfeeding – a period that lasted shortly before she was diagnosed. She brought us a sample of BM that she had stored in her freezer – more than a year before her diagnosis.

Despite knowing that breast cancer cannot be transmitted through BM, we decided to analyze the sample in search of markers that could help us in our research. To our surprise, when we examined the patient's BM, we found DNA with the same mutation that was present in her tumor. And thanks to her, we decided to initiate a study to investigate BM-based diagnosis.

Due to the proximity of BM to the tumors in the breast, we thought it could be an alternative source for a liquid biopsy, which has been used to screen blood, saliva, and urine as a non-invasive diagnostic for solid tumors.

As with other liquid biopsy samples, we analyzed the BM and blood samples using next-generation sequencing (NGS) and droplet digital PCR (ddPCR).

What were the key findings?

We have shown for the first time that breast milk obtained from breast cancer patients contains sufficient cell-free tumor DNA (ctDNA) to be detected by liquid biopsy.

It is even possible to detect ctDNA before the patient can be diagnosed using conventional imaging. We have successfully demonstrated that we would be able to diagnose early breast cancer in women postpartum by our technique – based on DNA sequencing and ddPCR analysis of BM.

We were also able to detect early signs of breast cancer in a healthy woman who enrolled in the study – which emphasizes how BM analysis could be used for prevention and prognosis of breast cancer.

Where does your approach fit in with regular breast cancer screening?

Our study focused on women during a specific period of their lives. In fact, the physiological changes that occur in the breast during pregnancy and postpartum make tumors more difficult to detect. Moreover, women become pregnant at ages when population screening with mammography is not yet carried out; in Spain, for example, these check-ups do not start until women reach the age of 50.

Our BM liquid biopsy approach could become a new tool for early breast cancer diagnosis, considering its non-invasive nature, if our initial results are confirmed in a prospective trial.

Some women might develop anxiety about breastfeeding – is this a potential problem?

Breastfeeding is a mother's choice that they must freely take. In any case, we are only taking a sample of breast milk during the first month after pregnancy. If women freely choose to breastfeed, participating in the screening should not be a cause for anxiety.

In women that may have positive results on breast milk analysis, exhaustive additional exams will be performed to diagnose or rule out a cancer diagnosis.

We planned in the prospective trial specific psychological support for those patients to accompany them during this process.

What's next for your research?

We need to confirm the usefulness of using BM as a new liquid biopsy tool for the early detection of breast cancer in the postpartum period in a much larger cohort.

Indeed, based on the results published, we are initiating a study to collect breast milk samples from 5,000 healthy women worldwide who became pregnant at 40 years of age or older – or women at any age who carry mutations that increase their risk of breast cancer *(BRCA1, BRCA2, PALB2, RAD51C/D).*

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qPCR: Infectious Disease Detective

How quantitative polymerase chain reaction really hits the mark in epidemic control and ID detection

By Angelica Olcott

When it comes to molecular diagnostics of infectious disease, the application of quantitative polymerase chain reaction (qPCR) continues to evolve, covering not only the need for rapid, accurate, and multipurpose diagnostic tools for pathogen detection in clinical settings, but also epidemiologic control.

Extraction of viral RNA obtained from nasopharyngeal swabs followed by real-time reverse transcription qPCR (RT-qPCR) enables the rapid and quantitative detection of viral nucleic acids after they are converted to cDNA. This technology was successfully applied in a multiplex assay format during the SARS-CoV-2 pandemic to reduce the processing time of individual tests. Specifically, multiplexed qPCR was used to amplify several viral genes encoding structural proteins, envelope and nucleocapsid, and non-structural proteins, including the RNA-dependent *RdRp* gene (1).

I believe the role of qPCR can only grow. And to support my point, I'll share three exciting applications.

Syndromic panel testing

qPCR can enable the simultaneous detection of multiple pathogens in a single reaction and enable differentiation between them. Such multiplex assays can enable faster and more comprehensive diagnostics for infectious diseases and are used when co-infections are a concern between several pathogens with similar clinical symptoms at onset. For example, during the latter stages of the recent SARS-CoV-2 pandemic, clinicians noted that influenza strains (A and B) and respiratory syncytial virus (RSCV) shared similar initial symptoms with COVID-19. The ability to enable differentiation between these three infections was important because treatments differ for COVD-19 versus influenza versus RSCV infections. As a result, demand grew for testing of multiple pathogens during the 2021–2022 flu season.

Genotyping and variant analysis

qPCR can easily differentiate strains or subtypes of pathogens. This application is crucial in epidemiological studies to trace the foodborne sources of outbreaks and to understand the genetic diversity of pathogens present. A recent study of *E. coli* and other bacterial subtypes demonstrated how qPCR can be used to evaluate the different bacterial populations present in a patient population for rapid assessments (2). While whole genome sequencing (WGS) is employed for characterization of SARS-CoV-2 variants worldwide, RT-qPCR can also provide a rapid method for the identification of known VOCs geographically (3).

Emerging pathogen detection

The flexibility of qPCR facilitates the rapid development of assays for newly emerging pathogens, such as the human mpox virus (MPV). A recent study investigated the specificity and suitability of generic primers and probes used in commercially available real-time diagnostic assays for MPV and revealed that the current real-time generic assay may not be optimal for accurate detection. The reason? The researchers used qPCR to uncover sequence variation between presently circulating MPV strains and earlier MPV strains (4). A similar study demonstrated how modern real-time qPCR systems and reagents can be used to design an assay that ensures accurate detection of the DNA virus in human samples while distinguishing it from related viruses (5).

Though reliable qPCR instrumentation is required for pathogen detection, good PCR practices alongside high-quality qPCR reagents and well-designed assays are also essential. As noted by the Minimum Information for Publication of Quantitative Real-Time PCR Experiments (MIQE) guidelines, the correct primer and probe design ensures detection of the target sequence and, as demonstrated by a large study of toxoplasmosis in pregnant women, using more than one replicate for testing is useful to reduce the potential for false positives or low positive samples (6). In addition to implementing a well-designed assay, the inclusion of positive and negative controls, and internal controls for PCR inhibitors is also required.

Accurate diagnostics are fundamental for successful epidemic control and disease diagnosis; from this perspective, qPCR continues to excel in this regard, providing a rapid, reliable, and cost-effective tool for targeting a pathogen's specific genome in human samples.

Angelica Olcott is Senior Applications Manager at Bio-Rad Laboratories Inc, USA.

See references online

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Infectious Disease

Cyto' the storm To learn more about the pathogenesis of sepsis, a team has decoded "the cytokine cacophony in sepsis into a pairwise cytokine message capturing the gene, cell and tissue responses of the host to the disease." Specifically, to understand which molecules controlled organ states in sepsis, the researchers looked at organ gene expression of 6 single recombinant cytokines and 15 pairs of recombinant cytokines. "Strikingly, we find that the pairwise effects of tumor necrosis factor plus interleukin (IL)-18, interferon-gamma or IL-1β suffice to mirror the impact of sepsis across tissues," write the authors.

The fungus among us New work has revealed insights into how *Aspergillus fumigatus* – a fungus that causes infection in thousands of people annually – produces mycotoxin gliotoxin, one of its key metabolites (PMID: 38167253). The team found that the fungus has to attenuate its production of gliotoxin to not negatively affect itself. They also observed that Mitogen-Activated Protein kinase MpkA is crucial for this balance between production and self-preservation. Özgür Bayram, from the international research team, commented, "The newfound knowledge might lay the foundation for a treatment targeting aspergillus infections in patients. Such a breakthrough could have profound implications for individuals undergoing cancer treatments, organ transplants, those with cystic fibrosis, and those managing chronic obstructive pulmonary disease."

Sitting in the sidelines New research published in Science Advances has uncovered a mechanism that explains how *Mycobacterium tuberculosis* (Mtb) is able to lay dormant in the human body for years (PMID: 38091389). The team engineered a version of Mtb without a particular gene that helps the bacteria survive – IscS – and found dramatically reduced virulence in mouse models. The team believe that the IscS gene operates the SUF operon and, when both are depleted, the virulence of Mtb is significantly reduced. The findings could inform future anti-tuberculosis drug development.

Some (don't) like it hot Mosquitoes are a globally significant vector for a number of infectious diseases, but models to forecast transmission often assume that their behaviour is similar across populations. A new paper has revealed that heat tolerance is much higher in larvae than in adults, and that tolerance also varies depending on local climate. The annual precipitation of a given area particularly affects the vectors' tolerance to heat, with greater tolerance observed in wetter regions. This is thought to be due to reduced desiccation of the insects in humid areas.

IN OTHER NEWS

This time for Africa
New One Health network establishes importance of tackling neglected tropical disease across the African continent (PMID: 38172632).

Class of their own
Newly-discovered antibody class capable of neutralising a number of influenza viruses shows potential for vaccine development (PMID: 38127922).

GI No!
Researchers explore how troublesome pathology of GI tract infections can lead to actionable diagnoses (PMID: 37863566).

Bacteria bonanza
The University of Basel discovers over 30 species of novel bacteria in patient samples – many belonging to either Corynebacterium or Schaalia genera (PMID: 38178003).

Making Specters of the Vectors

Could colorimetric LAMP testing enhance surveillance of vector-borne disease?

By Nathan A. Tanner and Samuel Wanji

The recent SARS-CoV-2 pandemic drove an unprecedented demand for molecular diagnostic methods that could be used in environments outside the traditional clinical laboratory. Of the available methods, loop-mediated isothermal amplification (LAMP) immediately attracted interest because it can be performed in under 30 minutes at a single temperature – without requiring instrumentation.

Adding to the method's simplicity and flexibility, LAMP tests can be assessed by visual inspection. In colorimetric LAMP, a positive result is reflected by a color-change; colorimetric indicators interact with the byproducts of extensive DNA synthesis (1). This combination of a simple, fast, and easily interpreted molecular diagnostic test made LAMP an optimal candidate for at-home testing – and colorimetric LAMP enabled the first-ever molecular diagnostic test approved for at-home use.

Although the pandemic catapulted LAMP's popularity as a diagnostic tool, a number of fields – from agriculture to public health – can benefit from a molecular test that easily identifies DNA and RNA targets. For example, many infectious diseases are spread via insect vectors, and the surveillance of infectious disease in those vectors can contribute to a better understanding of disease propagation and reservoir geography, helping inform appropriate public health measures. With LAMP, these insect vectors can be tested in the field or on-site – allowing for real-time data collection and surveillance in regions that lack easy access to laboratory facilities.

Vector-borne disease detection and monitoring

Early work with LAMP, which was first described in 2000, has focused on neglected tropical diseases, particularly filarial parasite targets in which the diagnostic needs are high, but where the typical testing infrastructure is not in place (2). These ongoing efforts include not only testing human patients for infection, but also surveilling the vector population to inform epidemiology and control efforts. Here, LAMP's ability to tolerate crude and unpurified samples has proven to be a critical factor in its practical application to field and point-of-need tests in which sample processing must be kept as simple as possible.

For instance, researchers have used LAMP to identify the filarial parasite *Onchocerca volvulus* in black flies, which causes Onchocerciasis, commonly known as "river blindness." Pools of 50–200 black flies were crushed in a tube and DNA was extracted by simple boiling then added directly to colorimetric LAMP reactions. *Onchocerca volvulus* genomic DNA could then be detected down to 0.01 ng in a pool of 100 insects by visual inspection of the reaction color (3).

A colorimetric LAMP assay has also recently been validated for the identification of *Mansonella perstans* – a filarial parasitic nematode – which is one of the causes of Mansonellosis (4). Mansonellosis, which may down-regulate immune responses (enhancing susceptibility to other infections, such as tuberculosis and malaria, and negatively affecting the efficacy of vaccines) is the least studied of the filarial diseases, with few alternative reliable and accessible methods of diagnosis (5,6,7). At present, no other immunoassays have been developed, and available PCR-based methods rely on trained personnel and relatively expensive equipment that restrict widespread adoption.

In addition to detecting parasites responsible for vector-borne diseases, LAMP has also demonstrated promise in identifying insect vectors. Of these, mosquitoes are the most prominent and result in the most infections and death worldwide. Mosquitoes are responsible for the transmission of numerous parasitic diseases, as well as arboviruses, such as Zika, West Nile, Chikungunya, and more (8). As different species of mosquito serve as hosts for different pathogens, identifying the specific type of mosquito can provide value to surveillance efforts. LAMP tests have been demonstrated for mosquito speciation directly from larvae, enabling the identification of problematic species (for example, *Aedes aegypti* and *albopictus*) potentially at ports of entry or in control programs (9). Such LAMP tests have been described for crushed mosquitos or pools in laboratory and field settings.

Assessing vector-borne disease control efforts

Alongside vector-borne disease detection and monitoring, LAMP-assisted surveillance has proven to be a powerful tool for assessing the efficacy of vector-borne disease control efforts. For example, over the past two decades, there have been programs in place to control onchocerciasis with the mass drug administration (MDA) of ivermectin, which involves administering the drug to an entire community regardless of whether individuals are infected or not. The impact of these programs has been variable, and careful monitoring of infection in humans and vectors is now needed to evaluate where MDA programs are – or are not – successful.

However, the effectiveness of MDA programs has been difficult to evaluate through conventional microscopy-based methods of diagnosing onchocerciasis. These methods struggle to differentiate the filarial nematodes responsible for onchocerciasis from co-endemic infection by other parasitic filarial nematodes, including *Loa loa*, commonly known as the African eye worm, and *Mansonella*

perstans. Where conventional methods fail, LAMP assays that have been developed for *Loa loa*, *Mansonella perstans*, and *Onchocerca volvulus*, respectively, could prove vital to the surveillance efforts used by global health programs aimed at achieving the elimination of onchocerciasis (10).

Another exemplar of LAMP's utility in assessing vector-borne disease control efforts is the World Mosquito Program, which uses a method of controlling mosquito-borne diseases that involves the release of mosquitoes intentionally infected with a commensal bacteria called *Wolbachia*. This bacteria makes it harder for viruses – including infectious viruses, such as Zika and yellow fever – to reproduce in mosquitos. Programs that successfully spread the virus-suppressing commensal bacteria from the released population into native mosquitoes reduce the risk of mosquito-borne diseases in that region. The World Mosquito Program has been able to do surveillance of release trials in Australia, Brazil, and across Southeast Asia using LAMP tests targeting the introduced wMel *Wolbachia* bacterial endosymbiont, so that researchers could better understand the dynamics of the release programs and *Wolbachia's* stability in mosquito populations over time (11).

The growing need for surveillance

With climate change exacerbating the risk of vector-borne diseases, the need for surveillance of insect vectors and vector-borne diseases is likely to rise worldwide. In 2023, the US saw locally acquired malaria cases for the first time in 20 years and Spain observed an increase in dengue transmission, indicating a spread of vectors to new, warmer areas. And though mosquito-borne diseases have generally been seen as a problem for the Global South, surveillance efforts for Eastern Equine Encephalitis and West Nile viruses have established importance in areas where those diseases are endemic in North America (12).

Beyond flies and mosquitoes, surveillance efforts in North America and Europe have focused on tick-borne diseases, with a rising incidence of bacterial (*Borrelia, Anaplasma, Rickettsia*), parasitic (*Babesia*), and viral (tick-borne encephalitis virus, Powhassan) infections. As the tick host population spreads to new environments in which ticks had previously been unable to survive – facilitated by climate change – awareness and the need for identifying these pathogens is increasing; LAMP can serve as first-line detection. Although ticks are more difficult to easily process in field-based testing, they can be crushed or sufficiently lysed without full extraction protocols to provide sample material to a colorimetric or other simple LAMP reaction (13,14).

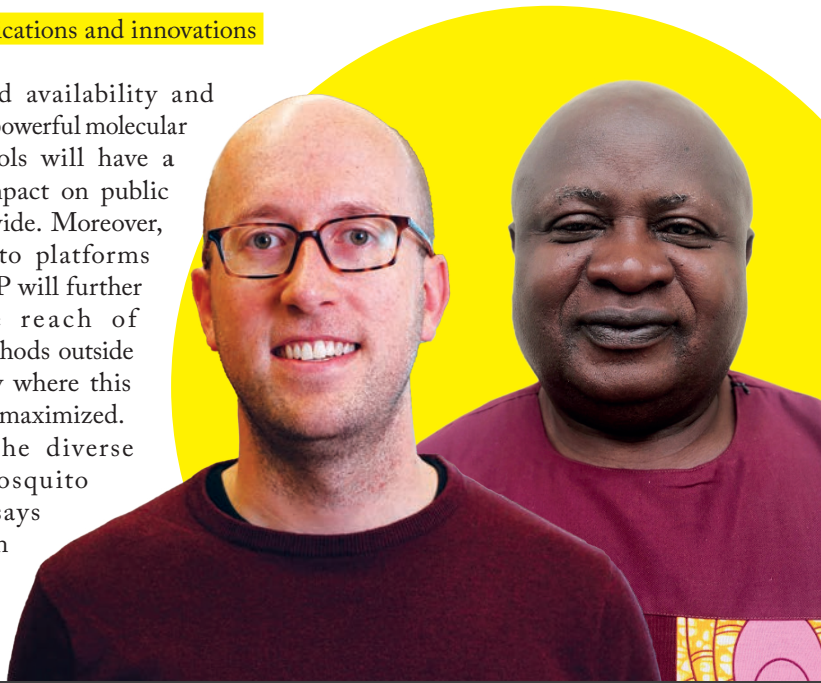
Evolving applications and innovations for LAMP

The increased availability and application of powerful molecular diagnostic tools will have a significant impact on public health worldwide. Moreover, innovations to platforms such as LAMP will further expand the reach of molecular methods outside the laboratory where this impact can be maximized.

Already, the diverse range of mosquito LAMP assays has resulted in a wide range of workflows and platform development, including a simple by-eye analysis of color change to more quantitative measurements using smartphones, or simple devices to measure fluorescence or lateral flow strip analysis. Maximizing portability and simplicity, LAMP has also been conducted in full paper-based systems in which sample treatment, incubation, and detection all occur within a disposable, low-cost paper device.

By enabling testing directly from samples in the field or at the point of need, LAMP can bring rapid and cheap identification of molecular targets to new environments. Insect vectors present a continual and growing threat, and increased use of LAMP will help expand our ability to monitor them and prevent the dangerous diseases they will spread to new populations.

See references online



the Pathologist

POWER List

WHO SHOULD BE ON THE PATHOLOGIST POWER LIST 2024?

It's time to shine a light on the pathology community, and recognize those who are making their mark in the world of laboratory medicine!

This is your chance to put forward the names of the influential people shaping the field in your specialty and to celebrate their work by seeing their name etched on to this roll-call of 100 Power Listers.

The first trial for any potential Power Lister? They must be nominated by you – the pathology community. The second test? Critical appraisal by an esteemed panel of independent judges.

THE POWER LIST NOMINATIONS OPEN FROM 22 MARCH 2024 - FIND THE FORM ON OUR WEBSITE!

Nominations will close on 31 May, 2024, and the final list will be published in August, 2024

Credit: Shutterstock

Foundation

Digital Pathology

iSpy To create a less resource-intensive alternative to transformers, researchers have created DPSeq – a digital pathology classifier capable of predicting cancer biomarkers (PMID: 37775043). DPSeq was constructed using H&E colorectal cancer images from The Cancer Genome Atlas and Molecular and Cellular Oncology datasets and demonstrated high accuracy in detecting key colorectal cancer biomarkers, including *BRAF* and *TP53* mutations. It was also able to detect hypermutation, as well as microsatellite instability and CpG island methylator phenotype status.

DP and the ink machine Automated scanning of the cell block technique can prove problematic, with incomplete scans leading to difficulties and inaccurate diagnosis. Researchers have tested the viability of overcoming this workflow hurdle by inking cell blocks prior to scanning (PMID: 37724610). Cell blocks were used in two tests: one in which blocks were inked one half green and one half black; and a second test where one half was black and the other unstained. The team found that, although inking required additional time and larger amounts of data, the method increased automatic detection by the scanner after immunostaining.

TLC for ILC Some forms of breast cancer, such as invasive lobular carcinoma (ILC) are difficult to detect with mammogram methods. Now, researchers have tested whether digital mammography and digital breast tomosynthesis can improve detection and patient outcomes (PMID: 37697031). The study pulled data from over 830,000 cases in the Breast Cancer Surveillance Consortium and followed examinations for up to a year. The team discovered that digital breast tomosynthesis showed greater cancer detection in ILC, alongside invasive ductal carcinoma and invasive mixed carcinoma.

Patient prediction There is a known link between pathological complete response to neoadjuvant chemotherapy and patient outcomes in cases of breast cancer. Unfortunately, the rates of pathological response can sometimes be below 30 percent with certain forms of the cancer. With this in mind, researchers used deep learning to predict outcomes of breast cancer chemotherapy using digital histology slides of pre-treatment biopsies (PMID: 37403567). The chemotherapy response was calculated for 207 patients through a hierarchical deep learning framework made up of convolutional blocks and self-attention modules. "The results of this study pave the way toward a response-guided therapy paradigm for individual breast cancer patients and motivate future studies on larger multi-institutional datasets for further investigation of the proposed methodologies," concluded the authors.

IN OTHER NEWS

Learning from experience
Case study of total transition to digital slides in six hospitals spotlights leaps in scanner capabilities in a short timeframe (PMID: 38142526).

Survey says
A survey of UK Liver Pathology Group members shows overall positive attitude towards digital pathology and AI in clinical practice (PMID: 36599660).

Deep infiltration
Neural network analysis of primary melanoma whole-slide images shows improved uniformity and reduced pathologist monitoring, with promise for routine use (PMID: 37734590).

Practice makes perfect
Self-supervised learning tasks relevant to lung adenocarcinoma subtype classification help neural network model better detect salient features in slide images (PMID: 37741228).

The Journey to Digital Pathology – Pathlab: a Case Study

As the digital pathology transition accelerates from "nice to have" to "need to have," we explore the pioneering steps of New Zealand's Pathlab

By Rob Monroe

This is part one of a three-part series showcasing how pathology laboratories in New Zealand, Germany, and Portugal have successfully tackled the transition to digital.

New Zealand is world-renowned for its sweeping landscape and wonderful panoramic views, so it's interesting to see this echoed by the team at New Zealand-based Pathlab, which takes a broad and comprehensive view to optimizing anatomical pathology services – for now and for the future.

"We've been able to invest early in technological advances to help us improve our processes and efficiencies for both our staff and our patients," says Corinne Hill, Lead Scientist – Histopathology/Molecular Oncology at Pathlab – an anatomical pathology lab that processes more than 60,000 cases and 200,000 slides annually.

"About the time we implemented a single-piece workflow with our integrated management system, we started to look closely at digital pathology. At the time – more than 10 years ago – digital was starting to become more robust," Hill reflects. "Even as we focused on our then near-term goal to minimize the risk to the audit trail within the histology laboratory, we could see very early on that digital was the next advancement for our service."

Pathlab's Director of Anatomical Pathology Richard Massey remembers the team learning about digital pathology when it was way out on the horizon. "We had been watching it very carefully, particularly with a view to modifying our workflows and taking advantage of the increased patient safety that digital pathology could offer," he notes. "We wanted to start with a view to gaining experience with the technology: how it actually felt to work with it."

The beginning of the journey – multidisciplinary team meetings

The Pathlab team initially focused on applying digital pathology to multidisciplinary team meetings (MDTs) for one service region, called the Bay of Plenty. "We integrated our digital system first with MDTs because we saw that as an easy way to get familiar with a technology without it being too onerous on the pathologists," noted Hill.

The team quickly learned that digital enables a different sort of work experience for a pathologist and for the clinicians with whom a pathologist collaborates. "My main experience is that, when you first start using digital pathology, like any other new skill, it takes effort and concentration," Massey explains. "Obviously, a screen is not a microscope. There are new sets of visual and motor skills to be learnt while reporting off a screen as opposed to reporting using a microscope. There is a learning curve; however, people interpret that as being inferior – and it's not."

To the contrary, gains in efficiency and productivity were evident from the outset. The team saw that both the pathologists and collaborating clinicians benefited from the ability to remotely share and view images and notes. "We found that converting to digital pathology enabled us to manage the workload for meetings, and it gave much greater visibility for the clinicians as to the material we were looking at," notes Massey.

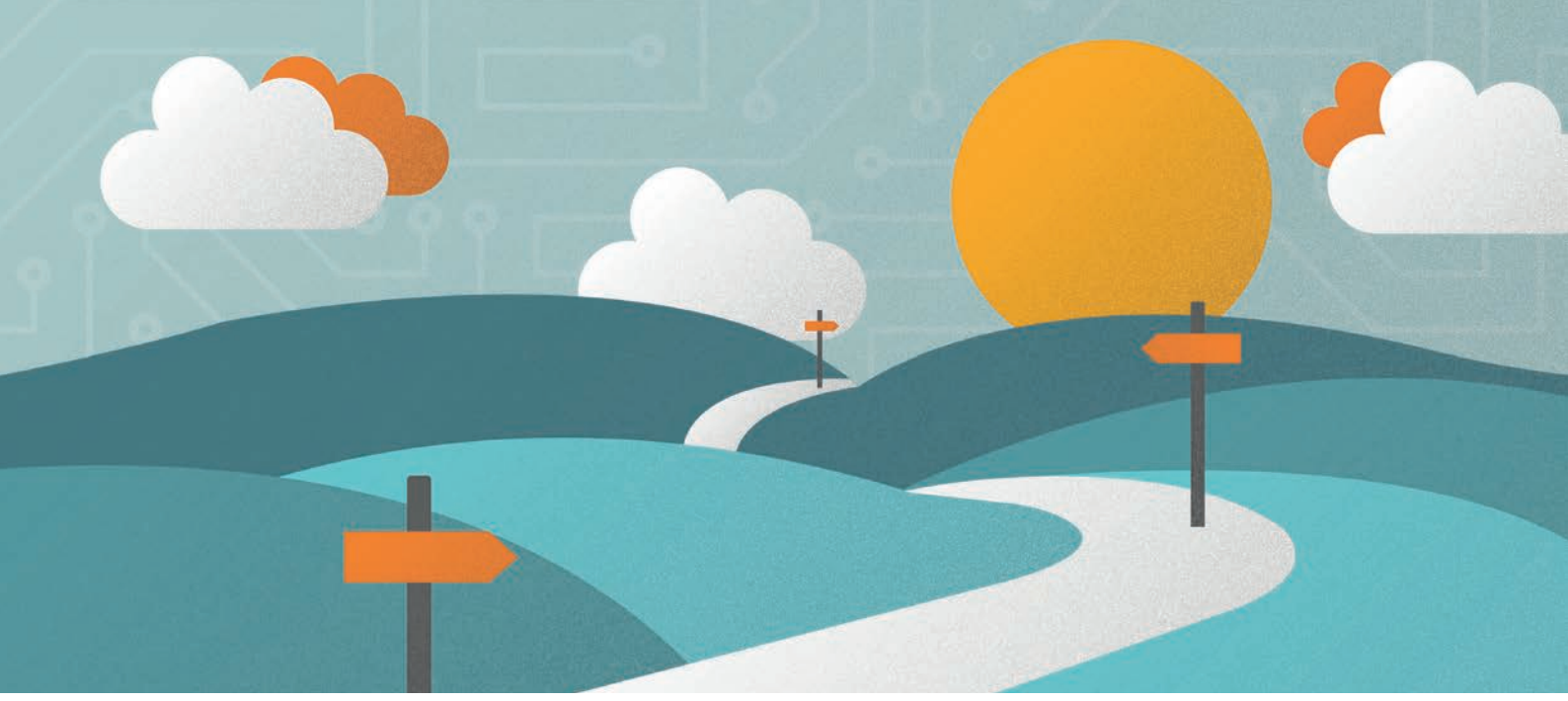
Hill adds, "We saw that MDTs do not have to be run in the meeting room. With this world of remote/hybrid work and social distancing or isolating because of exposures, a pathologist can still work from home and even manage an MDT across multiple sites using video conferencing tools. Pathologists used to have to walk across the carpark with piles of glass slides, which slowed us down and was very inefficient. With the digital tool, we prepare our images before we attend the meeting. It's a faster service, which provides more information to the clinician and, at the end of the day, the patient.

"Pathologists also reported satisfaction [...] to be able to effortlessly look up the previous biopsy of the resection specimen or the previous material belonging to that patient, enabling quick review and comparison. Even reviews from clinicians happen very easily with digital because pathologists just look up the patient details, open the report and review the slides, and then can immediately provide the clinician the information that they're looking for."

The digital approach also brought increased security. "We had to look at our workflows with glass in a whole new way. Having a secure locked-down workflow for digital pathology has made it plainly apparent how vulnerable traditional reporting processes are to human error," said Massey. "Now, with digital, you [know] you are not looking at the wrong slide from the wrong case. You are always looking at the right slide, and you are able to annotate easily."

The halfway point – scaling up to primary diagnosis

Success with MDTs gave the Pathlab team confidence to adopt digital pathology for primary diagnosis. "We transitioned from MDTs – looking at images and sharing images – to actually being able to report those images in a safe environment," says Massey. "To achieve that, it was really



important to have specimen integrity from the very beginning of the process right up until the end where a pathologist is signing out. For that to happen, digital systems and reporting systems must be integrated."

To enable the use of digital for primary reporting, the team created a rigorous quality control (QC) process. "A quality process makes sure that your system is safe," explains Hill. "We created a detailed set of QC steps. For example, we conducted a full audit comparing glass to the digital image, making sure that the interface was safe, everything matched, and that the image quality on the screen was of a higher quality than the glass. It required a lot of steps to finalize, but it has absolutely been worth it." QC actions included establishing parameters for image quality working with 4K panels for workstations, creating protocols for annotation, and developing guidance for accessing a patient's previous images and clinical details.

First and foremost of these is optimizing image quality, asserts Massey. "We scan everything at 40 times, and that gives you equivalent resolution to 40 times on the microscope. Annotation of a high-quality image then becomes second nature. Digital measurements are highly accurate, and the measurement rulers can be left in place so that you are able to show any reviewing pathologist exactly what you are interested in. Anybody who looks at that image (and they can even be looking at it at the same time as you) can see what you've done."

Throughout the implementation process, cost was examined. "When you're putting in a new piece of technology, which on the face of it may look like it doesn't increase any efficiencies, a barrier can be the cost-to-efficiency ratio," noted Hill. However, consider how "it's providing support for the pathologist, providing better service. It's about quality, and it is about the future. So over time, that cost is negated because you're looking at a higher-quality and more efficient service," she advised.

The next horizon: computational pathology and AI

Looking ahead, Massey muses, "The other biggie with digital pathology is returning our images into data; the things you can do with that data are almost limitless. Assisted diagnosis is on its way. It isn't a matter of if, but when. Our plan is to have several years' worth of live image data available to pathologists, perhaps as much as 10 years, so that we are prepared when the time comes."

The application of AI to digital pathology is exciting, holding the promise to not only improve the accuracy and reproducibility of diagnosis but also equip pathologists with new capabilities in prediction of therapy response and patient outcomes. There is significant potential for AI to help pathologists – and the physicians they work with – to provide better patient care.

Hill agrees and adds, "Look at what to start now so that, in the future, you're ready for AI. We're not quite there yet, but to get to that stage, you need the tools now so that you're ready for the next wave of technology which will come. Digital, of course, is critical to that preparation."

When implementing digital pathology, Massey and Hill have straightforward advice for fellow pathologists: begin with a bottom-up review of all processes and then focus on – and codify – your digital workflow. "A secure single-piece workflow is vital to implementation; just buying a scanner is not doing the job," says Hill. "You have to build a secure process around that technology. In our experience, the actual implementation of the digital component of the workflow is the final step of the whole process. It's not the first thing you do."

Ten years into their journey, both doctors are enthusiastic that the future is digital. "For the labs that aren't looking at digital pathology yet, it's a matter of when, not if."

Rob Monroe is a pathologist currently serving as Chief Medical Officer for Leica Biosystems and Chief Scientific Officer, Oncology, for Danaher Diagnostics. Monroe is board certified in cytopathology, anatomic pathology, and clinical pathology and holds a PhD in genetics. He has years of experience in the digital pathology space and frequently consults with pathologists around the world.

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Ring the Changes

Change management considerations for a technological transition

By Helen Bristow

King Whitney Jr., personnel thought leader, said, "Change has a considerable psychological impact on the human mind. To the fearful, it is threatening because it means that things may get worse. To the hopeful, it is encouraging because things may get better. To the confident, it is inspiring because the challenge exists to make things better."

Will 2024 bring big changes to your pathology lab? Perhaps it's the year you'll go fully digital – or introduce an automated sample reception system. Maybe NGS will move in house or you'll select an AI algorithm to assist with some specific task.

With new systems come new processes to develop, new software to learn, and more time spent at computers. And it's fair to say that's not everyone's bag. So, once the project has the green light and the install date is set, how do you bring the laboratory team on board with the change?

We posed this question to Giovanni Lujan, Director of Digital and Computational Pathology at Ohio State University (OSU). Falling very much into the "confident" category of the Whitney quote, he was hired by OSU in 2019 to help manage the transition to a 100 percent digital pathology workflow.

How (or why) did you become a digital pathology expert?

Back in 2016, when people were really beginning to talk about digital pathology, I started going to all the conferences and networking with people in the field. I wanted to know more. But there was no training available and very little literature. However, I picked up that Europe was more advanced in the digital field than the USA – so I set off for Europe!

The trip was self-funded initially, but eventually I received some sponsorship from vendors. I went and visited laboratories in places like the Netherlands and Spain. I learned all I could from them and saw pathologists, with my own eyes, signing out cases digitally. This was unheard of in the States. So I returned home super excited to try to achieve the same, and I was lucky enough to be hired by OSU.

Why do you think the OSU team were early adopters?

Because of the vision of our Chair, Wendy Frankel. She wanted to bring the center forward and was aware of digital pathology, but needed help from someone with the right "technology savvy" to make it happen. And so Anil Parwani joined the team as Vice Chair, bringing around 20 years' experience with digital technologies. With the combination of Frankel's vision and Parwani's dream, OSU's digital laboratory became a reality. In fact, Parwani was the first pathologist to sign out a case digitally in the US in March 2018. After some initial sluggish adoption, Parwani, knowing of my interest and enthusiasm, hired me as "fresh blood" to create some momentum around adoption of new technology.

What sort of resistance did you experience when implementing the change?

The main objections were: I'm very good at what I do, I'm very fast and efficient, and I don't want to go back to being slow. So I didn't see a fear of technology – more a fear of disruption to the workflow.

What were the other obstacles to digital implementation?

The main obstacle was the guidelines. In the labs I visited in Europe, the protocols came from the centralized governments – and pathologists were obliged to follow them. In the States, each institution issues its own guidelines for service provision and won't implement new systems without the approval of the pathologists.

We can enforce a set of guidelines, if they have been approved by the US regulatory bodies as the standard of care. But digital pathology is not yet the standard of care. So the institution can't make the use of digital pathology compulsory – it's the pathologist's choice.

How were the team brought on board with the changes?

We started with training. Everyone in the department received training. And I started meeting with every pathologist individually, so we could have one-

"Immediately we saw a benefit – you don't have to be in a lab to be a pathologist, you can do it from home."

to-one conversations to address any concerns. Next, I started asking people to be less dependent on their glass slides – to try working digitally for a full day, maybe two days, to see what happened.

In my division, nearly everybody jumped on the bandwagon almost immediately. And our colleagues in neuropathology were already using the systems to a large extent, so their expertise was established.

And then, in early 2020, the pandemic hit.

By that time, everybody was trained on the digital systems and we were preparing for a big upscale in digital sessions. The university issued everyone with laptops with VPN incorporated and started to ask doctors to manage their patients from home. We followed the example of radiology, which is a speciality more akin to pathology. The radiologists had all been working digitally for more than 20 years, so they just carried on at home.

Immediately we saw a benefit – you don't have to be in a lab to be a pathologist, you can do it from home or wherever you are. The only problem was the regulations for signing out cases from home – we needed to gain licenses.

The College of American Pathologists and the Digital Pathology Association took on the advocacy with the regulatory bodies – the US Centers for Medicare & Medicaid Services (CMS) and the Clinical Laboratory Improvement Amendments (CLIA). Sure enough, within days, a temporary guideline was issued that allowed signing out from home. The guideline was extended, and recently modified to allow sign-out from home as long as the home address is registered with a CLIA-certified organization.

Once that was in place, we had 100 percent adoption of digital pathology in our group of 60 or so pathologists (around 40 in the main hospital and 20 in other locations). The exceptions are those pathologists who sign out certain subsets of cases that have not been amenable to transition due to technical differences, like bone marrow counts, renal immunofluorescence, and cytopathology slides. We are diligently working with them to bring them up to speed now that the technology is catching up.

Throughout the process, what have you learned about change management?

Information is key. We can't just propose a change and expect the end users to jump on the bandwagon right away. We need to demonstrate that the processes for quality assurance and sign-out are equivalent whether performed digitally or with glass slides.

I keep on top of the literature and keep the pathologists informed of all the research, so they can see it for themselves.

And finally we need to spread the word – share the success story. We had around 12 abstracts accepted from our division by the United States and Canadian Academy of Pathology congress 2024. And we made the covers of two magazines in the last quarter.

What skills do you think are important for change managers?

I think anyone can find a way. Change management can be taught or, in my case, learnt by trial and error. You need to have a clear goal, to accept that people won't be forced to adopt change, and to share the success stories. Sometimes having an expert in change management brought in to assist may be helpful or, at least, the person spearheading the transition should have knowledge of the obstacles and how to overcome them. One of the most important lessons I learned is that you cannot alienate the pathologists, even those who are vocal about their disdain of the new technology. Sometimes those become your best allies down the road.

And you need passion! You need to live completely in that world, to have plenty of experience, and to talk with passion about that experience. If there's no passion, it won't happen soon enough.

"I Learned It from TikTok"

Meet the small-screen social stars who are educating pathologists globally

By Georgia Hulme

When you think about TikTok or Instagram Reels, a particular trend, meme, or dance may come to mind. Creators on these platforms usually put out funny and relatable content for their viewers to enjoy. But who says these videos can't also be educational?

Here, Casem Ballouk (@surgicalpathology on TikTok, @pathsurg on Instagram), a third year pathology resident at Wayne State University School of Medicine, and Kimberly Fiock (@thepathphd on Instagram and TikTok), a staff scientist at the University of Iowa and Director of the Iowa Neuropathology Resource Laboratory, help us understand how short videos can benefit the pathology community. They also discuss their content creation process, the dangers of misinformation, and their top tips on growing a medical-based platform.

How did you build your large followings? And what inspired you to start creating TikToks?

Ballouk: Reaching 554.2k followers on TikTok still feels surreal. It all began innocently enough, when my friends and I started to create light-hearted, silly videos for fun. We would challenge each other to come up with new, entertaining content. It took a turn when, on a whim, I posted a video grossing a specimen in the lab. The reception was astounding. It wasn't just my friends who were interested; the broader TikTok community seemed captivated too. My follower count skyrocketed after that video. Realizing the potential and seeing how engaged the audience was, I decided to lean into this niche. And here we are!

Fiock: I have both a master's degree and a PhD in pathology and have been in the field for the last five years. My research is focused on different neurodegenerative diseases caused by tau, and I use stem cells and human tissue to better understand how one protein causes multiple, distinct diseases. I started my PhD in 2020, during the pandemic, so I wanted to find a community in pathology. At the time, all I could find were MDs posting information for other people in the medical field. Without the same type of training, I struggled to understand what to look for in the images. That's when I decided to make simplified content that used real examples of pathology with a more broken-down approach to help people outside of medicine learn about the field. When Instagram expanded their platform, I started doing reels, which provided a new way to engage people by showing exactly how a given process happens in the lab.

Talk us through your content creation process…

Ballouk: When I'm at the gross bench or in the autopsy suite, I'm always on the lookout for those "Aha!" moments – things that intrigue or teach. If you think, "Hey, this could spark curiosity or offer some insight," it's prime material for a TikTok video. Make sure the video quality is crisp and add some trending audio at a low volume.

Fiock: Before I film anything, I like to write a script of what I want to say. I break it down sentence by sentence, so I can film in smaller chunks. I typically have my principal investigator look over the script to make sure everything looks accurate and is phrased in the best way possible. Once I'm happy, I start filming, which usually takes about an hour for a 60 second video.

I usually film 10–12 individual videos that I cut together in an editing software called InShot (though I probably shoot 50 or so clips including the outtakes). I use my phone on a tripod and memorize each line one at a time, so I can deliver it directly to the camera. Once I have all the videos, I put them into InShot and cut off the excess in the beginning and end of each one from starting and stopping. Then I add captions by copying the pre-written script and include photos and arrows to point out specific features when necessary. Finally, I type up a caption and post it! The whole process can take anywhere from two to six hours, depending on the complexity of the video and whether I have to take photos of the pathology I'm discussing.

Is there anything you have to keep in mind with showing medical content on videos?
Ballouk: Absolutely. Top of the list is ensuring patient confidentiality; no video is worth compromising that trust. I also try to ensure the content is both respectful and educational. It's not about sensationalism, but about informing and enlightening. TikTok can be strict, so avoiding blood or gore is crucial. Not only to keep the platform happy, but to ensure viewers get the value without unnecessary shock. A flag or strike on your account can really hinder the message and outreach, so it's always better to play it safe and smart.

Fiock: I like to use different pictures from multiple cases of the same disease to prevent anyone from identifying a specific person. I also make up all my case histories based on the average or most common symptoms of a disease, so it's not history from a specific case. Of course, I never include identifying personal information about cases and never offer medical advice in my videos. I tend to avoid showing fresh brains because people can be sensitive to blood, but I know there are creators in forensics who may show blood and be okay!

What advantage does short video content offer over YouTube videos or other long-form content?
Ballouk: Short videos, like on TikTok, cater to today's craving for quick dopamine hits. They deliver instant gratification by turning complex topics into bite-sized nuggets. These clips are not only more digestible, but their brevity also boosts shareability – increasing their potential virality. In a world where many seek swift content consumption, short videos offer immediate satisfaction, setting them apart from longer formats on platforms like YouTube.

Fiock: Short videos are attention grabbers! I think people turn to Youtube when they want to learn in-depth about a topic, so Instagram is more to get people's feet wet on a subject. I also like that it's more of a conversation starter. You can't possibly cover all the nuances of something in 60–90 seconds, but it opens the door to discuss something further, be it in the comments or in follow up posts.

Do you find any downsides – misinformation, for example – of TikTok when it comes to pathology and lab medicine?
Ballouk: Certainly. The challenge with brief content is that it can sometimes oversimplify, leading to potential misinformation. It's crucial to be clear and accurate.

Fiock: It can be really challenging to balance the beauty we find in our field with the sadness people experience being connected to disease. I try really hard to not sound too upbeat in videos discussing disease because I know how horrible they are to experience, but you also have to be engaging so people watch the whole video. There's also a ton of negativity on TikTok in particular because anyone can post anything they want and have it go viral, regardless of how truthful it is. I try to avoid getting bogged down in misinformation busting because it is so mentally draining as a creator.

"Giving [people] the tools to understand how we come to a diagnosis or why laboratory testing is so important makes them feel more like a participant in their health journey."

Pathology has struggled to recruit people into the field for a number of years now. How might TikTok be used to help alleviate that and increase interest?
Ballouk: By offering a visual insight into pathology, we can demystify the profession and highlight its significance, attracting potential future pathologists.

Fiock: I think a lot of the struggle with pathology is that it's a very visual field. If we're just describing what we do in words, people might not feel connected to the work and choose not to pursue it. But when we show people what we do through videos, I think it makes it much more exciting. People can watch a video and think, "Wow! I could see myself doing that." I also think people have a misconception that pathology is only about doing autopsies. Showing them different sides to the field helps them realize that there's room for everyone in many different capacities.

How does TikTok/Instagram allow you to reach new audiences and increase awareness of the field?
Ballouk: TikTok's vast user base gives us a diverse viewership. Each post can

"Social media is a huge networking opportunity. My career has been exponentially impacted by it."

educate a segment of the public, guide a student, or even clarify a concept for a patient.

Fiock: I think the algorithm on those platforms can work in your favor in that it's constantly pushing your content to random people who may not otherwise stumble upon it! So, even if someone has never heard the word pathology before, they could still find your videos without looking for them. I also think people are hungry for knowledge. When patients are first diagnosed, many of them turn to the internet to learn. If we can be a source of information for them, then that's incredibly special. People want to feel empowered to make decisions about their health, so giving them the tools to understand how we come to a diagnosis or why laboratory testing is so important makes them feel more like a participant in their health journey.

Would you recommend other pathologists to join TikTok or Instagram? How can it help their work and career?

Ballouk: The platform provides an opportunity to network with peers globally and to share and gain knowledge.

Fiock: I would definitely recommend other pathologists try out social media, even if it's just to see what other people in pathology are doing. Social media is a huge networking opportunity. My career has been exponentially impacted by networking, and it all occurred because people found my account on Instagram and loved what I do. It's also very satisfying to make a post and have someone comment that they learned something new. There's no going backwards with social media. You have to get smart about using it in your favor because that's where people are going to get information from.

In your experience, what type of pathology content gets the most attention on TikTok and Instagram?

Ballouk: Videos showcasing gross content, particularly those featuring cancers, truly captivate the audience. Many people may have come across radiologic images, but the gross visualizations remain a hidden gem. The real allure of pathology is in those behind-the-scenes moments: how we process specimens, orient them, apply paint, and so forth. These intricacies – which are often overlooked – drive significant engagement on the platform. It's the perfect blend of visual appeal and educational depth.

Fiock: Posts or videos that explain what people should be looking for tend to perform the best. Posting a picture that simply says "this is a tumor" isn't going to get engagement from people outside the field. But posting a picture of a tumor with arrows pointing out different features and descriptive words that help explain why those features are important will get people to stop. Also, adding in your own personality and creativity will help! Whether that be through pathology art, food that looks like pathology, memes, TikTok dances, and so on. People love relatable content, so finding ways to make pathology more relatable helps!

What are your TikTok and Instagram top tips? Any advice on how to gain traction and reach more people on the platform as a pathologist or medical professional?

Ballouk: Authenticity is paramount; always stay genuine and true to your expertise. Regularly posting content is crucial for maintaining a visible presence. Engaging actively with your followers can be transformative – their feedback can significantly influence the direction of your content. Feel free to adapt from my templates as they might provide a helpful foundation. Though credentials are important, it's essential to deliver content that dives straight into value. Research suggests viewers decide within 0.6 seconds whether to continue watching or swipe away. Consider incorporating trending music to further engage your audience. It's beneficial to limit external influences, especially when starting. Concerns about what friends, family, or coworkers might think can stifle creativity. Lastly, resilience is a crucial trait to have in this journey. Challenges will arise, but persistence and remembering your initial motivations can help you navigate them.

Fiock: Keep with it and keep it simple. You're probably going to only get a few likes in the beginning, but as you continue to post, people will follow! It takes a long time to build a brand, especially as the algorithms constantly change. Also, remember to post content that speaks to you. Avoid getting bogged down in the posts or accounts that emphasize supposed ways of making content to get big. Do what feels authentic to you. Your passion will come through and engagement will follow suit. Finally, try not to focus on the numbers. It's really easy to feel like you're not good enough when you judge your account by the number of followers you have or the number of likes on your posts. The people who want to follow you will, and the ones that don't won't. That's okay.

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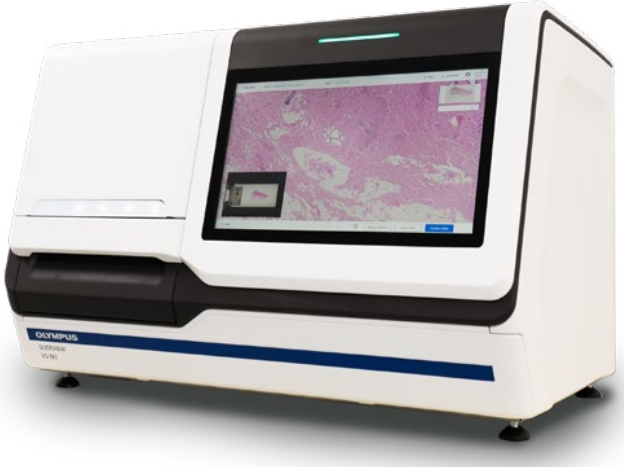

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Life Balance

Sitting Down With… Kamran Mirza,
Professor of Pathology and Director
of the Division of Education Programs,
Michigan Medicine, University of Michigan,
Ann Arbor, Michigan, United States

Could you describe a typical day – and how you manage being involved in so many different projects?

If I'm on clinical service, I will orient my day around the clinical schedule, looking at all the cases, triaging them, and coordinating the different ancillary studies. Alongside that I'll be working with my fellows, residents, and trainees at the microscope and delivering their patient-centric education.

The rest of the day might be a mixture of meetings and mentorship, checking in on the clinical service and working on lectures and presentations.

That's the key – that I really love what I do. It's what keeps me going, if the long list of tasks feels overwhelming.

Going back to the beginning – what was it that led you into pathology?

I wish I could tell you I had an epiphany, but I enjoyed all the disciplines in medical school. I went through different rotations thinking, "That's it, I'll be a psychiatrist … I'll be an obstetrician … I'll be a cardiologist …"

Ultimately, I saw that every subspeciality of medicine is represented in pathology. I had an innate curiosity about diagnosis of cancer or benign tissue – and about the beauty of the human body on a molecular level. Unraveling how all those pathways interact to create either diseased or normal tissue fascinates me.

You are one of the most popular pathologists on social media. How did that happen, and did you anticipate that it would become so important in your career?

I'm an immigrant to the United States; my family is in Pakistan. Initially, I only used social media to stay connected with my relatives. Then, in 2013, I did a fellowship in medical education research at the University of Chicago, and my course directors all spoke about the importance of harnessing the power of social media in our practice.

I immediately joined X (formerly Twitter), but I was unsure what to do or how it would actually help. Time passed and, in 2017, I was recognized as one of the rising stars by the American Society for Clinical Pathology. As a rising star, I was required to do some pathology advocacy on social media. I could see that, since I started on X, there had been a huge increase in the number of pathologists on the platform. Jared Gardner, Sara Jiang, all these social media superstars had established themselves, and I reached out and collaborated with them. They are very close friends now.

It took off once I saw that I had the ability to extend my educational outreach and provide access to education resources. I try to harness my social media following to educate people about pathology. And this is broad: it could be about mentoring, making new connections, collaborating with The Pathologist, or creating the PathElective website.

Could you tell us more about the PathElective project?

When the pandemic hit, the pathology elective rotations in most institutions shut down, because they relied on in-person teaching. I recognized this as a huge problem and decided to bring a sort of social media and web-based pathology elective to the students.

I partnered with one of my medical students, Cullen Lilly, now a pathology resident at UCLA, and we developed a free modular website, with anatomic and clinical pathology content. It's an honor system program, including post-course assessments.

People use it as part of their early medical school education, as well as for formal education within departments. We are so excited that it took on the energy that it did.

How do you manage to achieve a good work–life balance?

Because I love what I do, I think of it more as "life balance." I have a life at work and a life at home and I don't mind mixing them up a bit. For example, today I will leave a bit early to pick up the kids from school. Similarly, on weekends I will be with my family, but I might complete a work task.

Whereas things like negative attitudes or situations that I can't really fix can drain my energy, other things – like my family, my lectures, my courses, and social media – all give me energy.

Who inspires you?

Along with my social media mentors, I'm also inspired by my hematology colleagues (and what we can achieve together as a team) – and by all those colleagues who stay in touch with newer technologies to keep moving the needle forward for health care and for patients, research-wise.

In general, if you are a positive-spirited person who is putting out their best side into the world, it's very inspiring to me.

What advice would you give to someone starting out on their pathology career?

Firstly, I would say that it's an incredible field and you have chosen wisely! Obviously, your first responsibility is to your patients, so you will need an excellent knowledge base to do a great job in diagnoses. But there is also an indirect responsibility to advocate for pathology and laboratory medicine in the spirit of best patient care.

I think that embracing change, unlearning what you think you knew about pathology and relearning it over time, is the best way to grow. I wish you the best of luck in your pathology journey.

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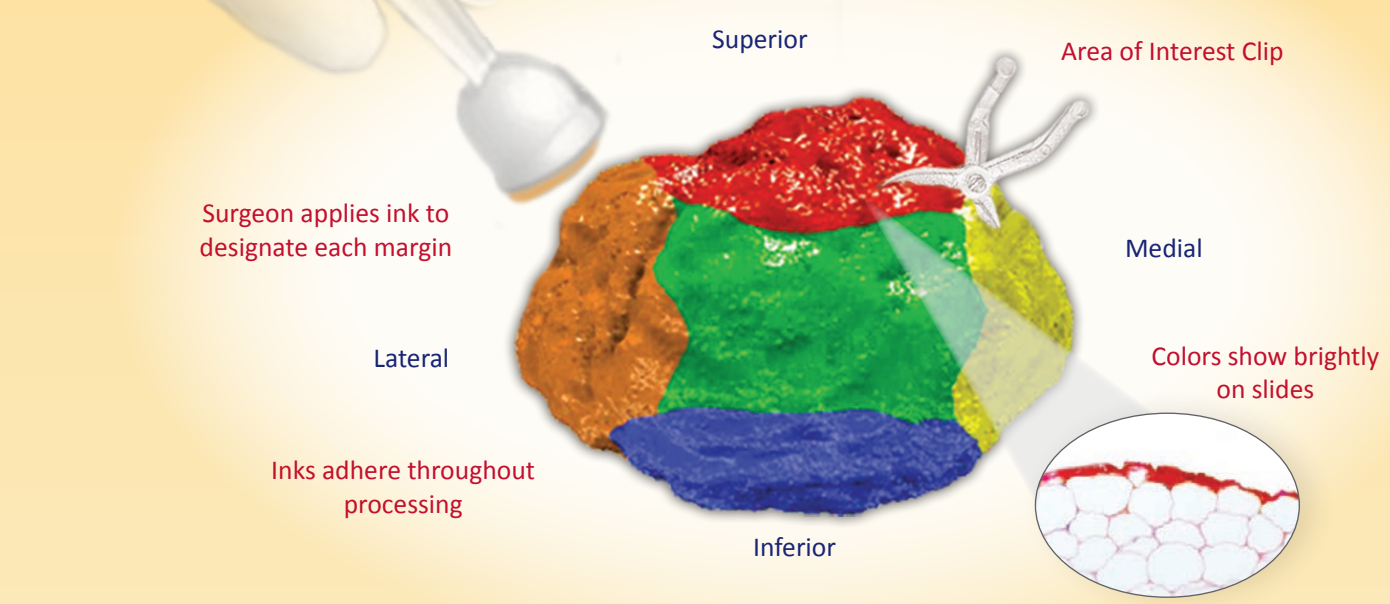

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