JULY / AUGUST 2023 # 91

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The Power List 2023

The Pathologist Storybook – tales of 25 laboratory professionals, told in their own words

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Celebrating Diversity in Pathology

The Pathologist Power List 2023 shines a spotlight on inspirational stories from the global laboratory medicine community

Welcome to The Pathologist Power List 2023! Following our annual tradition of honoring exceptional individuals who embody the spirit of excellence and dedication in the field of pathology, this year's List is nothing short of extraordinary.

Pathology is often referred to as "the hidden science," with pathologists and laboratory medicine professionals working tirelessly behind the scenes to analyze samples, interpret data and deliver accurate diagnoses – all while contributing to the advancement of medical research. As ever, the Power List takes a moment to acknowledge and celebrate you – the unsung heroes, who underpin healthcare.

Diversity is the hallmark of progress, and this year's Power List is a reflection of the tapestry of talent, featuring 25 remarkable individuals from all corners of the world. From thriving cities to remote villages, the stories told within this year's List present unique perspectives, cultural insights, and solutions to all kinds of challenges.

Though academic achievements and awards often define professional success, the 2023 Power List delves deeper, uncovering the driving forces behind each pathologist's dedication and passion. From those who championed healthcare accessibility in underserved regions to those who broke gender barriers in traditionally male-dominated societies, the Power Listers of 2023 are true trailblazers, showing the strength of character needed to overcome hurdles and drive positive change.

Our Storybook edition of the Power List allows us to throw a spotlight on a number of themes: resilience in the face of diversity, inventiveness when resources are tight, compassion that transcends borders, and a passion for advancing medical knowledge. Meanwhile, the personal narratives humanize the profession and remind us of the profound impact that pathologists and laboratory medicine professionals have on patient's lives.

And so, The Pathologist proudly presents the Power List 2023: Storybook Edition – tales of individuals who have shaped the medicine landscape and touched countless lives in doing so. May their journeys – and stories – be an inspiration for all.

Bibiana Campos Seijo
Senior Editor

Upon diagnosis of NSCLC,

The time for testing is NOW

Molecular testing in resectable and advanced/metastatic NSCLC can help identify the oncogenic driver at the earliest opportunity.[1,2]

Work with your multidisciplinary team to establish a standardized testing protocol to help optimize treatment for patients.[3,4]

Discover how timely, complete testing **at diagnosis** may inform critical treatment decisions[2] at **TestNSCLCNow.com**

NCCN, National Comprehensive Cancer Network® (NCCN); NSCLC, non-small cell lung cancer.

References: 1. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Non-Small Cell Lung Cancer V.3.2023. © National Comprehensive Cancer Network, Inc. 2023. All rights reserved. Accessed April 19, 2023. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way. **2.** Mitchell CL, Zhang AL, Bruno DS, Almeida FA. *Diagnostics (Basel)*. 2023;13(6):1117. **3.** Aggarwal C, Bubendorf L, Cooper WA, et al. *Lung Cancer*. 2021;162:42-53. **4.** Gregg JP, Li T, Yoneda KY. *Transl Lung Cancer Res*. 2019;8(3):286-301.

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Contents

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Credit: Image sourced from Unsplash.com

Blood on the Brain

Proteins that slip into the brain through blood are responsible for reversing immune cell behavior

Microglia are the first line of immune defense in the central nervous system, particularly in the brain. With roughly 10–15 percent of brain cells being microglia (1), researchers were keen to establish how these cells sometimes begin to show toxicity and start to work against our body's immune system.

A new study published in Nature has established that some of this toxic transformation is spurred on by blood entering the brain, which activates genes linked with the development of diseases in the brain and central nervous system (2).

"Epidemiological evidence shows that blood leaks in the brain correlate with early disease onset and worse prognosis in neurological diseases," says Katerina Akassoglou, a co-author on the paper. "I was intrigued by the gap in knowledge of whether blood proteins are drivers of pathogenic processes in the brain that can instigate diseases like multiple sclerosis or Alzheimer's disease."

The study showed that specific proteins that enter the brain through a disruption to the normal blood–brain barrier are able to hijack receptors in the microglia to elicit toxic effects on neurons. "We found that the blood protein fibrinogen – which normally aids blood clotting – is responsible for turning on harmful genes in microglia."

One interesting finding, according to Akassoglou, was the specificity that the blood proteins had on influencing the pathogenesis of brain disease – as well as the sheer number of responses that blood proteins can elicit in microglia. "I was surprised by the large number of shared neurotoxic gene pathways between multiple sclerosis and Alzheimer's disease," she says. "This finding could be important for developing therapies to target neurotoxic immune populations across neurodegenerative diseases."

The findings have implications beyond therapies, says Akassoglou. "[They] can also support the development of fluid and imaging biomarkers for neurological diseases. Blood leaks in the brain are early events that precede brain inflammation, and they correlate with worse prognosis for neurological diseases… These proteins can be further studied for their potential as biomarkers detected in body fluids or as targets for developing new imaging probes."

References

1. *SE Dos Santos et al., J Neurosci, 10, 4622 (2020). PMID: 32253358.*
2. *AS Mendiola et al., Nat Immunol (2023). PMID: 37291385.*

INFOGRAPHIC

The Pathologist Power List 2023 – in Numbers

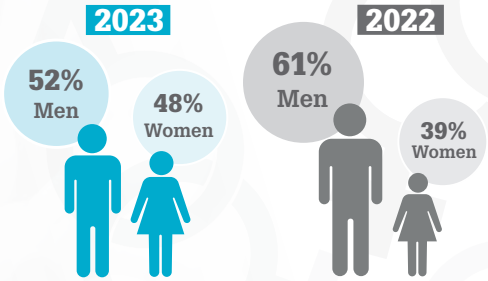
A breakdown of who, where, and how many times of this year's Power Listers!

Overview of nominations

240
NOMINATIONS

25
POWER LISTERS

Finalists by gender



RESEARCH ROUNDUP

From elephant anti-cancer genes to epigenetic drivers of CRC metastasis, we bring you the latest updates

Demystifying MS

A genome-wide association study has identified rs10191329 – located between the genes *DYSF* and *ZNF638* – as a risk allele associated with multiple sclerosis severity. Researchers found that individuals that inherit this variant from both parents have a high chance of needing a walking aid 3.7 years before non-carriers (1).

Flipping the script

A new study has uncovered 16 new risk loci associated with immunoglobulin A nephropathy (IgAN). The results showed that the genetic regulation of IgA production is the key pathogenic pathway in IgAN. This finding confirmed a previous hypothesis that IgAN actually starts outside of the kidney; researchers hope this new information will help contribute to new treatments for the disease (2).

Clearing the path

How does Optineurin (Opt) – an autophagy receptor – remove damaged mitochondria from the brain? Well, the long-standing question has finally been answered by researchers at the Walter and Eliza Hall Institute. The team discovered that Opt uses kinase TBK1 to initiate PINK1/Parkin mitophagy, revealing an unconventional pathway of selective autophagy (3).

CRC signature

Diagnosing colorectal cancer (CRC) before it metastasizes is crucial for increasing a patient's chance of survival. Now, after performing a whole genome-scale DNA methylation and full transcriptome analyses of primary colon tumors and liver metastases from CRC patients, researchers have discovered a new subset of loci that could be epigenetic drivers of CRC metastasis – a potential sign that cancer cells use specific methylation patterns to become more aggressive (4).

Don't drop the balls

Elephants rarely get cancer. Why? A study has hypothesized that excessive copies of the tumor suppressor gene, *TP53*, is actually a result of protecting their temperature-sensitive sperm. *TP53* is an active participant in germline cell division, and an elephant's testicles do not descend because, at high temperatures, the possibility of DNA mutation is increased (5).

See references online at: tp.txp.to/0823/roundup

Credit: Image sourced from Pexels.com

Bat News: Pandemic Potential

Wild bats in China are disease reservoirs

Researchers have analyzed individual bats and established potential candidates for a future pandemic (1). The study focused on Yunnan, China, an area known for its large pool of wild bat species and recorded viruses with zoonotic potential. The team discovered a case of recombinant coronavirus in a bat that was a mixture of a SARS-CoV-1-like and SARS-CoV-2-like bat virus – meaning they naturally exchanged genes within the bat population.

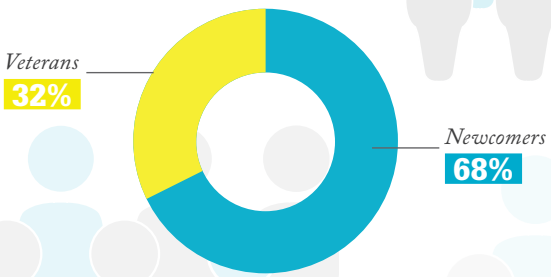
Strikingly, the unique recombinant coronavirus showed the genetic traits required to spread to humans. "This novel recombinant bat virus had a receptor binding domain that was very closely related to that found in SARS-CoV-2 – as close as any bat virus described to date," co-author Edward C. Holmes explained, "[It was] able to bind to the key receptor used by coronaviruses to infect human cells… So, bat viruses exist in nature with the genetic traits necessary to cause disease outbreaks in humans."

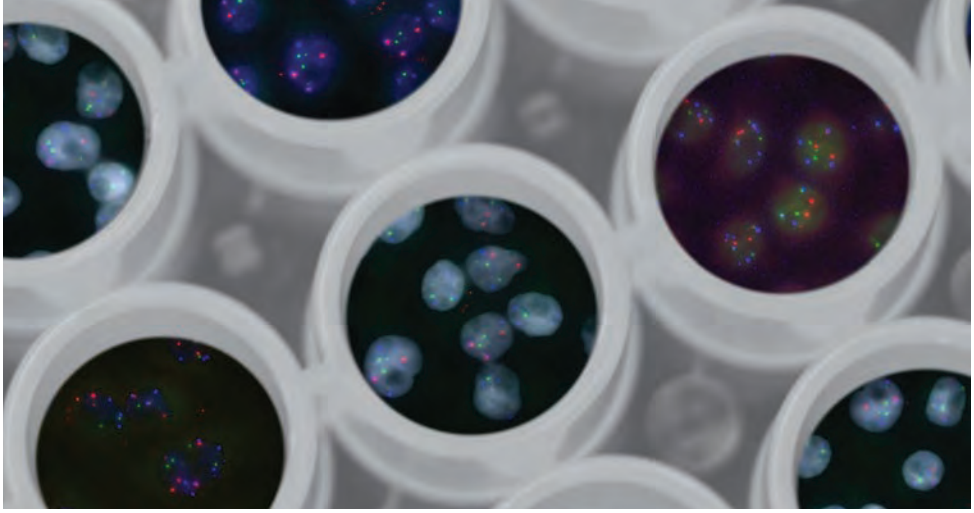
See references online at: tp.txp.to/0823/bat-news

Finalists by countries

US 11
UK 6
France 2
Czech Republic 1
India 1
Singapore 1
South Africa 1
Pakistan 1
Philippines 1

Who is new to the Power List?





Credit: National Cancer Institute / Unsplash.com

A Rare Resolve

How whole genome sequencing combined with multiomics provides a more rapid rare disease diagnosis

We chatted with Zornitza Stark, Clinical Research Fellow at Australian Genomics, to find out more about the The Acute Care Genomics program – a study that integrates whole genome sequencing (WGS) with multiomics to improve diagnostic outcomes for children and babies with rare diseases (1).

How can WGS and multiomics work together to provide the best outcomes?

WGS is well suited to ultra-rapid testing because of its ability to assess multiple variant types in a single test. WGS removes the need to perform genetic tests, such as chromosomal microarray or mitochondrial DNA testing, sequentially. However, it also generates vast amounts of data, and our sequencing ability currently still outstrips our ability to accurately detect and interpret many genetic variants. Integration with multiomic approaches, such as transcriptome sequencing and proteomics, improves diagnostic outcomes by clarifying the functional consequences of DNA variants. A quick diagnosis obviates the need for expensive and frequently invasive tests, relieves uncertainty, and enables access to appropriate supports.

Could you summarize the findings of your research?

The Acute Care Genomics program provided ultra-rapid WGS to 290 critically ill babies and children with rare diseases over a period of two years. Over half of our patients were younger than one month and presented a wide range of clinical issues, including seizures and unexplained organ failure. All WGS results were delivered in under five days, with an average time to result of 2.9 days. The diagnostic yield of clinically accredited WGS was 47 percent. Rapidly incorporating additional bioinformatic analyses, transcriptome sequencing, and functional validation of variants of uncertain significance increased the diagnostic yield to 54 percent. Timely diagnosis had a major impact on clinical care and informed precision treatments, surgical and transplant decisions, and palliation in 60 percent of those diagnosed.

Will the integration of genomic, transcriptomic, and proteomic data become standard practice in clinical settings?

We need to integrate these approaches into standard laboratory practice to fully capitalize on the diagnostic potential of genomic sequencing. The transition to diagnostic practice will require appropriate funding and assay validation but will also ensure reproducibility and timeliness of results.

Reference

1. *S Lunke et al., Nat Med, [Online ahead of print] (2023). PMID: 37291213*

Read the full interview online: tp.txp.to/0823/rare-resolve

Sugar, AR's Goin Down

Intestinal sialic acid is crucial for bacteria effectiveness in the gut

A new paper has established how gut bacteria that fuels antibiotic resistance (AR) thrives in our intestines (1). The study focused on Citrobacter rodentium – a pathogen unique to mice – that displays similar behavior to human E. coli. The team were able to identify sialic acid, a sugar derived from mucus in the intestine, as a key factor in bacterial gut infection. "This provides a crucial foundation for our ongoing efforts to discover ways to inhibit the ability of these pathogens to sense and access this sugar, as well as identify good bacteria (probiotics) that can outcompete the pathogenic bacteria by outcompeting them for these sugars," says Hongbing Yu, University of British Columbia research associate and co-author. By removing Citrobacter rodentium's ability to use sialic acid, the team was able to worsen the bacteria's overall ability to infect – including stymying its growth and lessening its ability to surpass our gut's defense mechanisms.

Reference

1. *Q Liang et al., "Sialic acid plays a pivotal role in licensing Citrobacter rodentium's transition from the intestinal lumen to a mucosal adherent niche," Proc Natl Acad Sci, 120, e2301115120. (2023).*

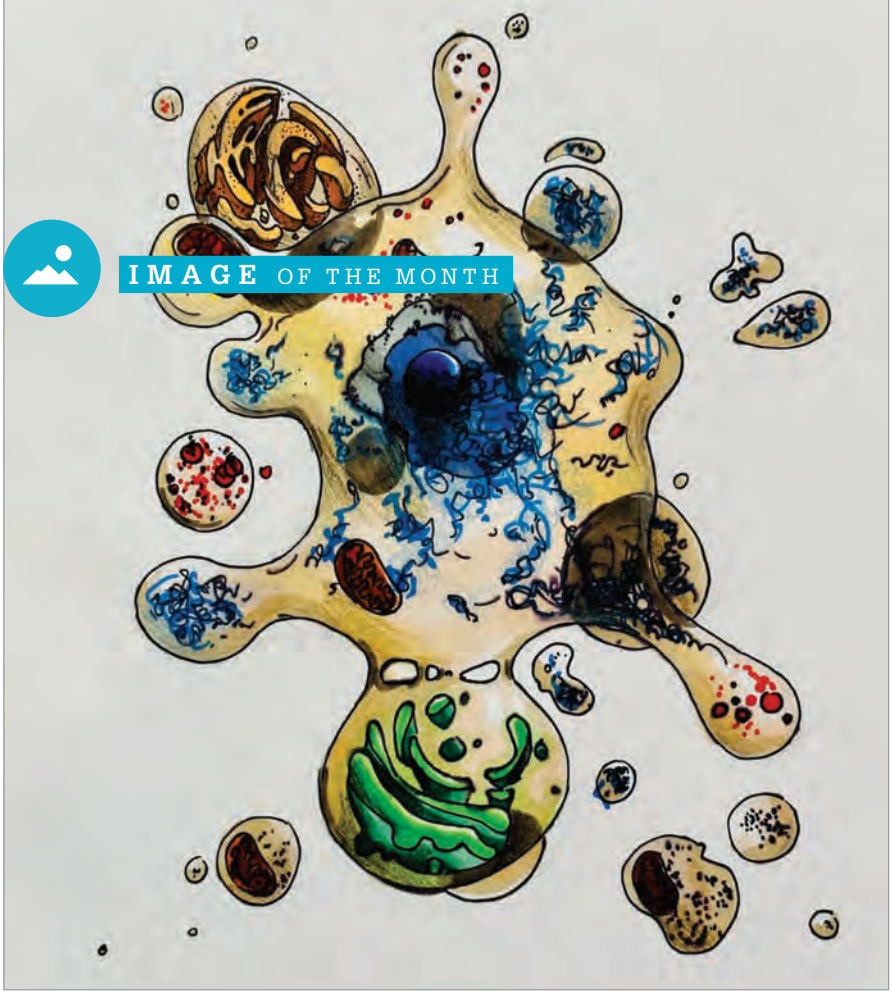


IMAGE OF THE MONTH

Beautiful Biochem

An artistic impression of cellular apoptosis

This month's image was illustrated by 15-year-old Emma from Salt Lake City, Utah, USA.

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

QUOTE of the month

Amid high-priority efforts to eliminate hepatitis as a major public health threat, diagnostics must play a crucial role. With the boon of additional molecular testing capacity built during the pandemic, many clinical laboratories now have the chance to scale up their hepatitis screening to contribute to these efforts – a rare and hard-won opportunity that could have significant benefits for global health.

Erica Frew is Product Manager at Asuragen, a Bio-Techne brand, where she specializes in molecular controls for clinical tests.

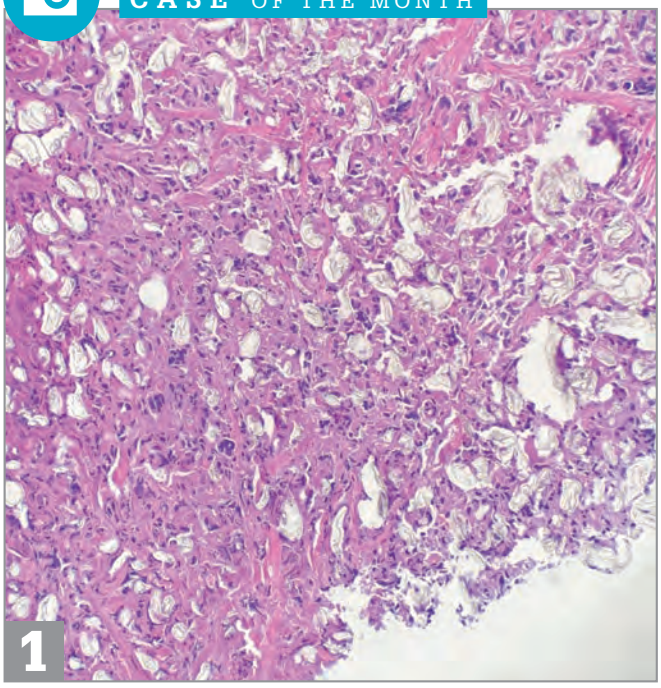
Lead by the Heart

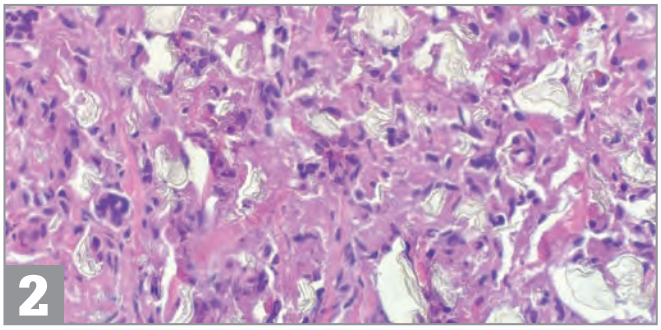
How exposure to contaminant metals increases the risk of cardiovascular disease

The American Heart Association has confirmed a close link between cardiovascular disease (CVD) and metal exposure – a factor that is hard to regulate and harder to avoid (1). "Work by us and others has found that contaminant metals – in particular lead, cadmium, and arsenic – are associated with increased risk of CVD across populations globally," says Ana Navas-Acien, Professor at the Department of Environmental Health Sciences, Columbia University. The paper focused on the clinical and public health implications of exposure and how particular sociodemographic factors increase CVD risk. US communities of lower socioeconomic status and communities of color are more affected by metal contaminants in the air and water. Exposure is greater for those living near industrial plants or in places where environmental complaints are not adequately addressed. The study recommends rigorous government and public health intervention including new medical treatments that eliminate metals or counteract toxicity of the heart.

See reference online at: tp.txp.to/0823/lead-by-heart

CASE OF THE MONTH





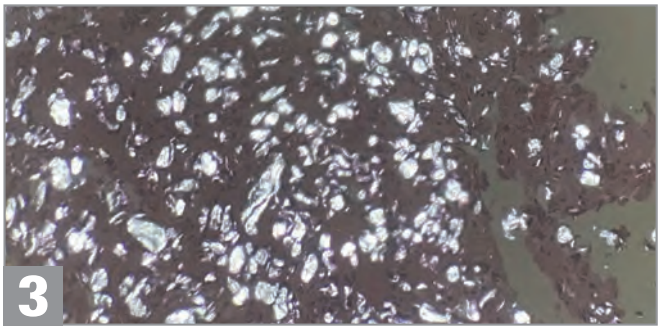


Figure 1. 10x, crystalloid structures with associated granulomatous inflammation and giant cells, Figure 2. 20x, crystalloid structures with associated granulomatous inflammation and giant cells, Figure 3. 20x, crystalloid structures under polarized light

A 62-year-old man undergoes biopsy of a vocal fold nodule during workup for dysphonia.

What might be discovered upon review of the patient's history?

a) An 80-pack-year smoking history
b) Distant motor vehicle accident
c) History of multiple myeloma
d) Treatment for dysphonia a decade prior to biopsy

Answer to last issue's Case of the Month…

b) Warty dyskeratoma

Histopathologic evaluation reveals a cup-shaped squamous proliferation with prominent acanthosis, dyskeratosis, and focal papillary structure formation. These findings are most consistent with a warty dyskeratoma. Squamous cell carcinoma and actinic keratosis can both demonstrate dramatic acantholysis, mimicking this lesion. However, warty dyskeratoma shows classic cup-shaped morphology and lacks the significant cytologic atypia of squamous cell carcinoma or actinic keratosis. Darier disease is a skin disorder that presents as multiple hyperkeratotic papules. Microscopic examination of a Darier disease papule will show acantholysis and dyskeratosis, histologically similar to warty dyskeratoma, but with an overall flat (not endophytic) architecture. Darier disease may also show mutations in ATP2A2, distinguishing it from warty dyskeratoma and another histologic mimic, Grover disease.

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

To register your guess, please go to http://tp.txp.to/0823/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.

Better Science, Better Health – for All

An interview with Yves Dubaquie

What is Revvity's purpose?

Our purpose is to expand the boundaries of human potential through science. We achieve this bold mission by being a visionary partner that develops technologies and solutions across disease pathways to help solve the world's greatest health challenges.

Please explain Revvity's origin?

The name "Revvity" represents our continued commitment to revolutionizing next generation breakthroughs. Revvity is the result of a change in our corporate strategy to become a much more streamlined and focused company in life sciences and diagnostics. This focus – when combined with our collaborative R&D efforts across the company – allows for rapid and increased innovation. We have a collection of highly innovative technology platforms that can be deployed in research and regulated diagnostics.

How does Revvity aim to combat the many challenges facing public health?

Diagnostics and therapeutics need to work together to improve human health. We are focused on supporting scientists and clinicians with solutions that help detect disease and predisposition to disease as early as possible. Genomics and multiomics have become more established in pharmaceutical and academic research – and we are committed to providing specific, high value tools that can bring this new science to life. Further, our close connections with different public health entities allow us to rapidly address new public health threats and form cross functional teams to develop diagnostic solutions.

What are the main trends in clinical technology?

In oncology, for instance, liquid biopsy remains an important technology for detecting cancer types. In infectious diseases, syndromic testing is important because many infectious agents result in overlapping symptoms that often complicate diagnosis. Syndromic testing circumvents complications by testing for a broader array of pathogens associated with different symptoms. From a technological perspective, next generation sequencing (NGS) has become mainstream. There is a great deal of discussion around NGS panels to look at specific genes or a particular number of genes.

How does Revvity plan to improve access to testing in resource-limited settings?

We should expect newborn screening (NBS) programs around the world to not only become more accessible and comprehensive, but also more accurate in diagnosing babies with rare diseases and inherited disorders. For instance, in Sub Saharan Africa, Ghana Health Services now recognize NBS as a health priority. Today, only 4 percent of newborns are screened for sickle cell disease. But there is a global goal to increase this number to 50 percent by 2030. These bold commitments drive our continued expansion and demonstrate how we impact these resource limited settings. Right now, NGS is a second-tier test, but Revvity is trying to apply NGS panels and whole genome sequencing more efficiently to detect rare diseases.

How do you aim to tackle lab efficiency?

A key issue in today's laboratories is personnel shortage. Fortunately, automation has helped combat this challenge. We now have smart, scalable, and reliable automated solutions on the market that enable labs to free up personnel for more sophisticated work and allow the non-expert to operate these instruments. These solutions improve accuracy and throughput, allowing physicians to make time-sensitive clinical decisions.

Could you provide some example workflows?

One great example is the BioQule™ NGS System – our fully automated NGS library preparation instrument. BioQule is designed to eliminate the challenges associated with genomic analysis by providing labs with complete, single source solutions. And, with a push of a button, it delivers libraries ready to load into your sequencer.

Another example: While supporting Egypt's presidential initiatives for health, we developed a new workflow that improves beta thalassemia screening methods and deployed it within four months at the CDC laboratory in Cairo. This equipment is capable of processing 5000 samples a day.

Also, with assay development in the drug discovery process being very time intensive, we have developed an assay development workstation based on our proprietary no wash immunoassay platforms that acts as a single solution for protein-protein interaction (PPI) assay development. This fully integrated solution requires zero programming and removes some risks associated with manual steps.

revvity

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In My View

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

Speaking the Same Language

Consistent communication is key to bridge the knowledge gap between computer scientists, and pathologists

By Aleksandra Zuraw, Veterinary Pathologist at Charles River Laboratories, Fairfield, Pennsylvania, USA, and founder of The Digital Pathology Place

Negative stereotypes about pathologists have long plagued the field. The average person may imagine a pathologist as someone who spends most of their time practicing medicine, alone, in front of a microscope – someone who only communicates through report writing, who chose this specialty because they don't want the challenges that come with treating patients. Now, imagine another stereotypical professional – an introvert sat at their computer, writing code to analyze images. The professional is very good at what they do, but chooses not to be bothered by other people. A computer scientist.

Computational pathology combines pathology with computer science, and more precisely, computer vision. Classically, pathology images are viewed through the eyepiece of a microscope. Now they can be viewed on the computer screen – but more importantly, they can be analyzed with computer algorithms!

There is an opportunity to automate repetitive tasks such as cell counting, and even unlock molecular properties of analyzed tissue without the need to perform expensive tests. To maximize this potential, we need one thing: close collaboration between pathologists and computer scientists. The pathologist needs to learn about image analysis tools and the scoring systems. The computer scientist needs to understand the pathology workflow, terminology, and have a basic understanding of different tissue components.

When collaborating on a computational pathology project, each side takes out their respective notes on computer vision and pathology. However, they soon realize there is a rather big expertise gap – and therefore a communication gap – between the two professions.

I experienced this divide when I started working at a digital pathology company. Brilliant programmers and bioimage analysis scientists were doing their best to develop tissue image analysis algorithms without actually understanding the tissue. When I joined I had to learn a lot about image analysis, the tools, and the strengths and limitations of different methods – including classical and deep learning image analysis approaches and the post-processing of images.

I also realized that to optimize the analysis for a particular output, I had to live with the fact that the algorithm was not always perfect in the irrelevant parts of tissue. (For a pathologist, it is a big visual discordance when tissue image analysis markups do not match the actual tissue – we are trained for years to spot things that don't fit).

I realized that this knowledge gap was not unique to my workplace. My computer vision colleagues also needed to acquire the relevant pathology knowledge to work independently on their projects. We just needed to know enough about each other's fields to figure out the best solution for our tissue image analysis problems. We needed a bridge. This missing bridge was a result of a siloed approach to science, combined with the highly specialized and individual nature of the professions involved in the discipline of computational pathology. So, I created a pathology training program for non-pathologists involved in tissue image analysis.

I founded The Digital Pathology Place in 2019. Fast-forward four years, the platform has expanded to a podcast, a YouTube channel, and a series of courses. My mission is to bridge the gap between pathology and computer science, advance digital pathology, and ultimately improve patient care.

When I started my digital pathology journey, it was a bit of a lonely place, but now, the landscape looks a lot better. The recent Pathology Vision Conference organized by the Digital Pathology Association (DPA) sold out to over 800 people! The vendors are engaging in conversations with users, and the users are initiating new developments in this space. Pathologists are starting their own digital pathology companies and are an integral part of digital pathology startups. The DPA is constantly expanding and there are now five digital pathology podcasts (there were none when I started podcasting in 2019)!

Although collective expertise is growing, there are always more beginners. As a community, it is our responsibility to spread knowledge and bring everyone up to speed. Constant communication between computer scientists and pathologists is key to maintaining a seamless digital pathology workflow.

Embracing Challenges to Create Opportunity

The importance of leadership in pathology and laboratory medicine

By E. Blair Holladay

Pathology's role in diagnosing diseases, advancing medical research, and ensuring high-quality patient care cannot be underscored enough. We are the foundation of healthcare. Leaders – whether they are seasoned professionals or new in practice – are essential in shaping the future of our profession. The infusion of fresh perspectives, innovative thinking, and employment of emerging technologies help pave the way for discovery and advances in care, with the potential to revolutionize the field.

Pathology and medical laboratory science thrive on a continual flow of ideas and perspectives. As new leaders emerge, we have the opportunity to challenge norms, rethink how we solve problems, and empower pathologists and laboratory professionals to explore new territory. This way, we can further connections with patients and other healthcare teams. Integrating these ideas and perspectives into our practices can open doors that lead to enhanced efficiency, accuracy, and collaboration. The universal goal is always to provide the highest-quality care for patients around the world.

To be a leader in pathology and laboratory medicine – especially in today's ever-evolving healthcare landscape – is no easy feat. Expectations are high and varied, and the dedication that leaders must maintain is extensive. Leaders must excel at communicating, foster respect, and promote a culture of collaboration with their own laboratory teams as well as multidisciplinary teams. Effective leaders recognize that investing in the development of their laboratory team is a must. Their efforts must go beyond the lab to attract top talent to the field. Effective leaders provide mentorship to aid professional growth, and advocate for appropriate resources and recognition to build awareness outside of the laboratory. Leaders must champion a culture of continuous improvement, place a significant emphasis on quality assurance, and adhere to rigorous standards. Without development, other healthcare teams could lose faith in the laboratory, which could ultimately take an adverse toll on patient care.

Although leadership within pathology and laboratory medicine is often met with challenges – the fact remains that leaders are essential to the continued success of the laboratory. Our leaders are the ones who share knowledge and ensure a sustainable continuum of growth and innovation in the field. Now is the time to celebrate the leaders within pathology and laboratory medicine, both those who have pioneered before us, and those who are leading us into the future. Their vision, guidance, and commitment are torches we must carry, for ourselves and for our patients.

The Power of Gene Expression Profiling

Using GEP as a tool to evaluate ambiguous melanocytic lesions: perspectives from dermatology and dermatopathology

Gene expression profiling (GEP) is becoming an important tool in cancer diagnosis and prognosis. In melanocytic lesions, GEP can be particularly helpful in differentiating benign from malignant lesions. GEP measures the RNA expression level of targeted genes known to have differential expression in benign versus malignant tissue. A computer-generated algorithm analyzes these expression levels to classify the lesion as likely benign or likely malignant.

The results of GEP, therefore, can aid both in achieving a definitive diagnosis and guiding appropriate patient care in difficult to diagnose melanocytic lesions. Etan Marks, DO, board certified in AP/CP, hematopathology and dermatopathology, affiliated with Skin Pathology Associates, Delray Beach, and Aaron Farberg, MD, double board-certified dermatologist and Mohs surgeon affiliated with Bare Dermatology and with Baylor Scott & White Health, are two specialists who have integrated the Castle Biosciences MyPath Melanoma GEP test into their practices. Here, they share insights on when and how GEP testing should be used, as well as its impacts on collaboration and, ultimately, patient care.

In what situations do you use GEP testing?

Marks: The situations I have found to be most appropriate for GEP testing are when the clinical features are consistent with melanoma, but the histologic features are ambiguous. Maybe there's a little bit of pagetoid spread. Maybe there's simply pleomorphism or rare mitotic figures. Regardless, the definitive criteria for melanoma – which would typically make me confident – are just not there. GEP testing helps to resolve the ambiguity among all of these various factors.

I've created my own algorithm – and I'm sure other people have as well – of when it's appropriate to use GEP testing. The basic principle is this: Only use it when you're going to know what to do with either a negative or a positive result. If you order something, you have to be willing to use the results. It's very similar to an immunohistochemical stain, in that it is a piece of information that will either build or break down your case for whatever diagnosis you are considering.

Farberg: There are many instances where I'll order GEP testing for a melanocytic neoplasm. For example, if I biopsy a lesion that I am highly suspicious of being melanoma, and the pathology is benign, then I'll use GEP testing to resolve the mismatch. Another example is when the diagnosis is ambiguous, such as in the case of a moderately dysplastic nevus, as I would need more clarity on the malignant potential of that type of lesion.

In what ways does GEP testing impact treatment?

Marks: What we're trying to accomplish with GEP testing is the ability to get rid of an ambiguous diagnosis to determine how to treat these lesions in the best possible way. It allows the pathologist to be more definitive – and even provides an opportunity for the pathologist to have a conversation with the clinician – so that the appropriate treatment can be applied.

Farberg: GEP testing provides a more accurate understanding of a melanocytic lesion. I biopsied the lesion because I had a concern for malignant potential. If histopathology does not provide a confident answer, then additional information from GEP is necessary.

It's important for management plans to integrate GEP results, while also considering histopathologic features, laboratory information, and clinical features. The same GEP result could have a different clinical impact for a patient, depending on the specific nature of the testing situation. For example, in a dysplastic nevus with unusual features, a benign GEP result could indicate that the patient may benefit from a narrow reexcision, instead of a wide local excision. In the same clinical scenario, if the GEP result is malignant, the test result may be integrated into the diagnostic evaluation to arrive at a definitive diagnosis of invasive melanoma or melanoma in situ.

Having the most accurate understanding of the malignant potential of a melanocytic neoplasm allows for the best management discussion and more appropriate treatment management decisions. More data allows a collaborative decision-making process between a dermatologist and the patient.

How does GEP testing affect collaboration between dermatologists and dermatopathologists?

Marks: Communication allows you to take into account more of the clinical

CASTLE BIOSCIENCES

FIGURE 2. A summary list of some frequently encountered scenarios by dermatopathologists and dermatologists in which gene expression profiling (GEP) ancilary testing might be most appropriate to aid in the diagnosis of melanocytic lesions.

perspective than just what's on the slide. There's an old school of thought in which the slide is all that should be diagnosed by the dermatopathologist, and the dermatologist should take that into consideration with regard to how to treat patients.

But I learned a more integrated approach, in which you take the clinical perspective into account when you're looking at the slide, which is what the GEP test can encourage in some instances. You can give much more clinically relevant information to your dermatologist, and give more definitive guidance on the malignant potential of the lesion. So it's much more collaborative in that way, and you are taking some of the decision burden off of the dermatologist.

What has been the impact of this increased collaboration?

Marks: I feel that clinical input can be especially valuable with ambiguous lesions. I only see a picture, and sometimes I want to know how worried the dermatologist is about this clinically, or whether they just need me to do as much workup as I can. When you do get this valuable input, it can help you modify how extensive your workup is, which is why I like the collaborative approach.

Farberg: Greater communication between the pathology lab, the dermatology clinic, and patients is the best way to determine treatment strategy for ambiguous melanocytic lesions. With nonphysician providers performing increasing numbers of skin biopsies, particularly in underserved areas where dermatology services are limited, this has become more important than ever.

It is work, and it requires more time and effort. But, this is what is best for our patients. We know that collaborative healthcare leads to improved outcomes. This is no different, and, by working together, we're able to better help our own patients.

How is incorporating GEP testing into your workflow valuable?

Marks: Whereas I used to have more ambiguous diagnoses, GEP has allowed me to be more definitive. For example, in the case of a compound melanocytic proliferation with unusual features that looks atypical and lacks the definitive features of melanoma, I still can't exclude a melanoma. In those situations, I might order NGS testing but, unless it shows certain mutations, the results won't necessarily be conclusive. Now, I'm able to use a GEP test after that – and nine times out of ten it will provide a definitive diagnosis.

Farberg: Incorporating GEP testing into the clinical workflow is important as it increases reliability, and helps avoid mistakes – such as misdiagnosis – or delays in treatment. Similar to a pilot's workflow for takeoff and landing, doctors use similar regimented workflows to avoid mistakes.

Our dermatopathology colleagues are experts, and they are able to accurately diagnose melanocytic neoplasms. However, there are some lesions that are simply difficult to diagnose, and require additional investigation and data to determine the most appropriate treatment for the patient. GEP testing offers additional accurate, objective, and clinically actionable information for these difficult-to-diagnose lesions.

Welcome to The Pathologist Power List 2023, featuring the tales of 25 laboratory professionals – told in their own words

The 2023 iteration of our annual Power List is a veritable pathology anthology – a collection of topical, anatomical, and sometimes comical stories from the lab. After hundreds of submissions, our expert judging panel believed these final 25 tales to be symbolic of the amazing work that goes on day in, day out across the field – spanning multiple topics, subspecialties, and continents.

When brainstorming for a theme for this year's Power List, we wanted to flip the idea on its head somewhat. We wanted to shake things up and get to the heart of the laboratory experience. And who would be better equipped for the task than the people who live and breathe pathology and laboratory medicine every day? And so, we asked for your tales from the lab – the highs, the lows, the unexpected twists. The final result signals that each and every person working in the lab has a unique story to tell.

Whether inspiring or interesting, heart-warming or funny (thank you, Mr Head-Holes), we believe that the Power List 2023: Storybook Edition has something for everyone – while shining a spotlight on the important work that you all do.

ALAN DEACON

Pathology has been a significant part of my career for the past 33 years – ever since I stumbled into biomedical science as a fresh-faced graduate hoping to pay off my student debt. This accidental opportunity sparked a passion and enthusiasm for laboratory medicine which has never left me and has guided my development from trainee to ever more senior and complex roles.

I initially had a keen interest in training and education, but, as my knowledge and experience gained momentum, I became much more involved with service redesign and collaboration. Today, the latter part of my career has been centered on using systemic leadership to effect positive change both within pathology services and the wider health system.

Unfortunately, all good stories have adversity and mine is no exception. I suffered a stroke in 2015 which saw me interact with a variety of diagnostic modalities up close and personal! On reflection, it showed me the important interplay between diagnostics and clinical decision making. When I recovered, it reinforced my commitment to do all that I could to support the services that had made me well again.

I've been the National Pathology Programme Lead in Wales since 2022. I have seen not only the excellent work that pathology services deliver but also the significant challenges they face. Following a critical reevaluation, and with strong remit from the Welsh government, I have worked hard to effect positive change. I absolutely love my current role, as it allows my team to make a significant difference for services on the ground. I am in an incredibly privileged position to lead a program that can influence national policy, as well as strategic decision-making and operational delivery. I believe this tripartite sweet spot is a once-in-a-lifetime role that has tangible effects on pathology.

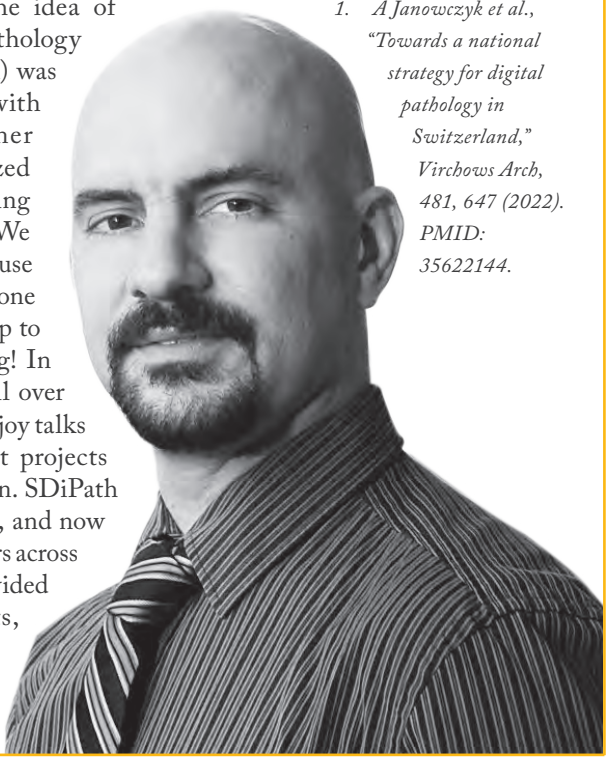
ALEŠ RYŠKA

My path to pathology started by chance. I had gone to convince my pathology teacher to help me with a student project. To my surprise, he suggested I volunteer in his department performing fine needle aspiration cytology. By then I was planning my medical career in surgery, but I knew that real pathology was quite different from the "Robbins pathology" we were learning. Years later, I have had the privilege of meeting many outstanding diagnosticians and scientists who have helped me navigate through the vast ocean of our field. Recently, I have been fascinated by the change in the status of pathology among other disciplines; we are now a true cornerstone of the diagnostic process and pathologists have a key position at every multidisciplinary team meeting. With so many methods at our disposal, we can touch the roots of most diseases and uncover their mechanisms. And it's not just out of curiosity – though every pathologist is curious (it's our nature!) – it's because our understanding helps patients. However, to be perfectly honest, the latest developments in science evoke somewhat mixed feelings in me.

The concept of personalized medicine is exciting, very promising, and demonstrably effective. Yet, if we take off the rose-tinted glasses and look at medicine from a global perspective, it is questionable how sustainable it is for certain regions of the world. Secondly, the hype around AI in various areas of our lives has raised huge expectations among pathologists. Will we finally get rid of counting mitoses, assessing hormone receptor expression, and even scratching our heads in recognizing unusual lesions? Or should we be more skeptical so as not to overestimate benefits or overlook drawbacks to our field? Will tomorrow's graduates choose pathology if they expect it to be replaced by computers in a few years? I am really curious to see what the future will show us – it is certain to be exciting.

ANDREW JANOWCZYK

One day in 2018, the head of the Bioinformatics Core Facility of the Swiss Institute of Bioinformatics called me into his office. He told me there was another person in Switzerland engaged in digital pathology research and suggested I reach out to her. Sometime later, Inti Zlobec and I met for the first time in the Geneva train station café. We immediately hit it off and discussed digital pathology for hours, and came to realize that there was no established Swiss network for people like us. There were many individuals engaging in digital pathology independently around the country, but there was no mechanism for them to meet, exchange best practices, and network. It was at that moment that the idea of the Swiss Digital Pathology Consortium (SDiPath) was born – and, along with our colleague, Rainer Grobholz, we organized our first society meeting later that year in Bern. We were very nervous because we weren't sure if anyone would actually show up to the inaugural meeting! In the end, folks from all over the country came to enjoy talks and learn about what projects others were engaging in. SDiPath has continued to grow, and now boasts over 170 members across the country, evenly divided between pathologists, researchers, and the exceptional support staff needed to deploy and sustain digital pathology at our various institutions. What amazes me most is that Inti, Rainer, and I don't consider ourselves special. We were just regular folks that asked people if they would like to meet. Somehow that nucleated a vibrant community that is releasing Swiss Digital Pathology Recommendations (under review), as well as Swiss Digital Pathology Research Infrastructure under the leadership of our other colleague, Viktor Koelzer (1). My takeaway is simple: find people that share your interests and take risks. Who knows what great relationships you'll create and what fascinating things you'll learn!



Reference

1. *A Janowczyk et al., "Towards a national strategy for digital pathology in Switzerland," Virchows Arch, 481, 647 (2022). PMID: 35622144.*

ANN M. GRONOWSKI

When I arrived at Washington University in 1993 to train, there wasn't a single female member of faculty in our division. By the time I joined the faculty, there was one other. I felt very much like an underdog. I have had great mentors during my career, but virtually all are male. I really wish there had been more senior, female role-models and mentors. I guess that is why I am passionate about mentoring – young women especially. There is nothing that gives me as much pleasure as watching the success of those I have mentored. I am proud to have played a small role in their achievements. If I had to provide words of advice for young faculty and trainees, I would say: you are smarter than you think you are. Don't be afraid to ask questions and be yourself. Embrace the attributes that come naturally to you. Many women tend to be more empathetic, nurturing, and maternalistic. If that's you, embrace it, don't try to change it. Women can be strong leaders just as they are, they don't need to change.

BARNALI DAS

I grew up in a very small town in India. Sometimes, when growing up in places like my hometown, it can be difficult to envision where you may end up. I am grateful for the many opportunities that opened up to me – everything from features in the national newspapers, three orations and many national and international awards from IFCC, AACC, ACBI, AMBI, and CAP. Accomplishments like the White Knight Award and Custodian of Humanity Award for my work within our COVID-19 taskforce launched me to higher pedestals of self-confidence. It's because of my upbringing that I am passionate about creating the same opportunities for young people entering medicine today. Public outreach and scientific literacy are areas very close to my heart, and so I proudly offer my time as a guide for graduate and postgraduate students in biochemistry, immunology, and chemical pathology across India and Sri Lanka.

Looking back to my childhood years growing up in that small town – back when the internet did not rule the world – I can see the effect that my surroundings had on me. It was my childhood love for reading and the nature around me that slowly metamorphosed into a passion for writing, painting, music, and public speaking – all things that are more relevant to pathology than you might think. Though I am proud of my professional accomplishments, it is important to remember that we are much more than people in lab coats. For me, that means starting and ending every day with meditation and yoga. It brings me calm to know that, though I love my career, there is a whole world out there to be a part of.

CHRISTOPHER ZAHNER

"What do you want to be when you grow up?" Many kids will say, "Doctor!" or "Astronaut!" I'm lucky to say that, over the course of my career, I have become something of a mix of both. Before I entered medicine, I took Mechanical Engineering from the University of Florida in 2005. Fascinated by space, I joined NASA's Spaceflight Operations in Mission Control for the International Space Station, where I played an important role in assisting astronauts to repair critical equipment. I later moved onto pathology, but, during the COVID-19 pandemic – while I was co-inventing a makeshift ventilator – I was approached with a unique opportunity to return to NASA through the IMPACT project. The project is a suite of system engineering tools designed to evaluate risk for human health in spaceflight scenarios – truly a once-in-a-lifetime opportunity. In the world of aerospace medicine, I have the privilege of working among a remarkable community of committed and intelligent individuals. As a clinical pathologist specializing in thrombosis and hemostasis, I was asked to assist in assessing the risk of thrombosis during spaceflight. For much of the last 60 years, it was widely believed that the risk of thrombosis in space was nearly zero. However, my involvement in the IMPACT project and collaboration with NASA revealed a significant shift in this understanding. Evaluating the risk with a sample size of only 11 patients proved to be a tremendous challenge (1). Leveraging my extensive experience in thrombosis, I worked to refine the risk profile. It was a complex endeavor, but our collective expertise and dedication enabled us to make substantial progress that would not have been possible without my clinical pathology experience. Being at the forefront of this important work within the aerospace medicine field has been both exhilarating and immensely fulfilling.

Reference

1. *J Pavela et al., "Surveillance for jugular venous thrombosis in astronauts," Vasc Med, 4, 365 (2022). PMID: 35502899.*

CONSTANTINE E. KANAKIS

Everyone has a story about their journey to medicine – and pathology – and I'm no different! When I was eight years old, I lost my younger brother to a rare histiocytosis. Decades later, enter your humble hematopathology and transfusion medicine graduate trainee. I have taken the memories and moments that informed my path to pathology and turned them into something special.

I make it my priority to place pathology and laboratory medicine into the limelight by pioneering for visibility, awareness, and advocacy. When patients understand that a few simple results come from an innumerable cohort of dedicated healthcare workers, and that their physicians collaborate with brilliant-yet-unseen specialists, they have a chance to play a larger role in their care. Not only do I advocate for patients at large, but for all roles in pathology and laboratory medicine, so we can feel *stronger together.*

As a student, medical laboratory scientist, teacher, advocate, mentor, physician, friend, and even patient – my role in medicine is as complex as the field itself. It continues to evolve and grow parallel to the excitement of illuminating our collective work as pathologists, as specialists, as physicians, and as people. At the end of the day, our role as advocates should be celebrated. We drive the data that makes the healthcare machine work, and our reports directly affect patient outcomes. Our choices affect the dynamics of our own environments – both in our offices and our communities. I strive to make sure that we recognize our talents as leaders in healthcare and advocate to help patients experience the full potential of our service. Everyday I meet more patients and colleagues who are interested in this exciting wave, and I hope you are too!

ELAINE CLOUTMAN-GREEN

It's my first day supporting Infection Prevention and Control (IPC) as a Healthcare Scientist, and I'm standing in front of my new boss – eager and ready to go. She looks at me, stares in fact, then moves her gaze down to my shoes. "You won't be able to run in those," she says and walks away. I look at my lovely heels, specially chosen for their professional look, and say aloud: "Why would I need to run?"

This was only the start of the wild and wonderful world of IPC. Three days in, two nurses headed to an all-day meeting and handed me the bleep. I looked at it, horrified. I panicked, "What do I do if it goes off?" I asked.

"Don't worry," they said. "The doctor is around so just ask for help". They trusted me! With a sigh of relief I watched them depart.

A couple of hours later, the bleep had gone a few times and I'd managed to provide, what I hoped, were the correct answers and advice. I was almost feeling a little cocky. It went off again and I phoned the number – one I hadn't encountered before.

"Hi, it's MRI, we need to bring in a komodo dragon from London Zoo for some imaging tonight, can you liaise with us to plan it and write a risk assessment?" What?! There are no SOPs for doing an MRI on a komodo dragon in the basement of a children's hospital at midnight! There are no papers for this on PubMed!

It was in that moment, as terrifying as it was, that I knew that IPC was where I belonged. In a world where thinking on your feet is an essential skill set, and where bringing science into everyday practice really makes a difference for the patient (or komodo dragon) at the bedspace.

HOLLY SMITH

The Phlebotomy Center came into existence after not one but two near-death experiences. After the birth of my eldest daughter in 2016, I had multiple episodes of sepsis – something that will forever shape my outlook on life. I had my blood taken countless times whilst I was in the hospital, and the procedure fascinated me every time. When I was released from hospital care, I had a tremendous urge to give back to my local community and the people who had saved my life. Although I had no prior knowledge of business management, I researched the profession and saw there was no regulation and no universal training or support for clinicians who perform phlebotomy. This led me to set up a phlebotomy membership body and training center, which became the first ever standalone clinic of its kind in the country that is CQC regulated. We are privileged to offer WHO standard training to individuals and organizations like NHS trusts, medical students, laboratories, nurses, midwives, dentists, doctors, and many more. We were even fortunate enough to be approached to support the national antibody testing program during the COVID-19 pandemic. Today we have the largest database of fully insured, DBS-checked, ready-to-work, and mobile phlebotomy practitioners in the country. Knowing how I first entered this field, it won't surprise you to hear that I promote wellbeing events for life changing illnesses. My time in hospital during 2016 truly changed the course of my life, and it's through my work today that I hope I can return the favor.

IAN A. CREE

Pathology is the study of disease, and I've dedicated my professional life to it. Pathology has no boundaries – it transcends those with other disciplines, as well as national borders. Personally, I've gone from Dundee to Lyon – via London, Portsmouth, and Coventry – and have spent years on the Indian subcontinent describing the transmission of leprosy. For decades, I have worked on personalized treatment for cancer, which was of interest to very few when I started in the 1980s, and it has been wonderful to see it become the standard of care. Early cancer detection and computational pathology are two more areas in which I've been able to work with colleagues across professional and geographical boundaries. There have been many other highlights, but my one failure to date has been retirement – I'm a serial failed retiree. First after a single month in 2015, where I went from my university post back to the NHS to help implement digital reporting, and then to the International Agency for Research on Cancer (IARC) shortly after retiring from my hospital post. The last six years at IARC in Lyon have been great; the fifth edition of the WHO Classification of Tumors is the first truly hierarchical taxonomy of neoplasms; it is having a major impact on individual patient diagnosis around the world and is providing a basis for cancer research. It includes the first classifications of pediatric tumors and of genetic tumor syndromes. There is a lot still to do, and more revisions in the sixth edition are already being planned. I'm immensely grateful to the more than 2000 experts who've been involved. It's been one of the great scientific projects of the decade, and the results speak for themselves. For now, the WHO has a mandatory retirement age, so I'm going to give that another go. We'll see how well I do…

JOANNA ANDREW

I have worked as a biomedical scientist for the entirety of my career. I first heard of the Institute of Biomedical Science (IBMS) while working as a placement student in the Biochemistry department at St Albans City Hospital. I discovered the "gazette" and liked the idea of joining a magazine and a club.

I quickly started to take an active role in the IBMS. I first became an assessor for the registration portfolio and then for the specialist portfolio. I joined the IBMS Yorkshire Region and supported CPD events. I spent several years on the Clinical Chemistry specialist advisory panel, which included organizing the program for congress. In 2017, I was elected to council as the member for the Yorkshire region and this year I have been elected as President Elect – a huge honor which I will be very proud to fulfill. It will also be the first time there has been consecutive female presidents of the Institute.

After university, I began my career as a Medical Laboratory Assistant before working as Biomedical Scientist in three different hospital laboratories: the Chemical Pathology and Immunology department at Leeds General Infirmary, the Biochemistry department at the Royal County Hospital in Winchester and the biochemistry department at York Hospital.

My main passion is supporting the training and development of our biomedical scientists. The time I spent as training officer for the biochemistry department in York was one of the happiest times of my career. I am an active promoter of apprenticeships to help support the development of our laboratory staff. The opportunity to offer a fully funded Level 6 Healthcare Science apprenticeship has supported recruitment and retention. It has enabled ambitious laboratory support workers with fewer opportunities to study to a degree level. The first graduates from the apprenticeship scheme are now working as fully qualified biomedical scientists in our network.

KAMRAN MIRZA

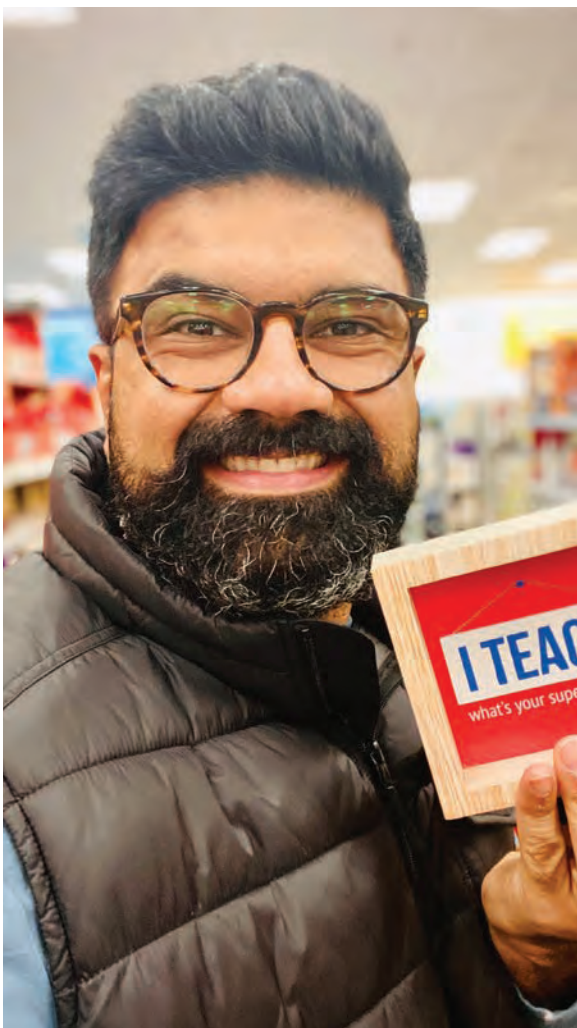
The loss of my grandmother to breast cancer ignited a fire in me – a curiosity about the intricacies of the human body. In medical school, my interests spanned across various subspecialties, but during my time in a pathology lab that I discovered my true calling. The microscope became my portal to a world where diagnosis met discovery – a realm where pathology intertwined with my desire to understand and heal.

As an immigrant American, my journey encountered obstacles, including visa delays and residency contract rescission. However, I persevered. Recognition as an exceptional educator and mentor has been both humbling and surprising. Teaching is my passion, and witnessing the success of those I guide brings me immense joy. I aim to nurture aspiring pathologists and foster a sense of community.

Co-founding www.pathelective.com has been a dream. The platform has become a global beacon of knowledge and provides a space for collaboration and shared insights. With my co-founders, the website is shaping a brighter future for the field of pathology.

Patient-facing pathology has profoundly impacted me and I anticipate the continued growth of this field as we bridge the gap between laboratory analysis and patient care. Collaboration has been essential to my professional growth. PathPod podcast, InsideTheMatch, MatchToPath, HemeReports, and others have allowed me to learn from brilliant minds, expand my knowledge, and contribute to making a positive impact.

I aspire to ensure that every medical student has the opportunity to explore the remarkable field of pathology. I believe in the power of informed decisions and the transformative impact pathology can have on patient care. I vow to make a difference, bring clarity to complex cases, and empower the next generation of pathologists.



KINAN DRAK ALSIBAI

I was born in Syria and studied medicine in Aleppo before specializing in Anatomic and Cytologic Pathology in France. While working, I obtained diplomas in Clinical Cancerology, Renal Pathology and Fetal, and Placental Pathology, and also a PhD degree in Genetics and Molecular Cell Biology.

In 2019, I traveled to the Amazonian territory of French Guiana to work on tropical diseases. I was the only pathologist in the area and studied the pathology of common tropical diseases, such as leishmaniasis, leprosy, histoplasmosis, tuberculosis, HTLV-1 and HPV, and their relation to cancer – accumulating over 50 publications and book chapters. My trajectory disproves the proverb: "A rolling stone gathers no moss." I even ventured into the pathological examination of wild animals to develop One Health perspectives on Amazonian zoonoses.

In June 2022, I became the medical director of the Cancer Registry of French Guiana and piloted the regional roadmap of the fight against cancer. I opened the doors of my department to students and researchers from all horizons, and developed multiple national and international partnerships.

Many boats hug the coast, but I fearlessly steered my boat straight into the uncertainties of the wide Atlantic ocean – from the east coast of the Mediterranean to mainland France and then to French Guiana. Doing not what's easy, but what's important, is an asset in the pursuit of new scientific ideas.

LINDA FILDEY

Over the past thirteen years, I've had the privilege of working with pathologists collaboratively, whether it be project managing our Digital Pathology Center of Excellence with Leeds Teaching Hospitals NHS Trust or creating educational resources with industry leaders as part of our Thought Leadership initiatives. I've always been welcomed by this community of experts and encouraged to participate in industry discussions. I know the value of pathologists sharing their digital pathology expertise and learnings with one another. Unfortunately, not everyone in the pathology community can attend live events to network and ask questions. I wanted to bridge the gap between the experts who had the benefit of implementing digital pathology and those that wanted to learn. Luckily, I have an amazing role at Leica Biosystems, which offered me the opportunity to spearhead this initiative.

I sought the guidance of six pathologists from around the world, who later formed our Charter Group. We brainstormed ways to share knowledge in a safe, non-commercial space. Together, we created Digital Pathology Connections (DPC), a private LinkedIn group with three clear differentiators from other online groups: dedicated experts, focused conversations, and a global reach.

Pathologists who are at the start of their digital journey can now connect with those further along the path. Developed and developing countries can learn from one another. Academic centers can share knowledge with private provider practices. A collaborative community allows everyone to share the challenges and frustrations that come with implementing new systems. The goal is not to promote products and services but to accelerate the industry's adoption of digital pathology through educational resources.

We launched DPC at Path Visions 2022 to very enthusiastic attendees. DPC has over 400 members, and over 75 percent are pathologists. We choose weekly hosts to lead hot topics in the industry, and members chime in with questions and comments. We've discussed barriers to adoption, justifying a digital pathology system, IT alignment, storage requirements, and much more. We've also held exclusive DPC member events, including live panels with key leaders in the industry.

LUCIA R. WOLGAST

After years as a data analyst and clinical researcher at a pharmaceutical company, I changed my career path, attended medical school, and became an AP/CP and a hematopathology - boarded pathologist.

During 12 years as a laboratory director, I have focused on creating effective teams for laboratory inspections, quality assurance projects, and standardization committees. Whether it's creating and pulling reports to perform a workflow analysis, designing new specimen sorting solutions, creating order sets that focus on minimizing the number of collection tubes, or reviewing how results are formatted and viewed in the clinical information systems – these improvements have hugely impacted patient care. My focus on improving preanalytical and postanalytical processes allowed me to implement our laboratory's new automation system.

As Vice-Chair of Clinical Pathology, my focus has moved from the day-to-day operation of the laboratory to department and hospital wide initiatives; for example, exploring ways to expand testing capabilities and reducing reference laboratory testing costs. With the increased volume and complexity of reference laboratory test requests, my current focus is to create utilization committees of pathologists and clinicians to review reference laboratory tests to select high quality testing for our patients. Further, with utilization reviews, I can identify testing that would be more cost effective and beneficial for patient care if performed by the inhouse hospital laboratory. I am continually demonstrating the value of investing in the hospital laboratory.

MARIE CHRISTINE F. BERNARDO

I have worked as a pathologist for 12 years now, with a special interest in neuropathology. In 2015, I tried my hand at painting and discovered so much joy in it. My style juxtaposes the natural chaotic behavior of watercolor with controlled, repetitive patterns created with pens. In February 2018, I showcased 24 of my favorite works in an exhibit titled, "Human: The Phenomenon of Being" at the hospital I work in, which reflected on how the human body is purposely designed to be God's greatest masterpiece. It marked the start of many commissioned art requests, primarily from doctors who wanted anatomical art in their clinics.

In November 2018, one of my works was included in the art for advocacy auction at The American Society of Cytopathology in Washington, DC, USA. In August 2020, one of my works was unveiled and displayed in the Department of Anatomy at the Mayo Clinic College of Medicine, Rochester, MN, USA. What started as a means to break the monotony of everyday life has become a means of daily self-expression and reflection. I hope that my work inspires others to get creative!

MIN EN NGA

As a medical student, I struggled to study pathology. I enjoyed looking at pretty cells, but the science behind it felt too cerebral for me. Fast forward a couple of years, and – to my own surprise – I entered pathology residency and had to teach pathology to students of my own! My past struggles prompted me to create mind maps – the messier, the better – for my students. Mind maps helped to stitch disembodied facts together and allowed a logical flow of thought that anchored those troublesome bits of information.

As a teacher, I have been blessed with generous colleagues who have shared ideas and opened up new worlds to me. Amanda Charlton, a brilliant ex-colleague, introduced me to Explain Everything, an App which allowed me to capture these mind maps in video format. Gang Wang, then a research assistant in the radiology department, suggested I try out multi-angle photography of pathology specimens, leading to the birth of our first batch of Virtual Pathology Specimens.

Back in 2014, we piloted these digitized specimens in our tutorials and the students loved visualizing every nook and cranny of each specimen in high definition on a large screen. Three years later, Pathweb – our free pathology online resource – was born. Pathweb features more than 50 video mind maps, interactive quizzes, more than 300 talking pots and slides, and a virtual pathology museum housing more than 750 fully annotated virtual pathology specimens.

The journey wasn't easy, but the response has been affirming! As of June 2023, Pathweb has users from over 125 countries and 6 continents. To know that this free resource is making a difference at home and abroad is all that I could wish for.

Along the way, the Pathweb Teacher YouTube channel was created, featuring both undergraduate and postgraduate videos. We have close to 19,000 subscribers. Throughout this affirming journey, I have been patiently schooled in digital wonders by my very own students and residents, so much so that the pathology teacher becomes the digital novice, and the pathology novice the digital expert!

NICOLE R. JACKSON

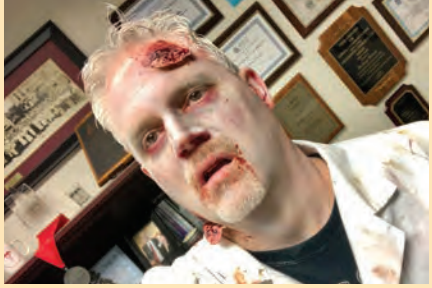
Out of more than 1000 autopsies, there have only been a handful where I looked at the deceased and thought, under different circumstances, that could have been me. When I tell people about my job, it is usually met with shock and awe. My response fluctuates between "It becomes academic and intellectual after a while," and "We're all built for something!" The reality is that much of this job requires you step away from cases – to mentally distance yourself from humanity for a brief period of time. One of my earliest and most memorable cases was one where I could not. It was a case of a relatively healthy Black woman roughly the same age, build, and skin tone as me. She was born on the "wrong side of town" – the poorer area of the city with limited access to quality healthcare. She trusted and married the wrong person: a repeat adulterer who unknowingly exposed her to HIV. She trusted a broken, under-resourced hospital that missed the fact that her HIV infection had progressed to AIDS. She died soon after in that very hospital after seeking help for dyspnea – not once receiving appropriate treatment or reaching her doctor's office. I don't often cry after cases, but I did then. So many things fatally failed this woman – her partner, her healthcare providers, her city.

Years later, her face has faded from my memory but I still remember her story. It is not a happy one, and, unfortunately, not unique in America. Much of what autopsy and forensic pathologists do is establishing what happened. We find answers on the individual level, bringing closure to grieving families and communities. We deliver those answers to care providers, public health departments, law enforcement agencies, and the criminal justice system to address huge issues. We speak for the dead, but our work informs systems that serve the living.

REZA ALAGHEHBANDAN

I want to make a lasting impact in the world of global health and cancer control. It's by no means a small goal. For years, I have been privileged to do pathology philanthropy, enhancing education and clinical services in sub-Saharan Africa and Southeast Asia. My recent focus is in the SE Asia region, where there is a significant gap in pathologist–patient ratio. I provide educational courses and workshops for both pathologists and surgeons, where I conduct fine needle aspiration clinics, online lectures, and case consultations through telepathology powered by social media platforms. I also promote educational "twinning" programs, where a host country partners with a sponsoring institution, creating ongoing educational collaborations. I am very passionate about envisioning a feasible design for pathology education in low- and middle-income countries (LMICs).

As someone who wants to make a global impact, there has been no greater opportunity than serving as an expert and contributor on developing the World Health Organization (WHO) Global Breast Cancer Initiative (GBCI) implementation framework in 2023. Launched back in March 2021, the objective was bold: to reduce global breast cancer mortality by 2.5 percent per year, thereby averting an estimated 2.5 million deaths between now and 2040. The project aims to define and improve high-quality, high-value cancer management focusing on the needs and limited resources in LMICs. I was invited along with 60-70 other global experts to assist in technical consultations, collaboration with working groups, and contributions to the writing, editing, and reviewing of the core technical package. To see the final documents – ones that outline a pathway for incremental, sustainable improvements tailored to country-specific needs – was a truly rewarding experience that showed how global pathology can come together to bring actionable change.



RODNEY E. ROHDE

You would expect me to react poorly to seeing my life's work flying out the window – let alone flying out of a plane. But before academia, I spent a decade with the Texas DSHS Bureau of Laboratories and Zoonosis Control Division as a public health microbiologist and molecular epidemiologist. One of my public health roles was in the inaugural Oral Rabies Vaccination Program, which eliminated canine rabies from Texas via the use of a recombinant rabies vaccine. The liquid vaccine was inside a sachet, which itself was inside a bait matrix (think: a cube of dog food). We distributed them aerially with Canadian Twin Otter aircraft along the state border, as well as central and southern Texas.

I was in a hybrid position working with the Centers for Disease Control and Prevention to create a molecular-based test to track all rabies virus variants in the wild. This role led to me helping establish the laboratory as a regional rabies reference typing center for the US, Mexico, and other countries – something it still does to this day, along with other rabies virus variants. As noted, I also participated in the aerial distribution of the vaccine baits and the surveillance portion to show vaccine efficacy in wildlife – coyotes, foxes, and other canids – via tetracycline biomarking of teeth and serology of wildlife antibodies. This effort was international in scope, and it truly was a once-in-a-lifetime event that set the groundwork for my future efforts in public health, clinical microbiology, and the medical laboratory healthcare environment. This experience has created a passion in how I teach, interact with colleagues, and mentor. I am passionate about advocating for everyone to seek out amazing opportunities – everything from internships to TEDx talks. It continues to be my source of fuel for advocacy and my efforts globally.

SARAH E. COUPLAND

I'm Australian and a bit of a "wanderer." After some sunny undergraduate and junior doctor years in Sydney, I decided to move to the much chillier city of Berlin, Germany, in 1990. That's where I undertook my PhD – and simultaneously where I learned German so I could work as a clinician. I did my pathology training shortly after, but, by 2005, I found myself, my husband, and my children crossing the channel to the even chillier UK.

Today, I live and work in Liverpool. I work as a clinical academic where 50 percent of my time is spent doing diagnostic work within the NHS; the other 50 percent undertaking research and administrative roles at the University of Liverpool. With support, I was able to establish the Liverpool Ocular Oncology Research Group (www.loorg.org), which focuses on translational and clinical research into adult ocular tumors. My postdocs and I have been quite successful in this somewhat niche area, having established a unique ocular oncology biobank that resulted in a range of national and international collaborative studies with clinical impact. Our lab has grown over the years, and we've trained quite a few students – and even consultant ophthalmologists and pathologists – in cellular, digital, and molecular pathology.

On the diagnostic front, I led the supraregional ophthalmic pathology service, receiving a wide range of samples from Liverpool, the UK, and across the globe. It pleases me to know that not only does my personal journey span continents, but my professional work does too. We work very closely with the ocular, medical, and surgical oncology teams located here, but we help to improve diagnostic and prognostic outcomes around the world. I've been fortunate that my career has allowed me to make a real impact, wherever I might wander to.

SYED T. HODA

I had three months left in my wonderful bone and soft tissue (BST) pathology fellowship and no plans afterwards and had not even applied for a job. Simultaneously, I had decided that I wouldn't do any more fellowships after this one as it felt like my training finale. It was 2011 and the pathology job market was not doing very well. Too many candidates and too few jobs. My residency colleagues had done between two to four fellowships after residency to ensure they were competitive.

I heard echoes of a certain attending in my residency telling me in commanding terms that doing only one BST fellowship was insufficient to build a career upon. Another attending incredibly told me they felt it wasn't a fellowship worth doing, which felt jarring to me. Through music and art I've learned that uncommon ways create their own pathways. Curiosity and fascination overcome so much, and this idea helped me greatly.

I had only two months left in my BST fellowship and made calls to kind senior visiting pathologists I'd met on grand rounds and through mutual connections. With one month left in my BST fellowship, I'd applied to a total of zero jobs. I then happened to speak to someone who led me to a person who told me about another person who told me to call their longtime friend to ask them about some situation and that person told me there was nothing, but they did advise me to simply wait. So I waited.

I finished my BST fellowship, and still hadn't applied to any jobs. The week after my fellowship ended, at an aptly titled coffee shop named Café Grumpy, I received a phone call from a department chair – a friend of the person who'd told me to wait – who then told me they will now need me. I was being recruited and I couldn't have been more ecstatic.

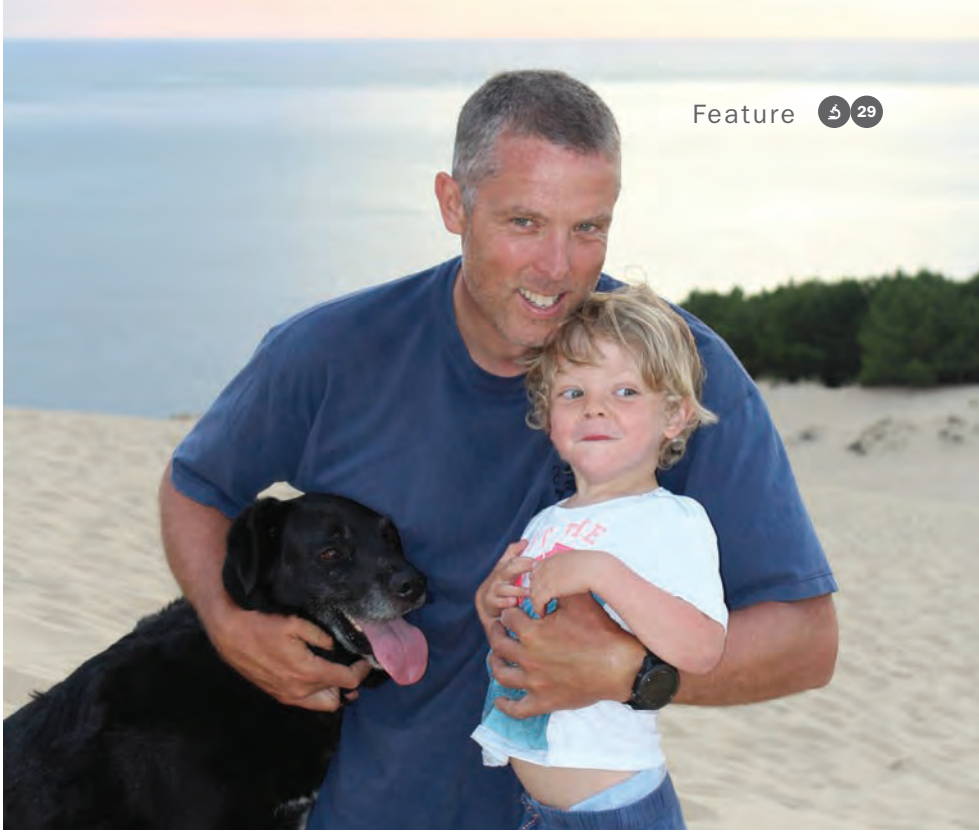
It's now 12 years since I finished my BST pathology fellowship and still haven't applied for any jobs. I was recruited for my first and second (current) job. I still get recruited often, in fact while writing this story I received an email asking me if I was interested in being vice chair at a large academic institution. Not interested at this time, since I still have my own angular plans!

This story is dedicated to all the trainees and pathologists who are boldly crafting their own stories rather than following someone else's.

TALAT ZEHRA

In early 2019 I was working in a lab where I used to see cases for histopathological diagnosis from across my province in Pakistan. These specimens often travel long distances to reach a lab with adequate facilities for histopathology diagnosis. If specimens were not placed in proper air-tight containers, formalin would spill out and the specimen became autolyzed – something that happened often. This caused frustration when it necessitated repeat biopsies, but things became grave in cases of excisional biopsies. Once, we received an axillary mass of a 13-year-old boy – four days after surgery. It was without formalin and on histopathology it turned out to be autolyzed Hodgkin's lymphoma. I felt sorry for the little boy – more perhaps because I am a mother. If only we had digital pathology and telepathology facilities, then small specimens and biopsies could be sent to labs with the help of scanners. We could also get second and third opinions so difficult cases could be taken easily across the globe.

I live in the developing world. More than two thirds of the world's population live here. The bulk of the world's diseases are here. But our less-equipped laboratories and diagnostic facilities result in delayed diagnoses and grave consequences. Yet digital and computational pathology appear as rays of hope. Despite all constraints and limited resources, my colleagues and I conducted the first country-wide survey among pathologists regarding the future of remote digital pathology after COVID-19. Using open source repositories and software, I have been involved in many different digital pathology projects. Of course, the fight is far from over. I am thankful to all those vendors, pathologists, AI scientists – and especially Dr. Anil Parwani – who helped me in my pathology journey.



TIM BRACEY

Over 10 years ago, I saw a very unusual case that involved a new consultant surgeon – who I will call Mr Head-Holes. The patient was a pale, unwell, young man presenting with weight loss and a noticeable lump. The lump was in his left supraclavicular fossa, a site associated with nasty tumors arising below the neck. After an ultrasound, the radiologist thought it was lymphoma.

I agreed it was malignant, but the clustered epithelioid tumor cells were definitely not lymphoma, and the varied features – including syncytial giant cells – made me think of a germ cell tumor. One great advantage I had in the clinic was the ability to solidify a diagnosis "in the moment" by getting more clinical information before reporting. So, after telling the patient I had collected a diagnostic sample I snuck out of the room to talk to the surprised-yet-skeptical surgeon, Mr Head-Holes.

"Can you examine his testicles?" I asked.

"I don't examine testicles!" he said, dumbfounded. "I'm an ear, nose, and throat surgeon! I only examine lumps above the clavicles and these five head holes," pointing to his ears, nose and mouth.

The nurse turned to him shyly and said, "Sorry, Tim is usually right. I think you'll have to do it!" Her mouth dropped when I added, "And would you mind running a pregnancy test as well?"

Of course, a testicular lump would confirm a germ cell tumor. And if it contained a significant proportion of choriocarcinoma, he may also produce a positive pregnancy test. Mr Head-Holes reappeared triumphantly telling me, "The balls were normal!" But further tests confirmed my suspicions.

"And the pregnancy test?" I hear you cry. It was negative. Amazingly, despite chemotherapy and neck and retroperitoneal lymph node dissections, a positive pregnancy test did eventually occur (for his partner), and he is now a father.

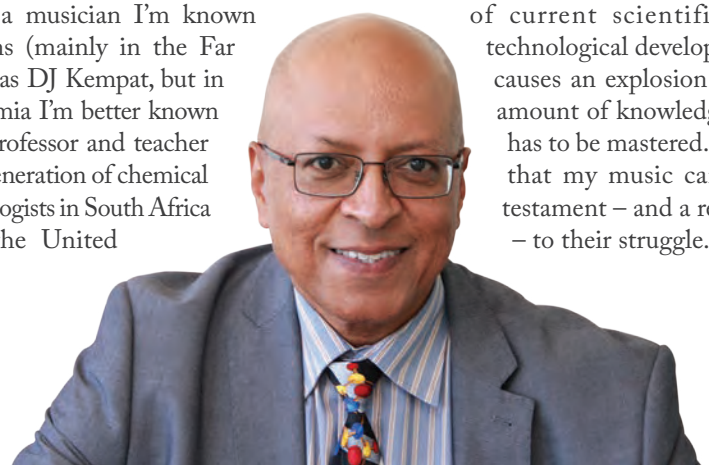
Mr Head-Holes was impressed with my diagnostic skills, but said it was the last time a pathologist would coerce him into examining anyone's testicles…

TAHIR PILLAY

I started making music through boredom. Yet, out of all my achievements, it's my music of which I'm most proud. As Chair of the Communications and Publications Division of the International Federation of Clinical Chemistry (IFCC), I am the first person from the African continent to lead any division of the IFCC in its more than 70 year history. During my busy schedule, on one particularly long intercontinental flight, I couldn't fall asleep in my economy seat. Far too tired to read or watch movies, I started to mess with my phone and discovered GarageBand and found I had a knack for creating EDM songs. To date, I've released over 50 songs and two full albums.

As a musician I'm known to fans (mainly in the Far East) as DJ Kempat, but in academia I'm better known as a professor and teacher of a generation of chemical pathologists in South Africa and the United Kingdom. But these achievements shouldn't be seen as separated. I often describe myself as an "acoustic Picasso" and believe that pathology is a fusion of skills – an art and a science.

In fact, much of my music is directly inspired by pathology. My song *Soul of Seoul* was inspired by IFCC Worldlab Seoul in 2022, while *Freiheit* interprets the liberation of a trainee after a grueling specialist qualifying examination. My other tracks draw inspiration from the angst of trainees grappling with personal life challenges alongside career aspirations – my newest song *Resilience* particularly captures this anguish. Many trainees struggle to get to grips with clinical chemistry and laboratory medicine as the rapid exponential growth of current scientific and technological developments causes an explosion in the amount of knowledge that has to be mastered. I hope that my music can be a testament – and a reprieve – to their struggle.



Powerful Profiles

Industries are made by the figures within them. Without these powerful personalities seeking to transform the status quo, the field of medicine would look very different. Join us in highlighting some of the key movers, shakers, and innovators that mold laboratory medicine in our "Powerful Profiles" series.

ASCP is heading into another century of innovation and growth

ASCP

In 2022, the American Society for Clinical Pathology (ASCP) celebrated 100 years of growing, innovating, and advancing pathology and laboratory medicine to improve clinical care for patients.

ASCP is actively committed to raising the visibility of pathology and laboratory medicine among the healthcare industry and consumers. We strive to further establish the laboratory's role as the foundation of high-quality patient care.

As part of this commitment, over the past few years ASCP has undertaken a wide range of initiatives to strengthen and build the pathology and laboratory workforce while bringing awareness to the critical role the laboratory plays in patient care, including:

- The development of the Blueprint for Action, which identifies 12 workforce initiatives to address the challenges facing the laboratory workforce.
- The continued operation of the 40 Under Forty program, which recognizes high-achieving pathologists, laboratory professionals, and residents under the age of 40 for their achievements, leadership, and ability to effect change.
- The ASCP Career Ambassadors and Pathology Ambassadors programs, which recruits hundreds of volunteers to introduce pathology and laboratory medicine to students of all ages.
- Partnering with The Lab Drawer(TM), an innovative company that provides children STEAM educational kits. Through this partnership, new laboratory-focused kits have been created and will be deployed to schools across the country.
- The development of a strategic plan through the Council of Medical Specialty Society's Equity Matters initiative to address anti-racism, diversity, equity, and inclusion within its governance and membership.
- A partnership with The Joint Commission to launch Leading Laboratories, which recognizes excellence while raising visibility of the laboratory's critical role in patient care.
- Continued support to resource-limited countries through ASCP's Center for Global Health.
- Supporting pathologists, laboratory professionals, and students through a range of grants and scholarships from the ASCP Foundation.

The first century of ASCP brought innovation and growth; the next 100 years will bring even more. ASCP continues to advocate on behalf of our members and the profession with the goal of creating change in healthcare that makes the laboratory accessible and recognizable to all.

ASCP STRONGERTOGETHER

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Madhuri Hegde

Senior Vice President and Chief Scientific Officer, Revvity

Madhuri Hegde is Senior Vice President and Chief Scientific Officer at Revvity, serving as the internal and external face of Revvity's scientific strategy. Hegde is also a board-certified diplomate in clinical molecular genetics and the Head of Revvity Omics – a network of laboratories offering services across the globe. In this latter role, she guides her team to provide families and healthcare partners with access to innovative multiomic-derived diagnostic technologies in over 155 countries.

Hegde is a recognized and highly respected leader in the field of clinical genomics. She has presented over 100 keynote presentations at national and international conferences, and is credited as author or co-author on more than 150 peer-reviewed publications and eight book chapters. For more than two decades, Hegde's research in neuromuscular disorders has contributed to a number of pharmaceutical drug discovery programs, such as The Lantern Project – in which Revvity Omics is an active partner. Her work and experience follows a larger movement reflecting the rise of precision medicine – a drive towards more omics-based testing, and even beyond.

Hegde's interest in genomics was sparked at an early age, and it was a video on DNA extraction during a sixth-grade science class that proved to be the seed that would grow into a flourishing career. Hegde is grateful to her family for nurturing her initial curiosity, as well as to have had many fantastic mentors – many of whom are leaders in their fields. Having benefited from the support shown to her by her own mentors, Hegde is a real believer of "paying it forward" – always making time for her colleagues, direct-reports, and other scientists-in-training who look to her. As a woman in science, she feels strongly about supporting other women in her field, whether that's through one-to-one mentorship or by contributing to Revvity's Women's Employee Resource Group.

Hegde is inspired by the spirit of humans to keep exploring. She is passionate and perpetually curious; a leader who is energized by uniting people to harness science to positively impact human health. It comes as little surprise that this passion extends to her hobbies, as her fiery support for Indian cricket and keen sense of competition are well known to her family and colleagues alike.

revvity

Jeff Carmichael
Senior Vice President of Engineering,
XiFin

Delivering the Best of AI for Clinicians

Artificial intelligence (AI) is not new in healthcare. AI has taken a foothold in the clinical domain, including digital pathology and AI-driven next generation sequencing analytics, as well as more recently in speech conversion to clinical notes.

Clinicians' primary focus is on the delivery of healthcare services. Yet the administrative burden related to coding, claim processing, and ensuring that all billable services are appropriately collected are critical to funding their mission. Clinicians are also increasingly being pressed to reduce the cost of operations and maximize revenue growth while managing missing or incorrect information or payor requirements. These challenges are compounded by labor and supply shortages, which have fueled a demand for outsourced billing partnerships and for best-in-class revenue cycle management (RCM), according to the recent 2023 Black Book report, which rated healthcare information technology company XiFin in the top 10 percent of competitors in each of the 18 evaluation categories.

All too often, claims are rejected or can't be processed because of missing or incorrect information that can take days and sometimes months to resolve. This phase of the RCM process is sometimes referred to as financial clearance and is an area ripe for AI. Consider for a moment, a patient who has Blue Cross Blue Shield insurance. They provide the subscriber number at the time of service. That number alone is not sufficient to confirm eligibility or benefits coverage and it is essential to providing an accurate estimate of their potential out-of-pocket expenses.

AI applied to this challenge can remove the onus on the patient and the physician by uncovering the underlying payor details. More specifically, to determine eligibility, coverage, and patient responsibility for a particular claim, AI can discover the payor plan details for that claim so that it can be processed without manual intervention.

Leading the AI transformation at XiFin is Senior Vice President of Engineering, Jeff Carmichael, and his Data Science team. Since 2018, Jeff has been leveraging various types of AI and building them into the industry-leading RCM platform.

Jeff and the XiFin team have invested significant effort in structuring the complex RCM data required to develop effective machine learning and AI models. Building upon XiFin workflows that determine if a claim is likely to be rejected because of incorrect or incomplete payor information or patient ineligibility and use automation to resolve most issues, XiFin's rich and highly configurable AI can then quickly determine probability of reimbursement to help prioritize the claims that still require intervention, and then redirect those needing human attention to the best available team member.

Jeff knows that clinicians got into the lab business to help physicians and other providers solve problems. Saving time and money on these claims tasks means better insights, less expense, and more opportunities to take on additional workloads and deliver better results. Ultimately, XiFin's AI-powered workflows help clients do more good for more people.

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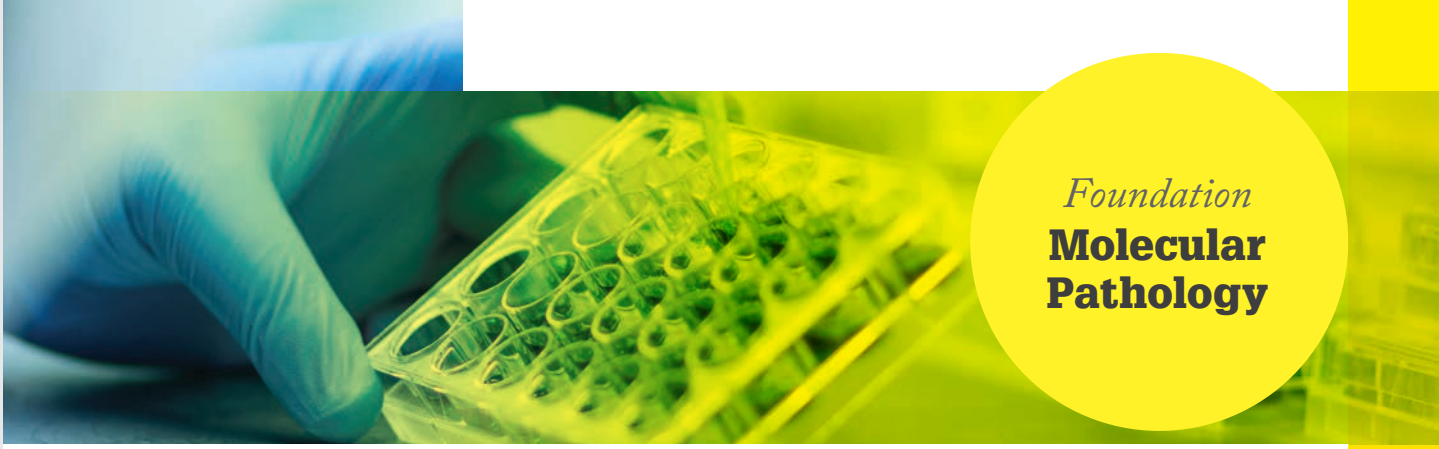

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Foundation
Molecular Pathology

Pathology with Pin-Point Precision

The role of the pathologist in modern medicine

By Jane Gibson

Precision medicine continues to shape the practice of medicine – and it continues to expand the role of the pathologist in patient care. Historically, anatomic and clinical pathology services dominated the field, and histologic examination was a core focus. Today, the emergence of molecular diagnostic technologies have become a central part of the role, causing a seismic shift across the whole of pathology. Below, I detail (some of) these changes – and offer a little advice on making the most of our increasingly sophisticated role.

Change at a rapid pace

Modern pathologists provide services that were solely associated with traditional anatomic and clinical pathology test menus. Precision medicine technologies are evolving at a rapid pace; for example, immunohistochemistry is used in diagnostics and therapeutic decision making; fluorescence in situ hybridization detects abnormalities in genes and numerical and structural chromosomal anomalies; and next-generation sequencing (NGS) has single-handedly expanded the role of the pathologist. Molecular profiling has seen substantial growth in this area. The use of NGS sequencing of gene panels to detect variants in nucleic acids from tumor tissue specimens and circulating tumor cells has not only fostered new opportunities for diagnosis and targeted therapy, but also earlier detection of metastatic spread.

Know thy data (or befriend a bioinformaticist)

The long-standing association between pathology and informatics – and the unprecedented amounts of data generated by NGS testing – has prompted an increased need for bioinformaticists. In my view, the marriage of bioinformatics and pathology has the potential to revolutionize the field of precision medicine. Why? Because bioinformaticists can use computational approaches to interpret complex data from genomes, exomes, transcriptomes, and proteomes – that can establish tumoral molecular signatures and predict treatment response.

Genomic data within electronic medical records (EMRs) is also noteworthy. Combining standard EMR data – diagnoses, medications, laboratory results, and imaging studies – with sequencing data, can provide additional insights into a patient's health and disease risk. This may help identify patients at increased risk for certain diseases, and could inform new strategies for personalized screening and prevention strategies. However, practicing molecular genetic pathology also demands familiarity with the databases referenced for sequence interpretation.

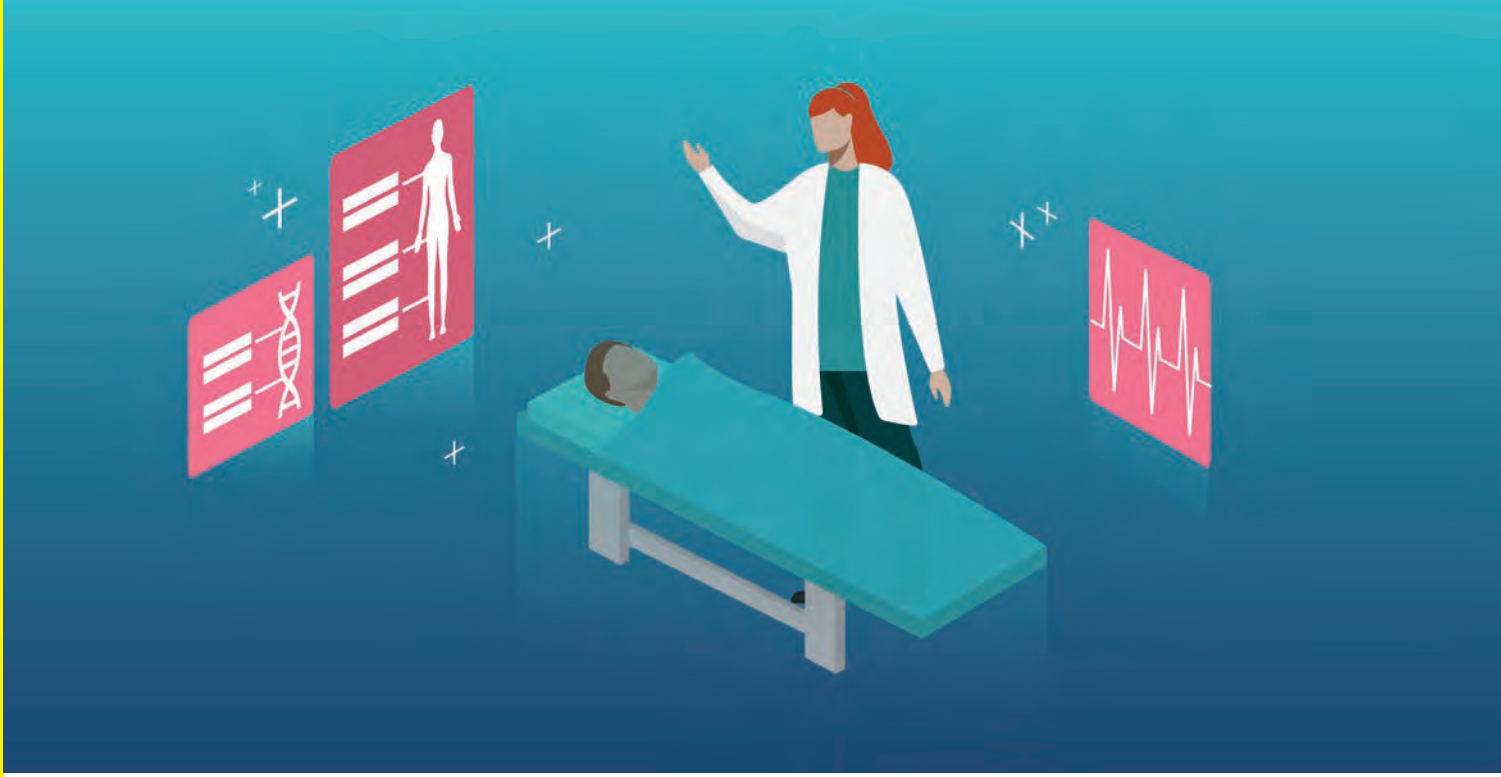
Precision medicine's poster child

Non-small cell lung cancer (NSCLC) is the poster child for biomarker profiling and cancer patient care. Typically, these cancers are treated with a combination of surgery, radiation therapy, chemotherapy, and/or targeted therapies directed by relevant NSCLC biomarkers found in blood, tissue, and fluids. For example, some pathogenic variants can be targeted with epidermal growth factor receptor inhibitors. Similarly, anaplastic lymphoma kinase (ALK) rearrangements (which disrupt normal gene function) can help guide treatment with ALK inhibitors. The availability of gene panels for cancer and other disorders – along with whole exome and whole genome sequencing – has expanded collaborations between pathologists, oncologists, geneticists, and genetic counselors, to mention just a few.

Keeping up

The importance of continuing education and training for pathologists is a secret to no one. Fortunately, new opportunities to develop skill sets in line with the changing needs of the field have arisen. The Molecular Genetic Pathology board was established in 2008 to recognize the unique expertise required by the subspecialty. The American Board of Pathology and the American Board of Preventive Medicine offer board certification in informatics and recognize the knowledge and skills needed to effectively use it in practice. There are also many continuing medical education opportunities offered by professional societies including the Association for Molecular Pathology.

Jane Gibson is Associate Dean for Faculty Affairs, Chair, Clinical Sciences, Professor of Pathology, University of Central Florida, USA.



The Innovator's Dilemma

How simulated patients can improve the process of clinical utility evidence generation

By Randy E. David

Demonstrating clinical utility is generally the last – and largest –principal requirement before securing coverage and reimbursement for a molecular diagnostic test. Popularized by the CDC's Office of Public Health Genomics, the term "clinical utility" refers, at its core, to how a technology or practice, by prompting an intervention, may impact a health outcome. Impacts can be derived through additional treatment options, or improved implementation feasibility, population health equity, and/or cost-effectiveness.

While life sciences companies grapple with establishing evidence of analytical and clinical validity, they can fail to prepare for a significant challenge: procuring direct, hypothesis-driven, utility data.

Indeed, the innovator's dilemma is that with the rapid advances in molecular technologies, AI algorithms, and biomarker discovery that are driving diagnostics, healthcare payers must be more rigorous in choosing what tests to cover. This challenge is often exacerbated by the context-dependent ways in which clinical utility can be evaluated (1). CMS' Molecular Diagnostic Services program, or "MolDX," developed in 2011 and administered by Palmetto GBA, currently creates coverage and reimbursement policies for four A/B Medicare Administrative Contractors (MACs), across 28 states. Thus, they are largely the de facto body for clinical utility judgments nationwide. While MolDX predicates its assessments on the CDC's ACCE model, McMaster University's GRADE Evidence to Decision (EtD) framework, and CMS' "reasonable and necessary" clause, these were all designed as industry standards or guiding principles, rather than roadmaps for evidence generation.

A purpose-built study design

Evaluating the real-world utility of a given diagnostic test requires the direct quantification of ever-elusive provider decision-making behaviors. Simulated patient studies – the examination of virtual patients presented on the screen of a device – are an optimal way to rapidly and accurately collect care data in line with national provider and patient demographics. Just like in real life, provider participants can progress through an entire medical interaction with a "patient," where they can receive vitals, record a medical history, conduct a diagnostic workup, make diagnoses, and ultimately, arrive at a recommended treatment plan.

Simulated patients might offer a convenient way to capture care practices, but for the high-quality evidence required by healthcare payers, care decisions must be quantified within a purpose-built statistical framework. Other than meta-analysis or a systematic review that filters multiple sources, individual randomized controlled trials (RCTs) are the most effective means of assessing cause-effect relationships (2). And so, for studies to yield results that payers can rely on, they should be designed as an RCT with a narrow confidence interval. This involves recruiting a large and representative sample of providers that would potentially utilize the test in real life. It also requires the use of realistic educational and marketing materials – such as fact sheets, slide decks, and short videos – about the test, which are used as the "intervention" in the RCT design.

Like other means of generating clinical utility evidence, studies should be presented in peer-reviewed publications that life sciences companies can include in their dossiers when applying for coverage and reimbursement. Published articles should explain how the utilization of a given diagnostic creates value in comparison to the current standard of care. For example, a test may streamline, consolidate, simplify or otherwise make results more intelligible; provide additional information for provider decision-making; hasten the discovery of an actionable insight; provide more accurate results; reduce the harm that may be caused by an alternative; or prevent wasteful spending related to hospital admittance. Publications should also be sure to expound upon specific identified use cases, and how a given test may differentially impact various patient groups.

So, why simulated patients instead of real-world ones?

Simulated-patient RCTs are not only much quicker – approximately one third of the duration – and more cost-effective than traditional methods, but they are also more scalable, customizable, and often more accurate too (see Figure 1). Overall, the benefits include:

- Reduced time commitment and effort required by the participant provider
- More accurate study samples from a national pool, rather than from a limited number of regional or mostly academic sites
- The diversity of the "patients" is reflective of demographic and epidemiological realities – reducing stigma and increasing equity
- Simulated patients can be designed for a broad range of disease areas and outcomes
- Statistical power needed to reach significance thresholds requires far lower sample sizes, since participants care for the same "patients," eliminating interpatient variability

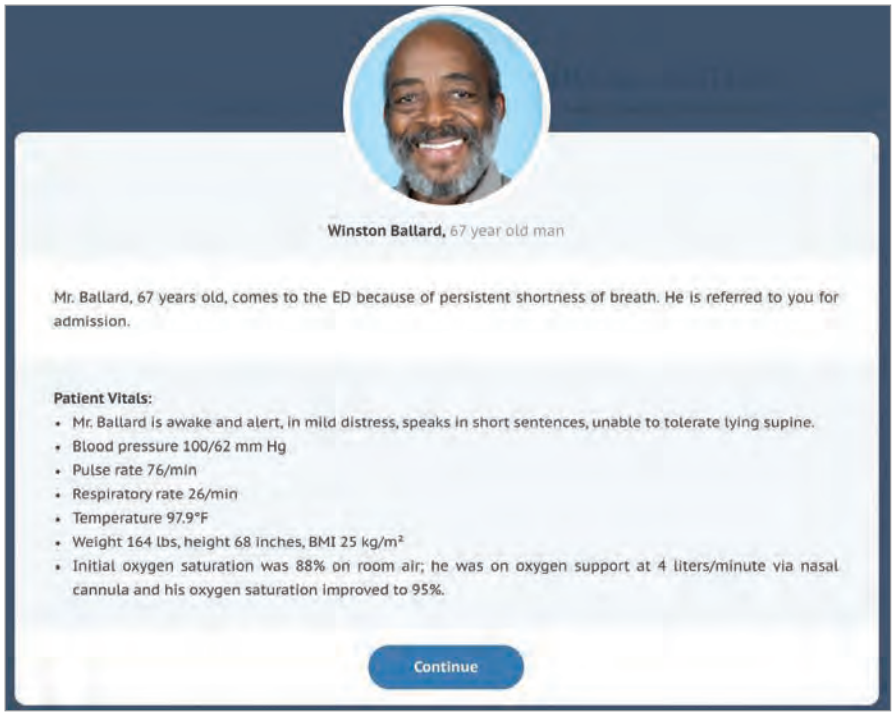


Figure 1. Example of a QURE® simulated-patient interface

Robust validation studies have been published that corroborate the effectiveness of simulated patients, both in relation to clinical utility and in healthcare generally (3–5). Some clinical utility RCT designs even combine the presentation of simulated patients with medical chart abstraction (from patients of the same participant providers), which allows for an additional layer of evidence generation and validation.

Nationally and internationally, healthcare payers are becoming increasingly aware of the enormous upsides of simulated patients in this unique context. Because of this, many have been promoting simulated patient clinical utility trials for rare diseases, diagnostics that prevent patient harm, novel technologies, and for trials that would otherwise be too costly. Simulated patient RCTs have also been used to inform commercialization efforts, gauge user adoption, and assess quality of educational/marketing materials. They have a proven return on investment, not only for clinical utility evaluation, but also for precision education of healthcare workers – as well as for reducing clinical variation in large health systems (6,7).

With the digitalization of many aspects of healthcare underway, it is vital that life sciences companies remain abreast of the latest trends and capabilities of implementation science – including the evaluation of clinical utility. Coverage for molecular diagnostics requires more direct evidence generation than ever before, and for logical reasons. A faster, cheaper, reliable method is bound to create a strategic advantage in bringing valuable diagnostics to market.

Randy E. David is Vice President, Clinical and Life Sciences Programs, QURE Healthcare San Francisco, CA, USA.

See references online at: tp.txp.to/0823/dilemma

Building Bridges, Transforming Pathology

How precision medicine can help prevent patients from falling through the cracks

Precision medicine has the potential to transform healthcare (1). If adopted seamlessly, it can quickly spotlight the ideal pathway for biopsies and biomarker-based testing to enable the use of the right treatment for the right patient at the right time – not only improving healthcare systems, but also patient outcomes (2,3). Unfortunately, despite the wide array of effective testing, many eligible patients may not receive targeted treatment due to barriers in the precision medicine pathway (4). Below, we explore how precision medicine can be used more effectively to bridge this gap and how it can transform pathology as a whole, with Umberto Malapelle, Chair of Predictive Molecular Pathology Laboratory, Department of Public Health, and Assistant Professor in Anatomic Pathology, School of Medicine, University Frederico II of Naples, Italy.

First, why is the adoption of precision medicine important for pathology?

Often, when we're thinking about precision medicine, we're thinking about tailoring treatment. But to tailor treatment we need to tailor the test because each patient, type of tumor, tissue, and biometric characteristics are ultimately different (2, 5, 6, 11). Precision medicine is our best weapon in assessing molecular status and defining if a targetable alteration is present (7, 8). It's a very important part of diagnosis because, in many cases, you need to integrate a morpho-molecular approach to better refine the diagnosis (2, 6). Once there, you can start the evaluation of predictive biomarkers and then start with a treatment process. In short, if we want to start precision treatment, we need to start with precision testing (9, 10).

How can the application of precision medicine enhance current approaches to treatment?

Precision medicine is the direction of travel for medicine. It allows you to do work backstage – before and within clinical trials – where you are able to define biomarkers and predict treatment (5, 11). In the field of positive predictive biomarkers, you need to pay attention to the specific type of alterations, because it will determine the treatment path for the patient (12). Today, this means one gene is not one biomarker, but one *mutation* is one biomarker (13–15). Epidermal growth factor receptor (EGFR) in non-small cell lung cancer (NSCLC) patients, for example, can help define if patients are eligible to receive specific types of treatment (16, 17). There are many different types of EGFR mutation, with each responding to treatments differently, depending on the mutation (18). Depending on the types of mutations, patients may respond better to a particular type of treatment or show resistance to different classes of treatment (14).

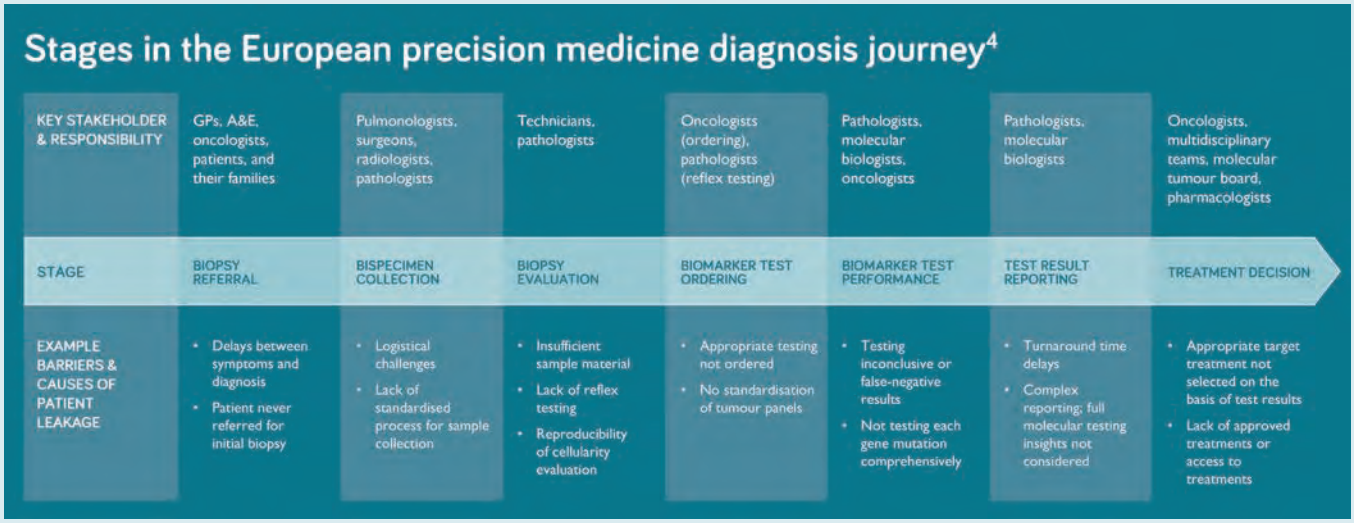
"Often, when we're thinking about precision medicine, we're thinking about tailoring treatment. But to tailor treatment we need to tailor the test because each patient, type of tumor, tissue, and biometric characteristics are ultimately different (2,5,6,11)."

What does the current biomarker testing process look like for cancer patients?

As mentioned, to start a precision oncology program, you need to start with precision biomarker testing (8, 9). And for different driver mutations in different settings, you may have different methodological and technological approaches (6, 19). For example, if we focus on NSCLC, we need to simultaneously test for more than 15 biomarkers (20).

We need to use different types of methodologies to gain this information, but we have to prioritize next generation sequencing, as it is the best way to glean specific information about the single types of alteration we are searching for (21–23). Going back to the *EGFR* example, you can only analyze roughly 77 alterations with a PCR approach – but we know there are likely more in *EGFR* (18). So we need to use next generation sequencing (NGS) upfront. And when it's possible, we need to start the biomarker assessment after we have the morphological diagnosis – without the need to wait for requests to test the other biomarkers (24, 25).

This pathologist-initiated approach is known as reflex testing, and it reduces the



likelihood of a suboptimal, non-targeted therapy being initiated prematurely, before determining the complete biomarker status of a patient (26). Furthermore, by standardizing the ordering of biomarker tests, fewer patients will be overlooked for testing, creating a more systematic and equitable system (19).

Why do some patients drop out of the precision medicine pathway – or not have access at all?

This is really difficult. Precision medicine is complex, with many stakeholders involved and points in the diagnostic and treatment pathway where patients could drop off (27, 28). If you look at the data coming from The European Society of Medical Oncology, there is a lack of equity in access to this type of assessment, in particular, for non-small cell lung cancer – where you need NGS (29, 30).

One major barrier is the sample collection (4). When you need to test several biomarkers, you must have an appropriate quantity of tissue (21). Remember that we are not only looking for a morphological diagnosis, but rather a morpho-molecular characterization of our patients – and the quality and quantity of samples can hinder this approach (6, 21, 32). Another challenge is access to effective technology (5). As I mentioned before, if we use a real-time PCR test, we may have problems finding the entire spectrum of biomarkers that we need to test for (23).

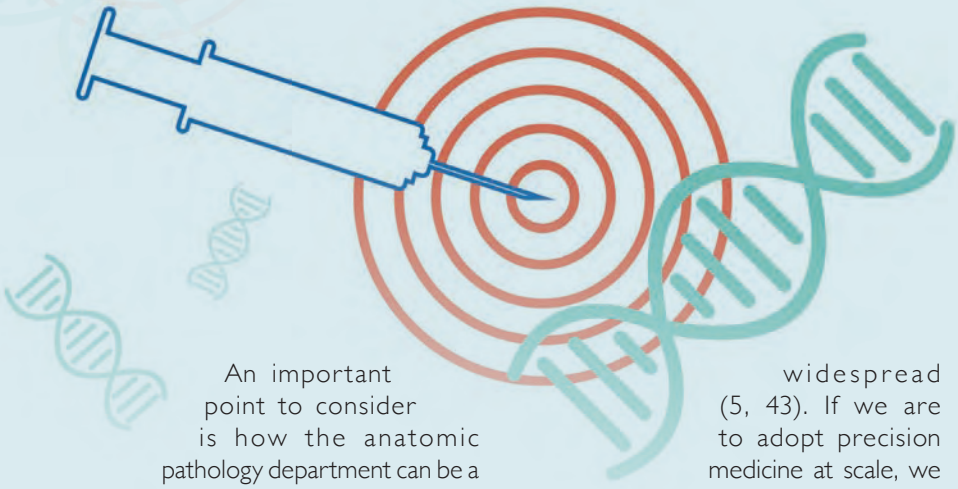
The third barrier is reimbursement; not every country has the same reimbursement for these types of tests. And that can quickly create a bottleneck for treatment (5).

The fourth barrier is the skillset of the professional (5). This is a complex treatment approach, so you need to have skilled people who have undergone specialized training in data interpretation, data management, and working within a multidisciplinary context to understand how this will impact treatment decisions, all whilst ensuring standardization of the reporting (33–35). For me, this step is integral, as we pull together the expertise from a number of experts to ensure that patients are given the best treatment for them. Regular communication between members of the multidisciplinary team helps to prevent disconnect between the specialists, working to provide timely treatment recommendations (35).

Unfortunately, there is a very human price to pay when eligible patients do not get the appropriate diagnostics and subsequently do not receive the appropriate treatment (36). Patients who find themselves in this situation may undergo treatment that has a lower chance of positive outcomes and overcoming disease (1). They may also have to undergo repeated rounds of treatment, which is not only inefficient for hospital care, with financial implications, but also a physically and mentally exhausting experience for the patient (1). And of course, in the worst case scenario, it can lead to suboptimal outcomes, where precision medicine could have been effective for those eligible patients (1).

What role can pathologists play in ensuring precision medicine for all eligible patients?

Pathologists must play a really important role. After all, pathologists are involved in every stage – from sample collection to analysis (22, 37). They are involved in the extraction of nucleic acids from samples, tissues, and liquid biopsies (38). Next, they must analyze the extracted nucleic acids, define molecular characterization, interpret data, and – most importantly – discuss with the oncologist and the other clinicians on the best course of action (39).



An important point to consider is how the anatomic pathology department can be a place where morphological and molecular evaluation coexist. To reemphasize, it's not a morphological diagnosis or a molecular characterisation – it is both (32). This new type of molecular pathologist is – and will continue to be – a key player.

What key stages of the precision medicine journey involve pathologists?

Several key stages involve pathologists – basic research, first clinical phase trials, evaluation in larger trials, approval in clinical practice, biomarker evaluation from patients, and, finally, treatment decisions (40). It's important to remember that the prescription of the treatment today is not only in the hands of the oncologist, but also supported by the pathologist after discussing the data (3, 41).

Pathologists, in clinical practice, are also involved in a number of key stages in the precision medicine pathway, from biospecimen collection to treatment decision making (4, 41, 42). [Figure 1] outlines this in more detail, as well as highlighting the breadth of the multidisciplinary team involved (42).

What obstacles currently prevent seamless precision medicine integration?

There are many barriers that we should – and can – begin to overcome. One of these is the standardization of guidelines – including reports – as this is not currently widespread (5, 43). If we are to adopt precision medicine at scale, we need stringent and widely accepted standards (5). In my view, without standardization, clinicians do not have a recommended pathway to treatment decision-making (5). But standardization doesn't just end there; it also requires digital tools that can host an accredited platform where we can all access standardized guidelines and best practices, regardless of location in the world (44). This approach can even extend to what people refer to as "centers of excellence" – institutions that have outstanding records of care that can offer training and education to other labs (44, 45).

Other barriers are also tied to geographical location – for example, availability of facilities or cost barriers (3). It is not uncommon to see delays or outright rejections in receiving test results across Europe because of the logistics required to facilitate them (3, 5). And that often means treatment decisions are made before results are received (3, 5). From experience, misdiagnosis can also occur when testing needs to be outsourced because of the added risk that accrues as more (unnecessary) links are added to the treatment pathway (3, 5).

In my opinion, us molecular pathologists must change our perspective. We need to obtain the largest amount of data possible and we need to use all the tools at our disposal – not just one. For example, we need to consider a marriage between tissue biopsy and liquid biopsy. We don't need to have a hard stance on whether liquid biopsy is better than tissue biopsy or vice versa; by using a combined approach, we are able to get more information from both. We have the ability to fully exploit the power of the data. In this sense, we need to be helped by other types of tools, not only technical tools, but also clinical ones, as well as mathematical modeling, digital imaging, integrative analysis, data collection, and administration. In my mind, this is the future.

Our biggest goal must be to challenge standard ways of thinking and usher in this new, more effective approach.

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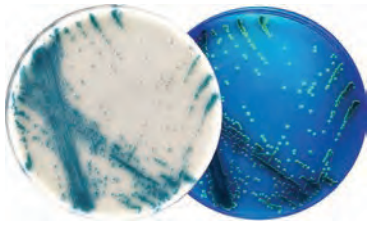

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Infectious Disease

How Germs Shaped History

We spoke to Jonathan Kennedy, author of new book Pathogenesis, about his view that disease has shaped human history for millenia

By George Francis Lee

"History is written by the victors," goes the oft-misattributed (to Winston Churchill) quote. It may be true if you only look at human conflicts – battles, wars, and the like. But one thing that is abundantly clear from reading Jonathan Kennedy's book *Pathogenesis* is that germs have been making losers out of us since the very beginning. Worst of all, we didn't even know it. It's a bold, striking hypothesis: Everything from the migration of hunter gatherers to the emergence of capitalism is fueled by our microscopic adversaries. I spoke with Kennedy at length about his approach to the book – and the science behind it.

What sparked your research into this topic?

I had quite a revelatory moment where I began to realize the importance of research done over the last 20 years – the increasing amount of evidence that showed that gut bacteria are capable of influencing our brain function. It really blew my mind, if you'll excuse the pun.

The broader context of this was COVID-19 – an event that quite quickly took on cliche to describe it: Unprecedented. As someone who has an interest in history, I knew that wasn't the case! I knew that infectious diseases have played a massive role in history and they've killed millions and millions of people at a time. But they've also created the space for new ideas and for new societies to emerge. And that got me thinking how this is one of the major driving forces of history. We often think about great men and women being the driving force of history or, if we're on the left, we may think about class struggle. But it was really interesting when I started looking at the topic of history through the lens of the pathogen. You start to see things differently.

What research surprised you while you were writing your book?

One of the really striking things for me as a layperson was reading about retroviruses and the way in which retroviruses could insert their DNA into ours, and if they infect a sperm or an egg, this gets passed down from generation to generation. Scientists talk about something like 8 percent of DNA in the human genome coming from these retrovirus infections. This knowledge was mind-blowing enough, but then to learn that there are studies that show this isn't only junk DNA that humans seem to have acquired. Things like the ability for the placenta to bind to the uterus or the ability to form memories. The way in which information seems to pass from brain cell to brain cell seems to have been acquired from retrovirus infections.

Why should we be studying and recontextualizing the history of disease?

For one, it's fascinating. It's a really interesting story that overturns the way that a lot of us think about the world. And it contains some really important lessons. Even if we go back as far as the first written histories, Athens went to war with Sparta and thought it would win. But the plague of Athens struck. Nothing did them more harm. I think there's a lesson there for our own times in a way that we shouldn't be too hubristic. In many ways, the success of our own society has created the kind of conditions that might bring about its downfall, whether that's AI, climate change, or infectious diseases.

How does your research affect your teaching and mentorship role?

If we look at what happened over the last couple of years, we see that particular groups suffered much, much more from the pandemic. They got sick at much higher rates and they died at much higher rates. And that really points to the fact that you cannot just see the pandemic as a virus spreading. You also have to think of it as a virus taking advantage of a habitat that human society has created for that virus to thrive. The past shows us that visionary politicians are capable of transforming public health and helping societies deal with the challenges that pathogens create for us.

What lies ahead for your work?

Oh, I'm not sure. I have to catch up on some sleep! I'm really interested in this interaction between the social world of humans and the world of microbes. So I don't think I'll move too far away from this topic…

Pathogenesis is published by Penguin Random House.

Colistin? Colist-out

Craig MacLean talks about how antibacterials are driving resistance – even among host AMPs

By George Francis Lee

Antibacterial resistance is one of the biggest emerging threats to health across the globe, but the relationship between drug usage and growth of resistance is a delicate scale to balance. The use of therapeutic antimicrobial peptides (AMPs), for example, is met with concerns that we are running the risk of creating resistance to naturally occurring AMPs in the human immune system.

A recent study led by the University of Oxford's Department of Biology seeks answers to this problem, and presents some striking results regarding the use of the antibiotic colistin in agriculture (1). I caught up with lead author Craig MacLean to find out what these results mean for the resistance crisis.

Before we talk about your recent study, could you introduce yourself?

I'm Craig MacLean, Professor of Evolution and Microbiology at the University of Oxford. I started my research career as an evolutionary biologist, trying to understand the kind of mechanics of evolution, how populations adapt by natural selection.

A really cool example of adaptation by natural selection is antibiotic resistance. I started using that as a model to test evolutionary theory, but as I've worked on it more and more, I've become interested in resistance for its own sake and, effectively, in bacterial disease. That's what we work on in my lab – trying to understand what are the evolutionary drivers of antibiotic resistance. How can we use evolutionary thinking? How can we combat it? Why does it go away? Those are the main questions we tackle using a number of approaches.

In our experiments we challenge bacteria with antibiotics in controlled environments and watch how resistance evolves, trying to understand resistance in the real world. Sometimes we take samples from patients before and after they've been treated with antibiotics and use that to infer the processes driving resistance during infections. That's the experimental side, but we also do genomic work where we use bacterial genome sequences to help us understand resistance.

How did you get involved in the study?

It was down to an antibiotic called colistin, which was discovered in the mid 20th century. It wasn't really used in humans; it's quite toxic and has side effects. However, it could be produced really cheaply and the side effects on animals weren't bad. In fact, researchers found that if you put it in the food of farm animals, it would be economically beneficial because they would fatten faster.

From there, colistin started to be used on a really big scale in agriculture. As resistance to other antibiotics increased, colistin emerged as an important last line of defense for treating infections in humans. I became interested because of this crazy situation where an antibiotic that was the last line of defense to treat serious infections in humans was the same one being used at a massive scale in agriculture, largely as a growth promoter.

The way colistin works is quite different from other antibiotics. It's a peptide; it has a chemical structure that's similar to the chemical structures of some of the compounds that our immune system uses to fight bacterial infections. And the way they attack bacteria is similar to how components of our immune system attack bacteria. In our case, it's suggested that perhaps the resistance that eventually spread in agricultural settings is mediated by a gene called *mcr-1*.

Is the use of colistin limited to a few countries?

It's mainly used as a growth promoter in Asia. The EU banned the use of antibiotics as growth promoters in 2006, and some other countries have followed suit. But at one point it was being used on a very big scale in China, which is where the best data comes from.

When the *mcr-1* gene appeared, the Chinese government banned the use of colistin as a growth promoter. That's another reason why I became interested in it – because we had samples that were taken before and after colistin usage, which is a good way to study the consequences of reducing use.

What were the overall findings of your study?

We found that the *mcr-1* gene – which spread because of the use of colistin in agriculture – confers increased resistance to antimicrobial peptides from humans, but also from pigs and chickens. This is important because these are important reservoirs of colistin-resistant bacteria.

We found that colistin also increases resistance to some other components of the immune system. The gene actually makes bacteria more virulent toward moth larvae. Wax moth larvae – Galleria mellonella – are being increasingly used to study how virulent bacterial pathogens are.

In short, the mass use of colistin in agriculture has driven the evolution of bacteria that are both more resistant to colistin and more resistant to some important components of our immune system.

What can we expect to happen as a result of using colistin in agriculture?

That's kind of an open question. I think the good news is that when China imposed a hard ban on the use of colistin, consumption dropped by about 90 percent, which was followed by a reduction in the prevalence of colistin-resistant bacteria, both in agriculture and in humans.

So – reduce consumption, reduce the prevalence of resistance. It suggests that if we stop using this antibiotic, resistance will go down. The worry here is that antibiotic resistance is becoming a bigger and bigger problem. It kills somewhere between about 1.2 and 5 million people a year, and that number is increasing. One of the ways we need to deal with it is with new antimicrobials. There may be all kinds of peptides out there that are effective antimicrobials.

The colistin story warns us that if we're going to use antimicrobial peptides to treat human infections, we may end up driving the evolution of bacteria that are resistant not only to those peptides but to our own immune system. This is really important because our immune system provides us with an important first line of defense for fighting off bacterial infection.

How would you go about solving this issue?

People are excited about these peptides for good reasons. A journalist asked me, "Should we be banning the development of these as antimicrobials?" I said, "No, we're in a position where we desperately need new antimicrobials." What we need to be doing is assessing – what are the risks in terms of resistance to our own immune system? So, we need to think about this carefully before we use any of these antimicrobial peptides.

Where does your research go from here?

That's a big question! We have three main ongoing projects in my lab. One is trying to understand what drives resistance during human infections. Another is developing new antibiotics, especially using phages – viruses that infect bacteria – as a potential alternative to antibiotics, and this is something that can complement antibiotics. The final line of research is trying to understand the mcr1 gene, how it is spread, how to stabilize it more. This has been a really interesting project and we'll be publishing a few more papers this year. It's like an onion – every layer we peel off, we find a new, interesting puzzle underneath.

See references online at: tp.txp.to/0823/colistin

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Get a Microscope!

What we can learn about hesitancy from the fight between horses and cars

By Asa Rubin

What fuels reluctance to digital pathology? We only need to look back to the emergence of the automobile to understand – welcome to part four of our six-part "Barriers to Adopting Digital Pathology" series.

In 1930, Alexander Winton – a pioneer of the automobile industry – penned an article titled, "Get A Horse! America's Skepticism Toward the First Automobiles." It's a fascinating account of the earliest days of cars in this country, in which he details not only the engineering and logistical difficulties the first car innovators faced, but also the skepticism they endured from the public. He wrote: "to advocate replacing the horse, which had served man through centuries, marked one as an imbecile."

Digital pathology – a technology attempting to displace the tried-and-true microscope – faces a similar battle. After two decades, many pathologists still remain dubious. Concerns about image quality and cost always come up. But there is an even simpler question that, in some ways, underlies the others: Why bother? After all, the microscope works perfectly well.

In order to answer this question, digital pathology can perhaps learn something from the automobile industry. Those early cars – once they finally did get going – not only matched their four-legged competitors, but surpassed them. In the same way, digital pathology can win the day by not only providing a streamlined experience equal to the microscope, but also by doing things unimaginable with a glass slide.

Until recently, reviewing slides digitally was a frustrating, physical exercise, requiring furious wheel scrolling and mouse clicking. Today, companies are taking a hard look at the ergonomics of slide review, optimizing their software and even creating simulators to perfectly emulate the experience of looking at a glass slide. Similarly, teams are innovating to allow for fine focus in the z-plane, oil immersion, and polarization.

These efforts, while critical, only get digital pathology to match a microscope. The exciting part of digital pathology is where it can transcend the microscope. This idea invariably evokes the promise of artificial intelligence (AI). Though the revolution is certainly coming, focusing exclusively on AI actually sells digital pathology short. What if digitized slides arranged tissue fragments in rows so they could be reviewed systematically without any piece being missed? What if digital viewers kept track of suspicious foci across deepers and immunohistochemical slides regardless of orientation, sparing the pathologist from doing it manually? What if software tracked high-power fields during a mitotic count and allowed the pathologist to quickly mark mitoses, ensuring that an accurate count was documented for future reference?

These saved seconds and minutes would quickly turn into hours. At that point, digital pathology wouldn't just be providing an easier experience, but a safer one. All the energy once expended on peripheral activities would be devoted to looking at slides, meaning less fatigue, fewer mistakes, and faster turnaround times.

The day will come when digital pathology not only meets but exceeds the high bar set by the microscope, leaving the microscope looking like a horse and buggy. Perhaps then, a historian will write a book about the early years of digital pathology. With any luck, they'll call it, "Get a Microscope!"

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Transforming Cancer Care – One Lab at a Time

Chaim Linhart explores the benefits of AI integration today – and envisions a better tomorrow

By Chaim Linhart

Credit: Ibex Medical Analytics

Though cancer diagnosis has evolved with the latest cutting-edge innovations – from the introduction of immunohistochemistry and genomics to the use of advanced imaging techniques – further advancement is needed to support pathologists who face unprecedented challenges. Specifically, there has been a pronounced increase in both the prevalence and complexity of cancer cases, placing significant burdens on pathologists to meet patient demand. Global cancer incidence increased from 18.7 million in 2010 to 23.6 million in 2019, leading to an overwhelming influx of tissue biopsies in diagnostic laboratories (1). Moreover, as research advances and new therapies become available, diagnosis becomes increasingly complex and demands additional specialized testing.

The rise in cancer cases is compounded by a pronounced shortage of pathologists across the US and Europe. Active pathologists in the field are experiencing heavy workloads as they review more biopsies than physically possible, risking burnout and distraction. Even in pathology labs that have digitized workflows to support caseloads, prioritization, slide review, and report drafting are still handled manually and are not easily scalable. These factors increase strain on pathologists and limit their ability to provide timely and accurate diagnoses to support treatment decisions.

Enter the autopilot of pathology

The incorporation of artificial intelligence (AI) into clinical workflows across healthcare is becoming more commonplace and has proven especially useful in the field of oncology. From assisting in mammogram analysis to localizing tumors in MRI scans, cancer care has advanced significantly with the advent of AI and machine learning tools. Although the use of AI solutions in pathology workflows has lagged, deep learning technologies are particularly suited to the field and have started to have a notable impact.

AI provides rapid and accurate identification of cancer regions in slides prior to the pathologist's review – an important benefit, but today's solutions go even further. Tumor grading, automated measurements, classification of cancer subtypes, detection of cancer-related findings, AI-assisted reporting, and other AI-powered decision support tools increase the accuracy of diagnosis, improve the pathologist's work experience, optimize ordering of ancillary tests, and accelerate diagnostic turnaround times.

Need a more concrete example? AI algorithms can successfully identify and distinguish between invasive ductal carcinoma, invasive lobular carcinoma, and DCIS in breast biopsies – allowing for the rapid ordering of biomarker tests, such as *ER, PR,* and *HER2,* that are necessary to complete the pathology report. AI solutions can further support pathologists in accurately scoring these biomarkers and ensuring patients receive the correct treatments. AI solutions can also provide objective Gleason grading for prostate cancer, triage cancer cases in gastric biopsies, and detect clinically relevant non-cancer features, such as *H. pylori.*

"Active pathologists in the field are experiencing heavy workloads as they review more biopsies than physically possible, risking burnout and distraction."

AI can also serve as a real-time quality control tool for pathologists. An algorithm can review slides and flag discrepancies between its findings and the pathologist's diagnosis. In doing so, AI can help pathologists detect potential diagnostic errors; for example, missed or incorrectly graded cancers. This capability can be considered essential for those laboratories with limited personnel, high caseloads, and an inability to regularly meet auditing requirements.

AI today for a better tomorrow

The combination of expert pathologists and AI is already reshaping the practice of pathology and cancer diagnoses. By incorporating input from a variety of sub-specialties into one seamless solution, AI is becoming a real-time "digital assistant" for pathologists.

Admittedly, more work needs to be done to actualize the full potential of the digital transformation. AI solutions should be fully integrated into pathology workflows and seamlessly embedded into existing image management solutions and lab information systems. But for this to happen, the industry must make open interfaces and interoperable products its de facto standard; it must be easier and simpler for laboratories to deploy digital workflows that include best-of-breed applications from different vendors.

Imagine this lab of the future: Pathologists begin their day with cases already digitized, prioritized, and ready for review. Each case includes all details necessary for a pathologist to confirm a diagnosis, including cancer and subtype detection, tumor measurement, grading, biomarker assessment, and more. Upon reviewing the AI tool's findings, pathologists quickly provide a diagnosis and report it to the referring physician – all using a single unified solution. With routine practices automated and more clear-cut cases completed more quickly, pathologists finally find themselves with the time to focus on more complex cases that require even more attention and expertise. And the patient? They benefit from more accurate, more comprehensive, and more timely diagnosis, while receiving more personalized care and enjoying much better outcomes.

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

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Lowering the Bar – to Treatment

Exploring the impact of the HER2-low biomarker in breast cancer stratification

WARNING: INTERSTITIAL LUNG DISEASE and EMBRYO-FETAL TOXICITY

- Interstitial lung disease (ILD) and pneumonitis, including fatal cases, have been reported with ENHERTU. Monitor for and promptly investigate signs and symptoms including cough, dyspnea, fever, and other new or worsening respiratory symptoms. Permanently discontinue ENHERTU in all patients with Grade 2 or higher ILD/pneumonitis. Advise patients of the risk and to immediately report symptoms.
- Exposure to ENHERTU during pregnancy can cause embryo-fetal harm. Advise patients of these risks and the need for effective contraception.

Please see Important Safety Information below.

Indication

ENHERTU® (fam-trastuzumab deruxtecan-nxki) is a HER2-directed antibody and topoisomerase inhibitor conjugate indicated for the treatment of adult patients with unresectable or metastatic:

- HER2-positive breast cancer who have received a prior anti-HER2-based regimen either:
  - In the metastatic setting, or
  - In the neoadjuvant or adjuvant setting and have developed disease recurrence during or within six months of completing therapy
- HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer, as determined by an FDA-approved test, who have received a prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy

Meet the Experts

Shabnam Jaffer is Chair of the Department of Pathology and Laboratory Medicine at Lenox Hill Hospital, Northwell Health, New York. She is also Professor of Pathology at the Hofstra Zucker School of Medicine. Jaffer has been practicing breast pathology for over 20 years.

Paolo Tarantino is a Breast Medical Oncologist and Advanced Research Fellow at Dana Farber Cancer Institute and Harvard Medical School. His research focuses on HER2-positive and HER2-low breast cancer, and the development of antibody drug conjugates.

Historically, how was human epidermal growth factor receptor 2 (HER2) in breast cancer classified and how is this binary HER2 classification evolving?

Tarantino: Back in the 1990s, we recognized that certain breast tumors – about 15 percent – harbored amplification of the HER2 oncogene that leads to overexpression of the HER2 protein on the cell membrane – an oncogenic event that makes tumor cells more aggressive (1-3). We also learned that we could improve outcomes for patients with HER2-positive breast cancers by blocking the HER2 signal with a monoclonal antibody (3, 4). In 1998, the first targeted therapy for HER2-positive breast cancer was approved by the United States Food and Drug Administration (FDA), and was subsequently approved for early-stage breast cancer, and ultimately followed by many other HER2-directed agents (3, 4). To be clear, these agents were only approved for the treatment of HER2-positive breast cancer as defined

Please see accompanying full Prescribing Information, including Boxed WARNINGS, and Medication Guide.

Prescribing Information

Medication Guide

by immunohistochemistry (IHC) testing – and not for the 85 percent of breast tumors defined as HER2-negative (1, 3).

However, this binary definition of positive and negative has been challenged by potent antibody drug conjugates (ADCs) that can exploit lower expression of HER2 on the cell membrane to selectively deliver potent chemotherapies (1). The first ADC to be approved for eligible patients with tumors that express lower levels of HER2 protein is fam-trastuzumab deruxtecan-nxki (5). Indeed, this advance has led to a three-tiered approach to HER2 classification: HER2-positive, HER2-low, and HER2-0* - some tumors for which HER2 cannot be detected by IHC (6).

In pathology, how relevant is HER2-low?

Jaffer: For a pathologist working in 2023, HER2-low is extremely relevant. Indeed, Dr. Tarantino and I both just attended the USCAP 2023 meeting in New Orleans, where the two most popular topics in breast pathology were HER2-low and artificial intelligence (AI) – with some of the AI material actually focused on HER2-low interpretation.

The positive results of the DESTINY-Breast04 trial, in particular, have highlighted the crucial role of the pathologist in identifying HER2-low patients for the treating oncologist (6). Pathologists are not only aware of HER2-low, but they are hungry to know more – particularly, how to effectively recognize and report HER2-low status.

In many ways, the pathologist and the oncologist are joined at the hip – if a subject, like HER2-low, becomes clinically relevant to the oncologist, it will always become clinically relevant to the pathologist.

How has treatment for patients with HER2-low metastatic breast cancer advanced over the last year? And what information related to treatment benefits and risks do you share with patients receiving ENHERTU® (fam-trastuzumab deruxtecan-nxki)?

Tarantino: We've seen a major evolution in the way we treat patients with HER2-low metastatic breast cancer. In the past, we did not really differentiate in treatment algorithms between HER2-low and HER2 IHC 0 – they were both included in the macro category of HER2-negative and treated only according to expression of hormone receptors (HR) (7). Consequently, we would treat HR-positive/HER2-negative tumors in one way and triple-negative tumors in another. Today, these two categories are further subdivided into HER2-low and HER2 IHC 0 (1, 8). As shown in the aforementioned DESTINY-Breast04 trial, ENHERTU significantly improved both progression free survival and overall survival compared with traditional chemotherapy in the overall study population, which included both HR-positive and HR-negative tumors that were demonstrated to be HER2-low using IHC and reflex in situ hybridization (ISH) (7).

Importantly, we know that HER2-low tumors are very frequent – representing around 60 percent of all HR-positive tumors and about 40 percent of all triple-negative tumors (10, 11). In short, we have a wide group of patients who may benefit from an additional treatment option that may improve overall survival (1, 5, 7).

In the DESTINY-Breast04 trial, the most common (≥20 percent) adverse reactions, including laboratory abnormalities, were nausea (76 percent), decreased white blood cell count (70 percent), decreased hemoglobin (64 percent), decreased neutrophil count (64 percent), decreased lymphocyte count (55 percent), fatigue (54 percent), decreased platelet count (44 percent), alopecia (40 percent), vomiting (40 percent), increased aspartate aminotransferase (38 percent), increased alanine aminotransferase (36 percent), constipation (34 percent), increased blood alkaline phosphatase (34 percent), decreased appetite (32 percent), musculoskeletal pain (32 percent), diarrhea (27 percent), and hypokalemia (25 percent).

"Despite objective criteria, interpretation of HER2 can be inconsistent; after all, the IHC test is semi-quantitative and observer dependent, making it susceptible to human error (11)."

Enhertu has serious Warnings & Precautions. ***Please see Important Safety Information, including Boxed WARNINGS, below.***

How will HER2-low evaluation impact pathology practice?

Jaffer: HER2-low has already impacted pathology practice! Oncologists are eager to identify HER2-low in patients with previously treated metastatic breast cancer, so pathologists are suddenly even more sensitive to any variables that can affect detection and interpretation of HER2 including tissue fixation, the antibody clone being used, antigen retrieval protocols, and so on.

The 2018 ASCO-CAP guidelines, which have been recently reaffirmed and updated, present well defined qualitative and quantitative criteria, which help the pathologist choose the appropriate IHC score of 0, 1+, 2+, or 3+ (8). It's this latter score of 3+ which is considered HER2-positive (8). HER2-positive includes IHC 3+ and 2+ ISH positive, which indicates that a patient may be

eligible for HER2-directed therapy. Accordingly, IHC 2+ undergo reflex ISH testing (8).

Before discussions on HER2-low, there was little incentive for pathologists to distinguish between the values of IHC 0 and 1+, which became grouped together with IHC 2+ ISH negative (8). The DESTINY-Breast04 trial brought new appreciation and recognition of HER2-low, which was defined in that study as IHC 1+ or 2+ with a negative ISH result (7). Suddenly, pathologists needed to pay more attention to qualitative and quantitative criteria – especially when distinguishing between IHC 0 and 1+. Indeed, our practices may need to evolve further as newer categories of HER2 expression are explored (10).

Despite objective criteria, interpretation of HER2 expression can be inconsistent; after all, the IHC test is semi-quantitative and observer dependent, making it susceptible to human error (12). Indeed, several studies have demonstrated high interobserver variability – particularly in the low range (12, 13). Some abstracts at USCAP 2023 showed how, with proper education and consensus between breast pathologists, the interobserver variability improves – but it never disappears (14). With borderline cases, where determination of the cutoff value of 10 percent become problematic, pathologists should confer to reach a consensus (15).

According to the FDA approval, where can you see ENHERTU fitting in for patients with HER2-low metastatic breast cancer. And how will this ultimately impact patient care? How can oncologists help lead this change?

Tarantino: I feel that the FDA approval is very clear and helpful. Right now, as well as being approved for eligible patients with previously treated HER2-positive metastatic breast cancer, ENHERTU is approved for treating patients with metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer that have been previously treated with at least one line of chemotherapy in the metastatic setting or have experienced recurrence during or within six months from completing adjuvant chemotherapy (5).

As I mentioned, this treatment may be potentially relevant for more than half of all patients with metastatic breast cancer – so that's a major population level impact (1). And, again, this drug improved progression free survival and overall survival in DESTINY-Breast04 (7).

How do you see pathologist–oncologist and multidisciplinary team communication changing?

Jaffer: The DESTINY-Breast04 trial results and subsequent approval and endorsement of T-DXd by the FDA and the National Comprehensive Cancer Network® (NCCN®) – certainly led to increased communication between pathologists and oncologists about identifying patients with HER2-low tumors. Since August 2022, I noticed there was a great deal of crosstalk that developed between pathologists and oncologists via phone calls, emails, and tumor boards – there has been a real buzz around the topic.

In this era of HER2-low breast cancer, pathologists and oncologists must collaborate to streamline requests and IHC reports – while educating each other. The CAP Breast Biomarker and Breast Invasive Resection report protocols were recently updated (March 2023) to include a note for HER2-low expression (9). We need to use all possible communication channels – national meetings, society meetings, publications, podcasts, social media, and so on – to optimize education and communication between pathologists and oncologists on this topic. In fact, we witnessed the importance of such active efforts at the USCAP 2023 meeting. Tarantino appeared as a guest speaker, further enlightening pathologists on the clinical relevance and importance of HER2-low. No doubt the conversation around HER2-low will continue to evolve with new drugs, trial results, testing advances, and a better understanding of HER2-low tumors. Working together, pathologists and oncologists can more accurately stratify patients and ensure they receive the most appropriate therapy.

**The 2018 ASCO/CAP guidelines classify HER2 status in breast cancer as positive or negative.*

Abbreviations: ASCO, American Society of Clinical Oncology; CAP, College of American Pathologists; HER2, human epidermal growth factor receptor 2; USCAP, United States and Canadian Academy of Pathology.

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Important Safety Information

Indication

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  - In the metastatic setting, or
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- HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer, as determined by an FDA-approved test, who have received a prior chemotherapy in the metastatic secting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy

Contraindications

None.

WARNING: INTERSTITIAL LUNG DISEASE and EMBRYO-FETAL TOXICITY

- Interstitial lung disease (ILD) and pneumonitis, including fatal cases, have been reported with ENHERTU. Monitor for and promptly investigate signs and symptoms including cough, dyspnea, fever, and other new or worsening respiratory symptoms. Permanently discontinue ENHERTU in all patients with Grade 2 or higher ILD/pneumonitis. Advise patients of the risk and to immediately report symptoms.
- Exposure to ENHERTU during pregnancy can cause embryo-fetal harm. Advise patients of these risks and the need for effective contraception.

Warnings and Precautions

Interstitial Lung Disease / Pneumonitis

Severe, life-threatening, or fatal interstitial lung disease (ILD), including pneumonitis, can occur in patients treated with ENHERTU. A higher incidence of Grade 1 and 2 ILD/pneumonitis has been observed in patients with moderate renal impairment. Advise patients to immediately report cough, dyspnea, fever, and/or any new or worsening respiratory symptoms. Monitor patients for signs and symptoms of ILD. Promptly investigate evidence of ILD. Evaluate patients with suspected ILD by radiographic imaging. Consider consultation with a pulmonologist. For asymptomatic ILD/pneumonitis (Grade 1), interrupt ENHERTU until resolved to Grade 0, then if resolved in ≤28 days from date of onset, maintain dose. If resolved in >28 days from date of onset, reduce dose one level. Consider corticosteroid treatment as soon as ILD/pneumonitis is suspected (e.g., ≥0.5 mg/kg/day prednisolone or equivalent). For symptomatic ILD/pneumonitis (Grade 2 or greater), permanently discontinue ENHERTU. Promptly initiate systemic corticosteroid treatment as soon as ILD/pneumonitis is suspected (e.g., ≥1 mg/kg/day prednisolone or equivalent) and continue for at least 14 days followed by gradual taper for at least 4 weeks.

Metastatic Breast Cancer and Other Solid Tumors (5.4 mg/kg)
In patients with metastatic breast cancer and other solid tumors treated with ENHERTU® (fam-trastuzumab deruxtecan-nxki) 5.4 mg/kg, ILD occurred in 12 percent of patients. Fatal outcomes due to ILD and/or pneumonitis occurred in 1.0 percent of patients treated with ENHERTU. Median time to first onset was 5 months (range: 0.9 to 23).

Neutropenia
Severe neutropenia, including febrile neutropenia, can occur in patients treated with ENHERTU. Monitor complete blood counts prior to initiation of ENHERTU and prior to each dose, and as clinically indicated. For Grade 3 neutropenia (Absolute Neutrophil Count [ANC] <1.0 to 0.5 x 10^9/L), interrupt ENHERTU until resolved to Grade 2 or less, then maintain dose. For Grade 4 neutropenia (ANC <0.5 x 10^9/L), interrupt ENHERTU until resolved to Grade 2 or less, then reduce dose by one level. For febrile neutropenia (ANC <1.0 x 10^9/L and temperature >38.3° C or a sustained temperature of ≥38° C for more than 1 hour), interrupt ENHERTU until resolved, then reduce dose by one level.

Metastatic Breast Cancer and Other Solid Tumors (5.4 mg/kg)
In patients with metastatic breast cancer and other solid tumors treated with ENHERTU 5.4 mg/kg, a decrease in neutrophil count was reported in 65 percent of patients. Sixteen percent had Grade 3 or 4 decreased neutrophil count. Median time to first onset of decreased neutrophil count was 22 days (range: 2 to 664). Febrile neutropenia was reported in 1.1 percent of patients.

Left Ventricular Dysfunction
Patients treated with ENHERTU may be at increased risk of developing left ventricular dysfunction. Left ventricular ejection fraction (LVEF) decrease has been observed with anti-HER2 therapies, including ENHERTU.

Assess LVEF prior to initiation of ENHERTU and at regular intervals during treatment as clinically indicated. Manage LVEF decrease through treatment interruption. When LVEF is >45 percent and absolute decrease from baseline is 10-20 percent, continue treatment with ENHERTU. When LVEF is 40-45 percent and absolute decrease from baseline is <10 percent, continue treatment with ENHERTU and repeat LVEF assessment within 3 weeks. When LVEF is 40-45 percent and absolute decrease from baseline is 10-20 percent, interrupt ENHERTU and repeat LVEF assessment within 3 weeks. If LVEF has not recovered to within 10 percent from baseline, permanently discontinue ENHERTU. If LVEF recovers to within 10 percent from baseline, resume treatment with ENHERTU at the same dose. When LVEF is <40 percent or absolute decrease from baseline is >20 percent, interrupt ENHERTU and repeat LVEF assessment within 3 weeks. If LVEF of <40 percent or absolute decrease from baseline of >20 percent is confirmed, permanently discontinue ENHERTU. Permanently discontinue ENHERTU in patients with symptomatic congestive heart failure. Treatment with ENHERTU has not been studied in patients with a history of clinically significant cardiac disease or LVEF <50 percent prior to initiation of treatment.

Metastatic Breast Cancer and Other Solid Tumors (5.4 mg/kg)
In patients with metastatic breast cancer and other solid tumors treated with ENHERTU 5.4 mg/kg, LVEF decrease was reported in 3.6 percent of patients, of which 0.4 percent were Grade 3.

Embryo-Fetal Toxicity
ENHERTU can cause fetal harm when administered to a pregnant woman. Advise patients of the potential risks to a fetus. Verify the pregnancy status of females of reproductive potential prior to the initiation of ENHERTU. Advise females of reproductive potential to use effective contraception during treatment and for 7 months after the last dose of ENHERTU. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with ENHERTU and for 4 months after the last dose of ENHERTU.

Additional Dose Modifications
Thrombocytopenia
For Grade 3 thrombocytopenia (platelets <50 to 25 x 10^9/L) interrupt ENHERTU until resolved to Grade 1 or less, then maintain dose. For Grade 4 thrombocytopenia (platelets <25 x 10^9/L) interrupt ENHERTU until resolved to Grade 1 or less, then reduce dose by one level.

Adverse Reactions
Metastatic Breast Cancer and Other Solid Tumors (5.4 mg/kg)
The pooled safety population reflects exposure to ENHERTU 5.4 mg/kg intravenously every 3 weeks in 984 patients in Study DS8201-A-J101 (NCT02564900), DESTINY-Breast01, DESTINY-Breast03, DESTINY-Breast04, and another clinical trial. Among these patients 65 percent were exposed for >6 months and 39 percent were exposed for >1 year. In this pooled safety population, the most common (≥20 percent) adverse reactions, including laboratory abnormalities, were nausea (76 percent), decreased white blood cell count (71 percent), decreased hemoglobin (66 percent), decreased neutrophil count (65 percent), decreased lymphocyte count (55 percent), fatigue (54 percent), decreased platelet count (47 percent), increased aspartate aminotransferase (48 percent), vomiting (44 percent), increased alanine aminotransferase (42 percent), alopecia (39 percent), increased blood alkaline phosphatase (39 percent), constipation (34 percent), musculoskeletal pain (32 percent), decreased appetite (32 percent), hypokalemia (28 percent), diarrhea (28 percent), and respiratory infection (24 percent).

HER2-Low Metastatic Breast Cancer

DESTINY-Breast04

The safety of ENHERTU was evaluated in 371 patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer who received ENHERTU 5.4 mg/kg intravenously every 3 weeks in DESTINY-Breast04. The median duration of treatment was 8 months (range: 0.2 to 33) for patients who received ENHERTU.

Serious adverse reactions occurred in 28 percent of patients receiving ENHERTU. Serious adverse reactions in >1 percent of patients who received ENHERTU were ILD/pneumonitis, pneumonia, dyspnea, musculoskeletal pain, sepsis, anemia, febrile neutropenia, hypercalcemia, nausea, pyrexia, and vomiting. Fatalities due to adverse reactions occurred in 4 percent of patients including ILD/pneumonitis (3 patients); sepsis (2 patients); and ischemic colitis, disseminated intravascular coagulation, dyspnea, febrile neutropenia, general physical health deterioration, pleural effusion, and respiratory failure (1 patient each).

ENHERTU was permanently discontinued in 16 percent of patients, of which ILD/pneumonitis accounted for 8 percent. Dose interruptions due to adverse reactions occurred in 39 percent of patients treated with ENHERTU. The most frequent adverse reactions (>2 percent) associated with dose interruption were neutropenia, fatigue, anemia, leukopenia, COVID-19, ILD/pneumonitis, increased transaminases, and hyperbilirubinemia. Dose reductions occurred in 23 percent of patients treated with ENHERTU. The most frequent adverse reactions (>2 percent) associated with dose reduction were fatigue, nausea, thrombocytopenia, and neutropenia.

The most common (≥20 percent) adverse reactions, including laboratory abnormalities, were nausea (76 percent), decreased white blood cell count (70 percent), decreased hemoglobin (64 percent), decreased neutrophil count (64 percent), decreased lymphocyte count (55 percent), fatigue (54 percent), decreased platelet count (44 percent), alopecia (40 percent), vomiting (40 percent), increased aspartate aminotransferase (38 percent), increased alanine aminotransferase (36 percent), constipation (34 percent), increased blood alkaline phosphatase (34 percent), decreased appetite (32 percent), musculoskeletal pain (32 percent), diarrhea (27 percent), and hypokalemia (25 percent).

Use in Specific Populations

- **Pregnancy:** ENHERTU can cause fetal harm when administered to a pregnant woman. Advise patients of the potential risks to a fetus. There are clinical considerations if ENHERTU is used in pregnant women, or if a patient becomes pregnant within 7 months after the last dose of ENHERTU.
- **Lactation:** There are no data regarding the presence of ENHERTU in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in a breastfed child, advise women not to breastfeed during treatment with ENHERTU and for 7 months after the last dose.
- **Females and Males of Reproductive Potential:** Pregnancy testing: Verify pregnancy status of females of reproductive potential prior to initiation of ENHERTU. Contraception: Females: ENHERTU can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment with ENHERTU and for 7 months after the last dose. Males: Advise male patients with female partners of reproductive potential to use effective contraception during treatment with ENHERTU and for 4 months after the last dose. Infertility: ENHERTU may impair male reproductive function and fertility.
- **Pediatric Use:** Safety and effectiveness of ENHERTU have not been established in pediatric patients.
- **Geriatric Use:** Of the 883 patients with breast cancer treated with ENHERTU 5.4 mg/kg, 22 percent were ≥65 years and 3.6 percent were ≥75 years. No overall differences in efficacy within clinical studies were observed between patients ≥65 years of age compared to younger patients. There was a higher incidence of Grade 3-4 adverse reactions observed in patients aged ≥65 years (60 percent) as compared to younger patients (48 percent).
- **Renal Impairment:** A higher incidence of Grade 1 and 2 ILD/pneumonitis has been observed in patients with moderate renal impairment. Monitor patients with moderate renal impairment more frequently. The recommended dosage of ENHERTU has not been established for patients with severe renal impairment (CLcr <30 mL/min).
- **Hepatic Impairment:** In patients with moderate hepatic impairment, due to potentially increased exposure, closely monitor for increased toxicities related to the topoisomerase inhibitor. The recommended dosage of ENHERTU has not been established for patients with severe hepatic impairment (total bilirubin >3 times ULN and any AST).

To report SUSPECTED ADVERSE REACTIONS, contact Daiichi Sankyo, Inc. at 1-877-437-7763 or FDA at 1-800-FDA-1088 or fda.gov/medwatch.

Please see accompanying full Prescribing Information, including Boxed WARNINGS, and Medication Guide.

This resource is intended for US healthcare professionals only. Interviewees were compensated for their time.

ENHERTU® (fam-trastuzumab deruxtecan-nxki) for injection, for intravenous use
Initial U.S. Approval: 2019

BRIEF SUMMARY: See package insert for full prescribing information.

WARNING: INTERSTITIAL LUNG DISEASE and EMBRYO-FETAL TOXICITY

- **Interstitial Lung Disease (ILD) and pneumonitis, including fatal cases, have been reported with ENHERTU. Monitor for and promptly investigate signs and symptoms including cough, dyspnea, fever, and other new or worsening respiratory symptoms. Permanently discontinue ENHERTU in all patients with Grade 2 or higher ILD/pneumonitis. Advise patients of the risk and the need to immediately report symptoms *[see Dosage and Administration (2.3) in the full prescribing information, Warnings and Precautions (5.1)]*.**
- **Embryo-Fetal Toxicity: Exposure to ENHERTU during pregnancy can cause embryo-fetal harm. Advise patients of these risks and the need for effective contraception *[see Warnings and Precautions (5.4), Use in Specific Populations (8.1, 8.3)]*.**

1 INDICATIONS AND USAGE

1.1 HER2-Positive Metastatic Breast Cancer

ENHERTU is indicated for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received a prior anti-HER2-based regimen either:

- in the metastatic setting, or
- in the neoadjuvant or adjuvant setting and have developed disease recurrence during or within six months of completing therapy.

1.2 HER2-Low Metastatic Breast Cancer

ENHERTU is indicated for the treatment of adult patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer, as determined by an FDA-approved test, who have received a prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy *[see Dosage and Administration (2.1) in the full prescribing information]*.

1.3 Unresectable or Metastatic HER2-Mutant Non-Small Cell Lung Cancer

ENHERTU is indicated for the treatment of adult patients with unresectable or metastatic non-small cell lung cancer (NSCLC) whose tumors have activating HER2 (ERBB2) mutations, as detected by an FDA-approved test, and who have received a prior systemic therapy.

This indication is approved under accelerated approval based on objective response rate and duration of response *[see Clinical Studies (14.3) in the full prescribing information]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

1.4 Locally Advanced or Metastatic Gastric Cancer

ENHERTU is indicated for the treatment of adult patients with locally advanced or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma who have received a prior trastuzumab-based regimen.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Interstitial Lung Disease/Pneumonitis

Severe, life-threatening, or fatal interstitial lung disease (ILD), including pneumonitis, can occur in patients treated with ENHERTU *[see Adverse Reactions (6.1)]*. A higher incidence of Grade 1 and 2 ILD/pneumonitis has been observed in patients with moderate renal impairment.

Advise patients to immediately report cough, dyspnea, fever, and/or any new or worsening respiratory symptoms. Monitor patients for signs and symptoms of ILD. Promptly investigate evidence of ILD. Evaluate patients with suspected ILD by radiographic imaging. Consider consultation with a pulmonologist. For asymptomatic (Grade 1) ILD, consider corticosteroid treatment (e.g., ≥0.5 mg/kg/day prednisolone or equivalent). Withhold ENHERTU until recovery *[see Dosage and Administration (2.3) in the full prescribing information]*. In cases of symptomatic ILD (Grade 2 or greater), promptly initiate systemic corticosteroid treatment (e.g., ≥1 mg/kg/day prednisolone or equivalent) and continue for at least 14 days followed by gradual taper for at least 4 weeks. Permanently discontinue ENHERTU in patients who are diagnosed with symptomatic (Grade 2 or greater) ILD *[see Dosage and Administration (2.3) in the full prescribing information]*.

Metastatic Breast Cancer and HER2-Mutant NSCLC (5.4 mg/kg)
In patients with metastatic breast cancer and HER2-mutant NSCLC treated with ENHERTU 5.4 mg/kg, ILD occurred in 12% of patients. Fatal outcomes due to ILD and/or pneumonitis occurred in 1.0% of patients treated with ENHERTU. Median time to first onset was 5 months (range: 0.9 to 23).

Locally Advanced or Metastatic Gastric Cancer (6.4 mg/kg)
In patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma treated with ENHERTU 6.4 mg/kg, ILD occurred in 10% of patients. Median time to first onset was 2.8 months (range: 1.2 to 21).

5.2 Neutropenia

Severe neutropenia, including febrile neutropenia, can occur in patients treated with ENHERTU.

Monitor complete blood counts prior to initiation of ENHERTU and prior to each dose, and as clinically indicated. Based on the severity of neutropenia, ENHERTU may require dose interruption or reduction *[see Dosage and Administration (2.3) in the full prescribing information]*.

Metastatic Breast Cancer and HER2-Mutant NSCLC (5.4 mg/kg)
In patients with metastatic breast cancer and HER2-mutant NSCLC treated with ENHERTU 5.4 mg/kg, a decrease in neutrophil count was reported in 65% of patients. Sixteen percent had Grade 3 or 4 decreased neutrophil count. Median time to first onset of decreased neutrophil count was 22 days (range: 2 to 664). Febrile neutropenia was reported in 1.1% of patients.

Locally Advanced or Metastatic Gastric Cancer (6.4 mg/kg)
In patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma treated with ENHERTU 6.4 mg/kg, a decrease in neutrophil count was reported in 72% of patients. Fifty-one percent had Grade 3 or 4 decreased neutrophil count. Median time to first onset of decreased neutrophil count was 16 days (range: 4 to 187). Febrile neutropenia was reported in 4.8% of patients.

5.3 Left Ventricular Dysfunction

Patients treated with ENHERTU may be at increased risk of developing left ventricular dysfunction. Left ventricular ejection fraction (LVEF) decrease has been observed with anti-HER2 therapies, including ENHERTU.

Assess LVEF prior to initiation of ENHERTU and at regular intervals during treatment as clinically indicated. Manage LVEF decrease through treatment interruption. Permanently discontinue ENHERTU if LVEF of less than 40% or absolute decrease from baseline of greater than 20% is confirmed. Permanently discontinue ENHERTU in patients with symptomatic congestive heart failure (CHF) *[see Dosage and Administration (2.3) in the full prescribing information]*.

Treatment with ENHERTU has not been studied in patients with a history of clinically significant cardiac disease or LVEF less than 50% prior to initiation of treatment.

Metastatic Breast Cancer and HER2-Mutant NSCLC (5.4 mg/kg)
In patients with metastatic breast cancer and HER2-mutant NSCLC treated with ENHERTU 5.4 mg/kg, LVEF decrease was reported in 3.6% of patients, of which 0.4% were Grade 3.

Locally Advanced or Metastatic Gastric Cancer (6.4 mg/kg)
In patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma treated with ENHERTU 6.4 mg/kg, no clinical adverse events of heart failure were reported; however, on echocardiography, 8% were found to have asymptomatic Grade 2 decrease in LVEF.

5.4 Embryo-Fetal Toxicity

Based on its mechanism of action, ENHERTU can cause fetal harm when administered to a pregnant woman. In postmarketing reports, use of a HER2-directed antibody during pregnancy resulted in cases of oligohydramnios manifesting as fatal pulmonary hypoplasia, skeletal abnormalities, and neonatal death. Based on its mechanism of action, the topoisomerase inhibitor component of ENHERTU, DXd, can also cause embryo-fetal harm when administered to a pregnant woman because it is genotoxic and targets actively dividing cells *[see Use in Specific Populations (8.1), Clinical Pharmacology (12.1), Nonclinical Toxicology (13.1) in the full prescribing information]*. Advise patients of the potential risks to a fetus.

Verify the pregnancy status of females of reproductive potential prior to the initiation of ENHERTU. Advise females of reproductive potential to use effective contraception during treatment and for 7 months after the last dose of ENHERTU. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with ENHERTU and for 4 months after the last dose of ENHERTU *[see Use in Specific Populations (8.1, 8.3)]*.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Interstitial Lung Disease/Pneumonitis *[see Warnings and Precautions (5.1)]*
- Neutropenia *[see Warnings and Precautions (5.2)]*
- Left Ventricular Dysfunction *[see Warnings and Precautions (5.3)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly

compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Metastatic Breast Cancer and HER2-Mutant NSCLC (5.4 mg/kg)
The pooled safety population described in WARNINGS and PRECAUTIONS reflects exposure to ENHERTU 5.4 mg/kg intravenously every 3 weeks in 984 patients in Study DS8201-A-J101 (NCT02564900), DESTINY-Breast01, DESTINY-Breast03, DESTINY-Breast04, and DESTINY-Lung02. Among these patients, 65% were exposed for greater than 6 months and 39% were exposed for greater than one year. In this pooled safety population, the most common (≥20%) adverse reactions (including laboratory abnormalities) were nausea (76%), decreased white blood cell count (71%), decreased hemoglobin (66%), decreased neutrophil count (65%), decreased lymphocyte count (55%), fatigue (54%), decreased platelet count (47%), increased aspartate aminotransferase (48%), vomiting (44%), increased alanine aminotransferase (42%), alopecia (39%), increased blood alkaline phosphatase (39%), constipation (34%), musculoskeletal pain (32%), decreased appetite (32%), hypokalemia (28%), diarrhea (28%), and respiratory infection (24%).

Locally Advanced or Metastatic Gastric Cancer (6.4 mg/kg)
The data described in WARNINGS and PRECAUTIONS reflect exposure to ENHERTU 6.4 mg/kg intravenously every 3 weeks in 125 patients in DESTINY-Gastric01.

HER2-Positive Metastatic Breast Cancer
DESTINY-Breast03
The safety of ENHERTU was evaluated in 257 patients with unresectable or metastatic HER2-positive breast cancer who received at least one dose of ENHERTU 5.4 mg/kg in DESTINY-Breast03 *[see Clinical Studies (14.1) in the full prescribing information]*. ENHERTU was administered by intravenous infusion once every three weeks. The median duration of treatment was 14 months (range: 0.7 to 30) for patients who received ENHERTU and 7 months (range: 0.7 to 25) for patients who received ado-trastuzumab emtansine.

Serious adverse reactions occurred in 19% of patients receiving ENHERTU. Serious adverse reactions in >1% of patients who received ENHERTU were vomiting, interstitial lung disease, pneumonia, pyrexia, and urinary tract infection. Fatalities due to adverse reactions occurred in 0.8% of patients including COVID-19 and sudden death (one patient each).

ENHERTU was permanently discontinued in 14% of patients, of which ILD/pneumonitis accounted for 8%. Dose interruptions due to adverse reactions occurred in 44% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose interruption were neutropenia, leukopenia, anemia, thrombocytopenia, pneumonia, nausea, fatigue, and ILD/pneumonitis. Dose reductions occurred in 21% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose reduction were nausea, neutropenia, and fatigue.

The most common (≥20%) adverse reactions, including laboratory abnormalities, were nausea, decreased white blood cell count, decreased neutrophil count, increased aspartate aminotransferase, decreased hemoglobin, decreased lymphocyte count, increased alanine aminotransferase, decreased platelet count, fatigue, vomiting, increased blood alkaline phosphatase, alopecia, hypokalemia, constipation, musculoskeletal pain, diarrhea, decreased appetite, headache, respiratory infection, abdominal pain, increased blood bilirubin, and stomatitis.

Tables 3 and 4 summarize common adverse reactions and laboratory abnormalities observed in DESTINY-Breast03.

Table 3: Common Adverse Reactions (≥10% All Grades or ≥2% Grades 3-4) in Patients Treated with ENHERTU in DESTINY-Breast03

Adverse Reactions	ENHERTU 5.4 mg/kg N=257		Ado-trastuzumab emtansine 3.6 mg/kg N=261	
	All Grades %	Grades 3-4 %	All Grades %	Grades 3-4 %
Gastrointestinal Disorders				
Nausea	76	7	30	0.4
Vomiting	49	1.6	10	0.8
Constipation	34	0	20	0
Diarrhea	29	1.2	7	0.4
Abdominal pain[a]	21	0.8	8	0.4
Stomatitis[b]	20	0.8	5	0
Dyspepsia	11	0	6	0
General Disorders and Administration Site Conditions				
Fatigue[c]	49	6	35	0.8
Anemia[d]	33	7	17	6
Skin and Subcutaneous Tissue Disorders				
Alopecia[e]	37	0.4	3.1	0
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal pain[f]	31	1.2	25	0.4
Metabolism and Nutrition Disorders				
Decreased appetite	29	1.6	17	0.4
Investigations				
Decreased weight	17	1.2	6	0.4
Respiratory, Thoracic and Mediastinal Disorders				
Respiratory infection[g]	22	0.8	12	1.1
Epistaxis	11	0	16	0.4
Cough	11	0.4	10	0
Interstitial lung disease[h]	11	0.8	1.9	0
Nervous System Disorders				
Headache[i]	22	0.4	16	0
Peripheral neuropathy[j]	13	0.4	14	0.4
Dizziness	13	0.4	8	0

Events were graded using NCI CTCAE version 5.0.
a Including abdominal pain, abdominal discomfort, lower abdominal pain, and upper abdominal pain
b Including stomatitis, aphthous ulcer, mouth ulceration, oral mucosa erosion, and oral mucosal eruption
c Including fatigue, asthenia, malaise, and lethargy
d Including anemia, decreased hemoglobin, and decreased red blood cell count
e This Grade 3 event was reported by the investigator. Per NCI CTCAE v.5.0, the highest NCI CTCAE grade for alopecia is Grade 2.
f Including back pain, myalgia, pain in extremity, musculoskeletal pain, muscle spasms, bone pain, neck pain, musculoskeletal chest pain, and limb discomfort
g Including respiratory tract infection, lower and upper respiratory tract infection, pneumonia, influenza, influenza-like illness, viral upper respiratory infection, bronchitis, and respiratory syncytial virus infection
h Interstitial lung disease includes events that were adjudicated as ILD for ENHERTU: pneumonitis, interstitial lung disease, organizing pneumonia, pneumonia, and pulmonary mass. For ado-trastuzumab emtansine: pneumonitis, interstitial lung disease, organizing pneumonia, and pulmonary embolism.
i Including headache and migraine
j Including peripheral neuropathy, peripheral sensory neuropathy, and paresthesia

Other clinically relevant adverse reactions reported in less than 10% of patients in the ENHERTU-treated group were:
- *Respiratory, Thoracic and Mediastinal Disorders:* dyspnea (8%)
- *Skin and Subcutaneous Tissue Disorders:* pruritus (8%) and skin hyperpigmentation (6%) [including skin hyperpigmentation, skin discoloration, and pigmentation disorder]
- *Nervous System Disorders:* dysgeusia (6%)
- *Metabolism and Nutrition Disorders:* dehydration (4.3%)
- *Eye Disorders:* blurred vision (3.5%)
- *Cardiac Disorders:* asymptomatic left ventricular ejection fraction decrease (2.7%) *[see Warnings and Precautions (5.3)]*
- *Injury, Poisoning and Procedural Complications:* infusion-related reactions (2.3%) [including hypersensitivity and infusion-related reactions]
- *Blood and Lymphatic System Disorders:* febrile neutropenia (0.8%)

Table 4: Selected Laboratory Abnormalities in Patients in DESTINY-Breast03

Laboratory Parameter	ENHERTU 5.4 mg/kg N=257		Ado-trastuzumab emtansine 3.6 mg/kg N=261	
	All Grades %	Grades 3-4 %	All Grades %	Grades 3-4 %
Hematology				
Decreased white blood cell count	74	8	24	0.8
Decreased neutrophil count	70	18	30	2.3
Decreased hemoglobin	64	7	38	6
Decreased lymphocyte count	55	14	23	3.9
Decreased platelet count	52	7	79	24
Chemistry				
Increased aspartate aminotransferase	67	0.8	83	5
Increased alanine aminotransferase	53	1.6	67	6
Increased blood alkaline phosphatase	49	0.8	46	0.8
Hypokalemia	35	4.7	39	1.5
Increased blood bilirubin	20	0	14	0
Increased blood creatinine	16	0.8	8	0.4

Percentages were calculated using patients with worsening laboratory values from baseline and the number of patients with both baseline and post-treatment measurements as the denominator.
Frequencies were based on NCI CTCAE v.5.0 grade-derived laboratory abnormalities.

DESTINY-Breast01 and Study DS8201-A-J101

The safety of ENHERTU was evaluated in a pooled analysis of 234 patients with unresectable or metastatic HER2-positive breast cancer who received at least one dose of ENHERTU 5.4 mg/kg in DESTINY-Breast01 and Study DS8201-A-J101 (NCT02564900) *[see Clinical Studies (14.1) in the full prescribing information]*. ENHERTU was administered by intravenous infusion once every three weeks. The median duration of treatment was 7 months (range: 0.7 to 31).

In the pooled 234 patients, the median age was 56 years (range: 28-96), 74% of patients were <65 years, 99.6% of patients were female, and the majority were White (51%) or Asian (42%). Patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 (58%) or 1 (42%) at baseline. Ninety-four percent had visceral disease, 31% had bone metastases, and 13% had brain metastases.

Serious adverse reactions occurred in 20% of patients receiving ENHERTU. Serious adverse reactions in >1% of patients who received ENHERTU were interstitial lung disease, pneumonia, vomiting, nausea, cellulitis, hypokalemia, and intestinal obstruction. Fatalities due to adverse reactions occurred in 4.3% of patients including interstitial lung disease (2.6%), and the following events occurred in one patient each (0.4%): acute hepatic failure/acute kidney injury, general physical health deterioration, pneumonia, and hemorrhagic shock.

ENHERTU was permanently discontinued in 9% of patients, of which ILD accounted for 6%. Dose interruptions due to adverse reactions occurred in 33% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose interruption were neutropenia, anemia, thrombocytopenia, leukopenia, upper respiratory tract infection, fatigue, nausea, and ILD. Dose reductions occurred in 18% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose reduction were fatigue, nausea, and neutropenia.

The most common (≥20%) adverse reactions, including laboratory abnormalities, were nausea, decreased white blood cell count, decreased hemoglobin, decreased neutrophil count, fatigue, vomiting, alopecia, increased aspartate aminotransferase, increased alanine aminotransferase, decreased platelet count, constipation, decreased appetite, diarrhea, hypokalemia, and cough.

Tables 5 and 6 summarize common adverse reactions and laboratory abnormalities observed in ENHERTU-treated patients in DESTINY-Breast01 and Study DS8201-A-J101.

Table 5: Common Adverse Reactions (≥10% All Grades or ≥2% Grades 3 or 4) in Patients in DESTINY-Breast01 and Study DS8201-A-J101

Adverse Reactions	ENHERTU 5.4 mg/kg N=234	
	All Grades %	Grades 3 or 4 %
Gastrointestinal Disorders		
Nausea	79	7
Vomiting	47	3.8
Constipation	35	0.9
Diarrhea	29	1.7
Abdominal pain[a]	19	1.3
Stomatitis[b]	14	0.9
Dyspepsia	12	0
General Disorders and Administration Site Conditions		
Fatigue[c]	59	6
Skin and Subcutaneous Tissue Disorders		
Alopecia	46	0.4[d]
Rash[e]	10	0
Metabolism and Nutrition Disorders		
Decreased appetite	32	1.3
Blood and Lymphatic System Disorders		
Anemia[f]	31	7
Respiratory, Thoracic and Mediastinal Disorders		
Cough	20	0
Dyspnea	13	1.3
Epistaxis	13	0
Interstitial lung disease[g]	9	2.6[h]
Nervous System Disorders		
Headache[i]	19	0
Dizziness	10	0
Infections and Infestations		
Upper respiratory tract infection[j]	15	0
Eye Disorders		
Dry eye	11	0.4[k]

Events were graded using NCI CTCAE version 4.03.
a Including abdominal discomfort, gastrointestinal pain, abdominal pain, lower abdominal pain, and upper abdominal pain
b Including stomatitis, aphthous ulcer, mouth ulceration, oral mucosa erosion, and oral mucosa blistering. One Grade 1 event of aphthous ulcer was not included in the summary of grouped term stomatitis (from DESTINY-Breast01).
c Including fatigue and asthenia
d This Grade 3 event was reported by the investigator. Per NCI CTCAE v.4.03, the highest NCI CTCAE grade for alopecia is Grade 2.
e Including rash, pustular rash, and maculo-papular rash
f Including anemia, decreased hemoglobin, decreased hematocrit, and decreased red blood cell count
g Interstitial lung disease includes events that were adjudicated as ILD: pneumonitis, interstitial lung disease, respiratory failure, organizing pneumonia, acute respiratory failure, lung infiltration, lymphangitis, and alveolitis.
h All events had fatal outcomes (n=6).
i Including headache, sinus headache, and migraine
j Including influenza, influenza-like illness, and upper respiratory tract infection
k This Grade 4 event was reported by the investigator. Per NCI CTCAE v.4.03, the highest NCI CTCAE grade for dry eye is Grade 3.

Other clinically relevant adverse reactions reported in less than 10% of patients were:

- *Injury, Poisoning and Procedural Complications:* infusion-related reactions (2.6%)
- *Blood and Lymphatic System Disorders:* febrile neutropenia (1.7%)

Table 6: Selected Laboratory Abnormalities in Patients with Unresectable or Metastatic HER2-positive Breast Cancer Treated with ENHERTU in DESTINY-Breast01 and Study DS8201-A-J101

Laboratory Parameter	ENHERTU 5.4 mg/kg N=234	
	All Grades %	Grades 3 or 4 %
Hematology		
Decreased white blood cell count	70	7
Decreased hemoglobin	70	7
Decreased neutrophil count	62	16
Decreased platelet count	37	3.4
Chemistry		
Increased aspartate aminotransferase	41	0.9
Increased alanine aminotransferase	38	0.4
Hypokalemia	26	3

Percentages were calculated using patients with worsening laboratory values from baseline and the number of patients with both baseline and post-treatment measurements as the denominator.
Frequencies were based on NCI CTCAE v.4.03 grade-derived laboratory abnormalities.

HER2-Low Metastatic Breast Cancer

The safety of ENHERTU was evaluated in 371 patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer who received ENHERTU 5.4 mg/kg in DESTINY-Breast04 *[see Clinical Studies (14.2) in the full prescribing information]*. ENHERTU was administered by intravenous infusion once every three weeks. The median duration of treatment was 8 months (range: 0.2 to 33) for patients who received ENHERTU.

Serious adverse reactions occurred in 28% of patients receiving ENHERTU. Serious adverse reactions in >1% of patients who received ENHERTU were ILD/pneumonitis, pneumonia, dyspnea, musculoskeletal pain, sepsis, anemia, febrile neutropenia, hypercalcemia, nausea, pyrexia, and vomiting. Fatalities due to adverse reactions occurred in 4.0% of patients including ILD/pneumonitis (3 patients); sepsis (2 patients); and ischemic colitis, disseminated intravascular coagulation, dyspnea, febrile neutropenia, general physical health deterioration, pleural effusion, and respiratory failure (1 patient each).

ENHERTU was permanently discontinued in 16% of patients, of which ILD/pneumonitis accounted for 8%. Dose interruptions due to adverse reactions occurred in 39% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose interruption were neutropenia, fatigue, anemia, leukopenia, COVID-19, ILD/pneumonitis, increased transaminases, and hyperbilirubinemia. Dose reductions occurred in 23% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose reduction were fatigue, nausea, thrombocytopenia, and neutropenia.

The most common (≥20%) adverse reactions, including laboratory abnormalities, were nausea, decreased white blood cell count, decreased hemoglobin, decreased neutrophil count, decreased lymphocyte count, fatigue, decreased platelet count, alopecia, vomiting, increased aspartate aminotransferase, increased alanine aminotransferase, constipation, increased blood alkaline phosphatase, decreased appetite, musculoskeletal pain, diarrhea, and hypokalemia.

Tables 7 and 8 summarize common adverse reactions and laboratory abnormalities observed in DESTINY-Breast04.

Table 7: Common Adverse Reactions (≥10% All Grades or ≥2% Grades 3 or 4) in Patients Treated with ENHERTU in DESTINY-Breast04

Adverse Reactions	ENHERTU 5.4 mg/kg N=371		Chemotherapy N=172	
	All Grades %	Grades 3 or 4 %	All Grades %	Grades 3 or 4 %
Gastrointestinal Disorders				
Nausea	76	4.6	30	0
Vomiting	40	1.6	13	0
Constipation	34	0.8	22	0
Diarrhea	27	1.3	22	1.7
Abdominal pain[a]	18	0.5	13	0
Stomatitis[b]	13	0.3	12	0.6

(continued)

Table 7: Common Adverse Reactions (≥10% All Grades or ≥2% Grades 3 or 4) in Patients Treated with ENHERTU in DESTINY-Breast04

Adverse Reactions	ENHERTU 5.4 mg/kg N=371		Chemotherapy N=172	
	All Grades %	Grades 3 or 4 %	All Grades %	Grades 3 or 4 %
General Disorders and Administration Site Conditions				
Fatigue[c]	54	9	48	4.7
Pyrexia	12	0.3	13	0
Skin and Subcutaneous Tissue Disorders				
Alopecia	40	0	33	0
Rash[d]	13	0	23	4.7
Blood and Lymphatic System Disorders				
Anemia[e]	39	10	27	5
Metabolism and Nutrition Disorders				
Decreased appetite	32	2.4	19	1.2
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal pain[f]	32	1.3	31	0.6
Investigations				
Decreased weight	16	0.3	8	0
Vascular Disorders				
Hemorrhage[g]	16	0	3.5	0
Nervous System Disorders				
Headache[h]	15	0.3	6	0
Peripheral neuropathy[i]	13	0	29	5
Dizziness[j]	11	0.5	6	0
Infections and Infestations				
Upper respiratory tract infection[k]	14	0.3	5	0
Respiratory, Thoracic and Mediastinal Disorders				
Interstitial lung disease[l]	12	1.3	0.6	0
Dyspnea	10	1.3	9	1.2

Events were graded using NCI CTCAE version 5.0.

a Including abdominal pain, abdominal discomfort, lower abdominal pain, and upper abdominal pain

b Including stomatitis, aphthous ulcer, mouth ulceration, and pharyngeal inflammation

c Including fatigue, asthenia, and malaise

d Including rash, pustular rash, pruritic rash, maculo-papular rash, palmar-plantar erythrodysesthesia syndrome, papular rash, macular rash, eczema, erythema multiforme, dermatitis, urticarial dermatitis, drug eruption, and dermatitis bullous

e Including anemia, decreased hemoglobin, and decreased red blood cell count

f Including back pain, myalgia, pain in extremity, musculoskeletal pain, bone pain, musculoskeletal chest pain, arthralgia, noncardiac chest pain, musculoskeletal stiffness, arthritis, spinal pain, and neck pain

g Including esophageal varices, hemorrhage, hemorrhoidal hemorrhage, epistaxis, hematuria, conjunctival hemorrhage, vaginal hemorrhage, gingival bleeding, genital hemorrhage, eye hemorrhage, hemoptysis, hemorrhagic cystitis, pharyngeal hemorrhage, rectal hemorrhage, upper gastrointestinal hemorrhage, and esophageal hemorrhage

h Including headache and migraine

i Including peripheral neuropathy, peripheral sensory neuropathy, peripheral motor neuropathy, polyneuropathy, paresthesia, hypoesthesia, dysesthesia, and neuralgia

j Including dizziness, postural dizziness, and vertigo

k Including upper respiratory tract infection, influenza, influenza-like illness, nasopharyngitis, pharyngitis, sinusitis, and rhinitis

l Interstitial lung disease includes events that were adjudicated as ILD for ENHERTU: interstitial lung disease, pneumonitis, organizing pneumonia, pneumonia, and radiation pneumonitis.

Other clinically relevant adverse reactions reported in less than 10% of patients treated with ENHERTU:

- *Nervous System Disorders:* dysgeusia (10%)
- *Respiratory, Thoracic and Mediastinal Disorders:* cough (10%)
- *Gastrointestinal Disorders:* abdominal distension (5%), gastritis (2.7%), flatulence (2.4%)

- *Eye Disorders:* blurred vision (4.9%) [including blurred vision and visual impairment]
- *Skin and Subcutaneous Tissue Disorders:* pruritus (3.2%) and skin hyperpigmentation (2.7%) [including skin hyperpigmentation, skin discoloration, and pigmentation disorder]
- *Metabolism and Nutrition Disorders:* dehydration (1.9%)
- *Blood and Lymphatic System Disorders:* febrile neutropenia (1.1%)
- *Injury, Poisoning and Procedural Complications:* infusion-related reactions (0.5%) [including injection site reaction and chills]

Table 8: Selected Laboratory Abnormalities in Patients in DESTINY-Breast04

Laboratory Parameter	ENHERTU 5.4 mg/kg N=371		Chemotherapy N=172	
	All Grades %	Grades 3 or 4 %	All Grades %	Grades 3 or 4 %
Hematology				
Decreased white blood cell count	70	9	78	25
Decreased hemoglobin	64	8	53	6
Decreased neutrophil count	64	14	73	38
Decreased lymphocyte count	55	18	40	11
Decreased platelet count	44	6	21	0.6
Chemistry				
Increased aspartate aminotransferase	38	2.2	38	4.1
Increased alanine aminotransferase	36	0.8	38	4.1
Increased blood alkaline phosphatase	34	0.3	24	0
Hypokalemia	25	3.3	17	1.2
Increased blood bilirubin	16	2.7	15	0.6
Increased blood creatinine	15	1.1	9	0.6

Percentages were calculated using patients with worsening laboratory values from baseline and the number of patients with both baseline and post-treatment measurements as the denominator.
Frequencies were based on NCI CTCAE v.5.0 grade-derived laboratory abnormalities.

Unresectable or Metastatic HER2-Mutant NSCLC

DESTINY-Lung02 evaluated two dose levels (5.4 mg/kg [n=101] and 6.4 mg/kg [n=50]); however, only the results for the recommended dose of 5.4 mg/kg intravenously every 3 weeks are described below due to increased toxicity observed with the higher dose in patients with NSCLC, including ILD/pneumonitis.

The safety of ENHERTU was evaluated in 101 patients in DESTINY-Lung02 *[see Clinical Studies (14.3) in the full prescribing information]*. Patients received ENHERTU 5.4 mg/kg intravenously once every three weeks until disease progression or unacceptable toxicity. Nineteen percent of patients were exposed for greater than 6 months. The median age was 59 years (range 30 to 83); 64% were female; 23% were White, 64% were Asian, and 14% were other races.

Serious adverse reactions occurred in 30% of patients receiving ENHERTU. Serious adverse reactions in >1% of patients who received ENHERTU were ILD/pneumonitis, thrombocytopenia, dyspnea, nausea, pleural effusion, and increased troponin I. Fatality occurred in 1 patient with suspected ILD/pneumonitis (1%).

ENHERTU was permanently discontinued due to an adverse reaction in 8% of patients. Adverse reactions which resulted in permanent discontinuation of ENHERTU were ILD/pneumonitis, diarrhea, hypokalemia, hypomagnesemia, myocarditis, and vomiting. Dose interruptions of ENHERTU due to adverse reactions occurred in 23% of patients. Adverse reactions which required dose interruption (>2%) included neutropenia and ILD/pneumonitis. Dose reductions due to an adverse reaction occurred in 11% of patients.

The most common (≥20%) adverse reactions, including laboratory abnormalities, were nausea, decreased white blood cell count, decreased hemoglobin, decreased neutrophil count, decreased lymphocyte count, decreased platelet count, decreased albumin, increased aspartate aminotransferase, increased alanine aminotransferase, fatigue, constipation, decreased appetite, vomiting, increased alkaline phosphatase, and alopecia.

Tables 9 and 10 summarize common adverse reactions and laboratory abnormalities observed in DESTINY-Lung02.

Table 9: Common Adverse Reactions (≥10% All Grades or ≥2% Grades 3 or 4) in Patients with Unresectable or Metastatic HER2-Mutant NSCLC in DESTINY-Lung02

Adverse Reactions	ENHERTU 5.4 mg/kg N=101	
	All Grades %	Grades 3 or 4 %
Gastrointestinal Disorders		
Nausea	61	3.0
Constipation	31	1.0
Vomiting[a]	26	2.0
Diarrhea	19	1.0
Stomatitis[b]	12	0
Blood and Lymphatic System Disorders		
Anemia	34	10
General Disorders and Administration Site Conditions		
Fatigue[c]	32	4.0
Metabolism and Nutrition Disorders		
Decreased appetite	30	1.0
Skin and Subcutaneous Tissue Disorders		
Alopecia	21	0
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal pain[d]	15	1.0

Events were graded using NCI CTCAE version 5.0.
a Including vomiting and retching
b including mucosal inflammation and stomatitis
c Including asthenia, fatigue, and malaise
d Including back pain, musculoskeletal stiffness, musculoskeletal chest pain, arthralgia, musculoskeletal pain, myalgia, and pain in extremity

Other clinically relevant adverse reactions reported in less than 10% of patients were:
- *Respiratory, Thoracic and Mediastinal Disorders:* interstitial lung disease (6%) [including interstitial lung disease that was adjudicated as ILD including pneumonitis, interstitial lung disease, pulmonary toxicity, and respiratory failure], dyspnea (5%), and epistaxis (3%)
- *Gastrointestinal Disorders:* abdominal pain (9%) [including abdominal discomfort, abdominal pain, and upper abdominal pain]
- *Skin and Subcutaneous Disorders:* rash (3%) [including rash and maculo-papular rash]
- *Infections and Infestations:* upper respiratory tract infection (4%) [including upper respiratory tract infection, pharyngitis, and laryngitis]
- *Nervous System Disorders:* headache (4%) [including headache and migraine]

Table 10: Select Laboratory Abnormalities in Patients with Unresectable or Metastatic HER2-Mutant NSCLC in DESTINY-Lung02

Laboratory Parameter	ENHERTU 5.4 mg/kg N=101[a]	
	All Grades[b] %	Grades 3 or 4[b] %
Hematology[c]		
Decreased white blood cell count	60	4.0
Decreased hemoglobin	58	10
Decreased neutrophil count	52	12
Decreased lymphocyte count	43	16
Decreased platelet count	40	4.0
Chemistry		
Decreased albumin	39	0
Increased aspartate aminotransferase	35	1.0
Increased alanine aminotransferase	34	2.0
Increased alkaline phosphatase	22	0
Hypokalemia	17	2.0

a Percentages were calculated using patients with worsening laboratory values from baseline and the number of patients with both baseline and post-treatment measurements as the denominator.
b Frequencies were based on NCI CTCAE v.5.0 grade-derived laboratory abnormalities.
c The denominator used to calculate the rate varied from 98 to 99 based on the number of patients with a baseline value and at least one post-treatment value.

Locally Advanced or Metastatic Gastric Cancer

The safety of ENHERTU was evaluated in 187 patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma in DESTINY-Gastric01 *[see Clinical Studies (14.4) in the full prescribing information]*. Patients intravenously received at least one dose of either ENHERTU (N=125) 6.4 mg/kg once every three weeks or either irinotecan (N=55) 150 mg/m^2 biweekly or paclitaxel (N=7) 80 mg/m^2 weekly for 3 weeks. The median duration of treatment was 4.6 months (range: 0.7 to 22.3) in the ENHERTU group and 2.8 months (range: 0.5 to 13.1) in the irinotecan/paclitaxel group.

Serious adverse reactions occurred in 44% of patients receiving ENHERTU 6.4 mg/kg. Serious adverse reactions in >2% of patients who received ENHERTU were decreased appetite, ILD, anemia, dehydration, pneumonia, cholestatic jaundice, pyrexia, and tumor hemorrhage. Fatalities due to adverse reactions occurred in 2.4% of patients: disseminated intravascular coagulation, large intestine perforation, and pneumonia occurred in one patient each (0.8%).

ENHERTU was permanently discontinued in 15% of patients, of which ILD accounted for 6%. Dose interruptions due to adverse reactions occurred in 62% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose interruption were neutropenia, anemia, decreased appetite, leukopenia, fatigue, thrombocytopenia, ILD, pneumonia, lymphopenia, upper respiratory tract infection, diarrhea, and hypokalemia. Dose reductions occurred in 32% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose reduction were neutropenia, decreased appetite, fatigue, nausea, and febrile neutropenia.

The most common (≥20%) adverse reactions, including laboratory abnormalities, were decreased hemoglobin, decreased white blood cell count, decreased neutrophil count, decreased lymphocyte count, decreased platelet count, nausea, decreased appetite, increased aspartate aminotransferase, fatigue, increased blood alkaline phosphatase, increased alanine aminotransferase, diarrhea, hypokalemia, vomiting, constipation, increased blood bilirubin, pyrexia, and alopecia.

Tables 11 and 12 summarize adverse reactions and laboratory abnormalities observed in patients receiving ENHERTU 6.4 mg/kg in DESTINY-Gastric01.

Table 11: Adverse Reactions in ≥10% All Grades or ≥2% Grades 3 or 4 of Patients Receiving ENHERTU in DESTINY-Gastric01

	ENHERTU 6.4 mg/kg N=125		Irinotecan or Paclitaxel N=62	
Adverse Reactions	**All Grades %**	**Grades 3 or 4 %**	**All Grades %**	**Grades 3 or 4 %**
Gastrointestinal Disorders				
Nausea	63	4.8	47	1.6
Diarrhea	32	2.4	32	1.6
Vomiting	26	0	8	0
Constipation	24	0	23	0
Abdominal pain[a]	14	0.8	15	3.2
Stomatitis[b]	11	1.6	4.8	0
Metabolism and Nutrition Disorders				
Decreased appetite	60	17	45	13
Dehydration	6	2.4	3.2	1.6
Blood and Lymphatic System Disorders				
Anemia[c]	58	38	31	23
Febrile neutropenia	4.8	4.8	3.2	3.2
General Disorders and Administration Site Conditions				
Fatigue[d]	55	9	44	4.8
Pyrexia	24	0	16	0
Peripheral edema	10	0	0	0
Skin and Subcutaneous Tissue Disorders				
Alopecia	22	0	15	0
Respiratory, Thoracic and Mediastinal Disorders				
Interstitial lung disease[e]	10	2.4	0	0
Hepatobiliary Disorders				
Abnormal hepatic function	8	3.2	1.6	1.6

Events were graded using NCI CTCAE version 4.03.
[a] Including abdominal discomfort, gastrointestinal pain, abdominal pain, lower abdominal pain, and upper abdominal pain
[b] Including stomatitis, aphthous ulcer, mouth ulceration, oral mucosa erosion, and oral mucosal blistering
[c] Including anemia, decreased hemoglobin, decreased red blood cell count, and decreased hematocrit
[d] Including fatigue, asthenia, and malaise
[e] Interstitial lung disease includes events that were adjudicated as ILD: pneumonitis, interstitial lung disease, respiratory failure, organizing pneumonia, acute respiratory failure, lung infiltration, lymphangitis, and alveolitis.

Other clinically relevant adverse reactions reported in less than 10% of patients were:
- *Cardiac Disorders:* asymptomatic left ventricular ejection fraction decrease (8%) *[see Warnings and Precautions (5.3)]*
- *Infections and Infestations:* pneumonia (6%)
- *Injury, Poisoning and Procedural Complications:* infusion-related reactions (1.6%)

Table 12: Selected Laboratory Abnormalities Occurring in Patients Receiving ENHERTU in DESTINY-Gastric01

Laboratory Parameter	ENHERTU 6.4 mg/kg N=125		Irinotecan or Paclitaxel N=62	
	All Grades %	**Grades 3 or 4 %**	**All Grades %**	**Grades 3 or 4 %**
Hematology				
Decreased hemoglobin	75	38	55	23
Decreased white blood cell count	74	29	53	13
Decreased neutrophil count	72	51	45	23
Decreased lymphocyte count	70	28	53	12
Decreased platelet count	68	12	12	5
Chemistry				
Increased aspartate aminotransferase	58	9	32	8
Increased blood alkaline phosphatase	54	8	34	10
Increased alanine aminotransferase	47	9	17	1.7
Hypokalemia	30	4.8	18	8
Increased blood bilirubin	24	7	5	3.4

Percentages were calculated using patients with worsening laboratory values from baseline and the number of patients with both baseline and post-treatment measurements as the denominator.
Frequencies were based on NCI CTCAE v.4.03 grade-derived laboratory abnormalities.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action, ENHERTU can cause fetal harm when administered to a pregnant woman. There are no available data on the use of ENHERTU in pregnant women. In postmarketing reports, use of a HER2-directed antibody during pregnancy resulted in cases of oligohydramnios manifesting as fatal pulmonary hypoplasia, skeletal abnormalities, and neonatal death (*see Data*). Based on its mechanism of action, the

topoisomerase inhibitor component of ENHERTU, DXd, can also cause embryo-fetal harm when administered to a pregnant woman because it is genotoxic and targets actively dividing cells *[see Clinical Pharmacology (12.1), Nonclinical Toxicology (13.1) in the full prescribing information]*. Advise patients of the potential risks to a fetus.

There are clinical considerations if ENHERTU is used in pregnant women, or if a patient becomes pregnant within 7 months after the last dose of ENHERTU (*see Clinical Considerations*).

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Monitor women who received ENHERTU during pregnancy or within 7 months prior to conception for oligohydramnios. If oligohydramnios occurs, perform fetal testing that is appropriate for gestational age and consistent with community standards of care.

Data

Human Data

There are no available data on the use of ENHERTU in pregnant women. In postmarketing reports in pregnant women receiving a HER2-directed antibody, cases of oligohydramnios manifesting as fatal pulmonary hypoplasia, skeletal abnormalities, and neonatal death have been reported. These case reports described oligohydramnios in pregnant women who received a HER2-directed antibody either alone or in combination with chemotherapy. In some case reports, amniotic fluid index increased after use of a HER2-directed antibody was stopped.

Animal Data

There were no animal reproductive or developmental toxicity studies conducted with fam-trastuzumab deruxtecan-nxki.

8.2 Lactation

Risk Summary

There is no data regarding the presence of fam-trastuzumab deruxtecan-nxki in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in a breastfed child, advise women not to breastfeed during treatment with ENHERTU and for 7 months after the last dose.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Verify pregnancy status of females of reproductive potential prior to initiation of ENHERTU.

Contraception

Females

ENHERTU can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*. Advise females of reproductive potential to use effective contraception during treatment with ENHERTU and for 7 months after the last dose.

Males

Because of the potential for genotoxicity, advise male patients with female partners of reproductive potential to use effective contraception during treatment with ENHERTU and for 4 months after the last dose *[see Nonclinical Toxicology (13.1) in the full prescribing information]*.

Infertility

Based on findings in animal toxicity studies, ENHERTU may impair male reproductive function and fertility *[see Nonclinical Toxicology (13.1) in the full prescribing information]*.

8.4 Pediatric Use

Safety and effectiveness of ENHERTU have not been established in pediatric patients.

8.5 Geriatric Use

Of the 883 patients with breast cancer treated with ENHERTU 5.4 mg/kg, 22% were 65 years or older and 3.6% were 75 years or older. No overall differences in efficacy within clinical studies were observed between patients ≥65 years of age compared to younger patients. There was a higher incidence of Grade 3-4 adverse reactions observed in patients aged 65 years or older (60%) as compared to younger patients (48%).

Of the 101 patients with unresectable or metastatic HER2-mutant NSCLC treated with ENHERTU 5.4 mg/kg, 40% were 65 years or older and 8% were 75 years or older. No overall differences in efficacy or safety were observed between patients ≥65 years of age compared to younger patients.

Of the 125 patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma treated with ENHERTU 6.4 mg/kg in DESTINY-Gastric01, 56% were 65 years or older and 14% were 75 years or older. No overall differences in efficacy or safety were observed between patients ≥65 years of age compared to younger patients.

8.6 Renal Impairment

No dose adjustment of ENHERTU is required in patients with mild (creatinine clearance [CLcr] ≥60 and <90 mL/min) or moderate (CLcr ≥30 and <60 mL/min) renal impairment *[see Clinical Pharmacology (12.3) in the full prescribing information]*. A higher incidence of Grade 1 and 2 ILD/pneumonitis has been observed in patients with moderate renal impairment *[see Warnings and Precautions (5.1)]*. Monitor patients with moderate renal impairment more frequently. The recommended dosage of ENHERTU has not been established for patients with severe renal impairment (CLcr <30 mL/min) *[see Clinical Pharmacology (12.3) in the full prescribing information]*.

8.7 Hepatic Impairment

No dose adjustment of ENHERTU is required in patients with mild (total bilirubin ≤ULN and any AST >ULN or total bilirubin >1 to 1.5 times ULN and any AST) or moderate (total bilirubin >1.5 to 3 times ULN and any AST) hepatic impairment. In patients with moderate hepatic impairment, due to potentially increased exposure, closely monitor for increased toxicities related to the topoisomerase inhibitor, DXd *[see Dosage and Administration (2.3) in the full prescribing information]*. The recommended dosage of ENHERTU has not been established for patients with severe hepatic impairment (total bilirubin >3 times ULN and any AST) *[see Clinical Pharmacology (12.3) in the full prescribing information]*.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Interstitial Lung Disease

- Inform patients of the risks of severe or fatal ILD. Advise patients to contact their healthcare provider immediately for any of the following: cough, shortness of breath, fever, or other new or worsening respiratory symptoms *[see Warnings and Precautions (5.1)]*.

Neutropenia

- Advise patients of the possibility of developing neutropenia and to immediately contact their healthcare provider should they develop a fever, particularly in association with any signs of infection *[see Warnings and Precautions (5.2)]*.

Left Ventricular Dysfunction

- Advise patients to contact their healthcare provider immediately for any of the following: new onset or worsening shortness of breath, cough, fatigue, swelling of ankles/legs, palpitations, sudden weight gain, dizziness, loss of consciousness *[see Warnings and Precautions (5.3)]*.

Embryo-Fetal Toxicity

- Inform female patients of the potential risk to a fetus. Advise female patients to contact their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.4), Use in Specific Populations (8.1)]*.
- Advise females of reproductive potential to use effective contraception during treatment with ENHERTU and for 7 months after the last dose *[see Use in Specific Populations (8.3)]*.
- Advise male patients with female partners of reproductive potential to use effective contraception during treatment with ENHERTU and for 4 months after the last dose *[see Use in Specific Populations (8.3)]*.

Lactation

- Advise women not to breastfeed during treatment and for 7 months after the last dose of ENHERTU *[see Use in Specific Populations (8.2)]*.

Infertility

- Advise males of reproductive potential that ENHERTU may impair fertility *[see Use in Specific Populations (8.3)]*.

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The Cancer We Can Eliminate

Today, scientific breakthroughs and access to effective cervical screening techniques give us the unique opportunity to eliminate cervical cancer in the UK

By Tim Simpson

Every year in the UK, there are around 3,200 new cervical cancer cases, yet we know it is preventable and highly treatable if detected early and managed effectively (1). This is because cervical cancer has one main risk factor: infection with human papillomavirus (HPV). There are over 100 different kinds of high-risk virus types, including HPV16 and 18 (2, 3).

In 2020, the UK signed up to the World Health Organization's (WHO) ambitious global strategy to accelerate the elimination of cervical cancer based on three key steps:

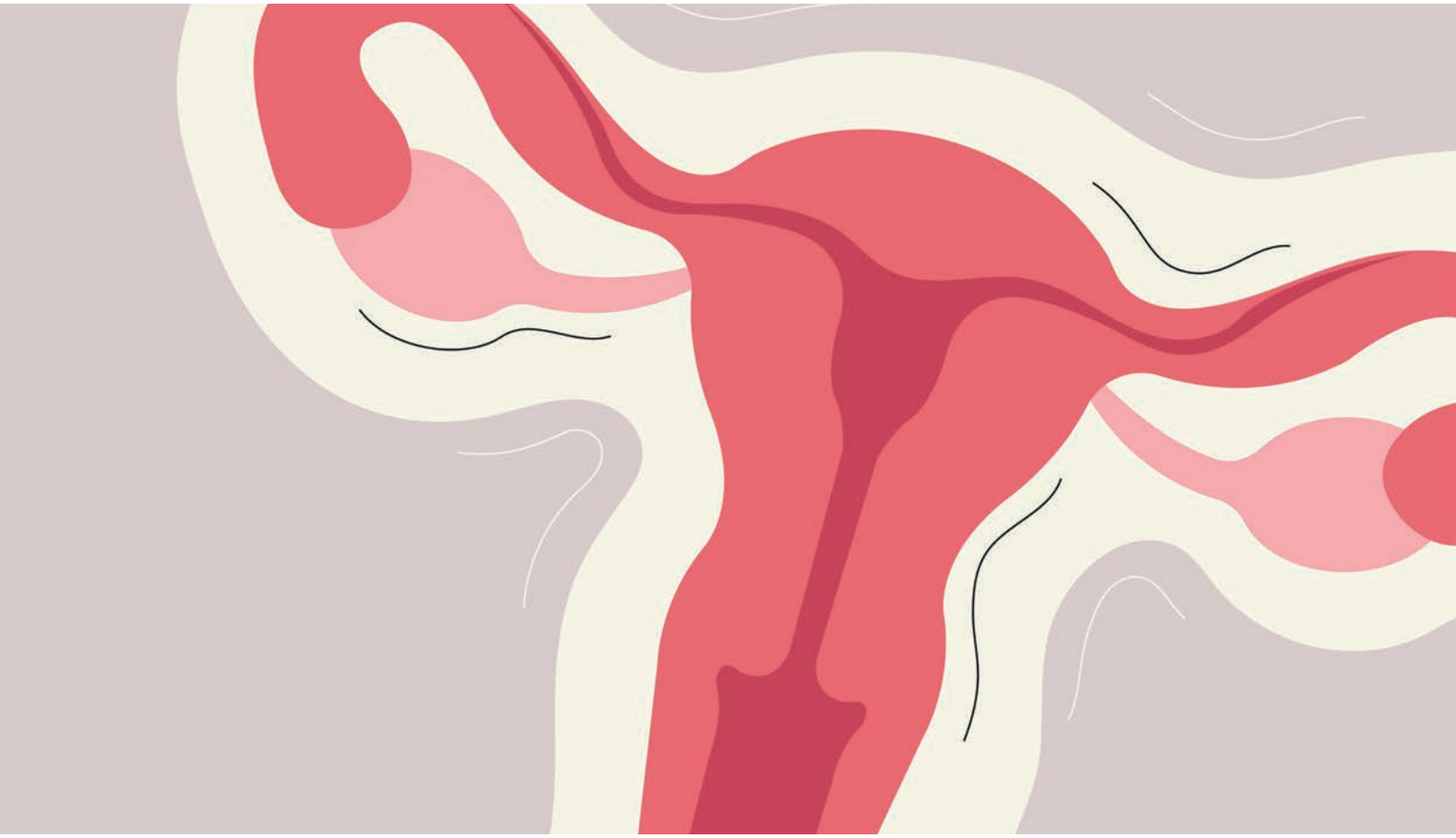
1. Achieving 90 percent of girls vaccinated against HPV by the age of 15
2. 70 percent of women screened with a high-performance test by the age of 35 and again by 45
3. 90 percent of women with cervical cancer receiving effective treatment

Successful implementation of the three above could reduce more than 40 percent of new cases of HPV, and could make a serious dent into the five million related deaths expected to occur across the world by 2050 (4). But success is dependent on making cervical cancer an explicitly (and adequately resourced) public health priority. And that means adequate cervical screening and strengthened efforts to harmonize and improve the surveillance of cervical cancer and screening data across the UK. Indeed, this ambition is reflected in the recent HPV Coalition's Roadmap towards making the elimination of all HPV-related cancers a reality across the UK.

With that said, such access to cervical screening requires leading-edge testing capabilities and technology. So, how can we provide it? Here are just a few ways we can deliver change.

HPV primary testing

Though cytology-based screening has been a key foundation of cervical cancer prevention for decades (5), recent advances in molecular diagnostics have elevated the role of HPV detection in population screening (6).



In 2017, the UK National Screening Committee recommended a move to primary HPV screening, which has been implemented across England, Wales, and Scotland (7). HPV primary screening allows healthcare professionals to find those at higher risk of developing cervical cell changes or cervical cancer sooner and more accurately thanks to tests with improved sensitivity and accuracy (8).

The role of mRNA technology

mRNA technology is pioneering advances in molecular diagnostics and medical science, particularly when it comes to cervical screening. Within screening, mRNA testing allows for greater specificity thanks to its ability to detect actively transcribing high-risk HPV mRNA as opposed to transient infections, while remaining as sensitive as DNA counterpart tests (9).

HPV infections are often transient and can be spontaneously cleared, so the presence of DNA does not necessarily indicate that a pre-cancerous abnormality will develop. However, the presence of mRNA specific to oncogenic markers indicates that HPV is not only present but is already affecting cells (9).

The other benefit of using mRNA technology when it comes to cervical screening is the cost benefit for healthcare

"We need to see a continued drive in innovation, boost screening access, and tackle inequalities head on. It's only through these steps that we can make cervical cancer a disease of the past."

providers. An analysis into the use of mRNA and DNA assays in screening for cervical cancer showed large cost savings, estimating that £15 million could be saved annually in the English cervical screening program.The results also showed that, by using mRNA instead of DNA, unnecessary testing and follow-ups were avoided, benefiting both women and healthcare services (9).

Exploring new approaches

There are also a number of exciting innovations and approaches that are emerging in cervical cancer screening. For example, a cervical screening swab test that examines DNA methylation was developed by researchers from University College London and the University of Innsbruck; it was found to identify potentially dangerous cervical cell changes up to four years before they happen (10).

In terms of reviewing results, we've seen the introduction of artificial intelligence and advanced imaging to help improve early diagnosis of precancerous and cancer cells. Creating digital images of samples that have tested positive for HPV means that they can be rapidly reviewed and provide the screener with an image gallery of the most diagnostically relevant cells. And that helps medical experts more rapidly identify and accurately diagnose abnormalities as they have fewer cells to analyze.

It is critical when introducing such innovations and methods that we prioritize patient pathways. Robust and clear processes must be in place to ensure adequate follow-up care and appropriate treatment.

Given we already know so much about cervical cancer, its risk factors, and how to prevent it, better cervical health outcomes for women are truly within our grasp. We need to see a continued drive in innovation, boost screening access, and tackle inequalities head on. It's only through these steps that we can make cervical cancer a disease of the past.

Tim Simpson is General Manager of Hologic UK and Ireland, Newcastle upon Tyne, UK.

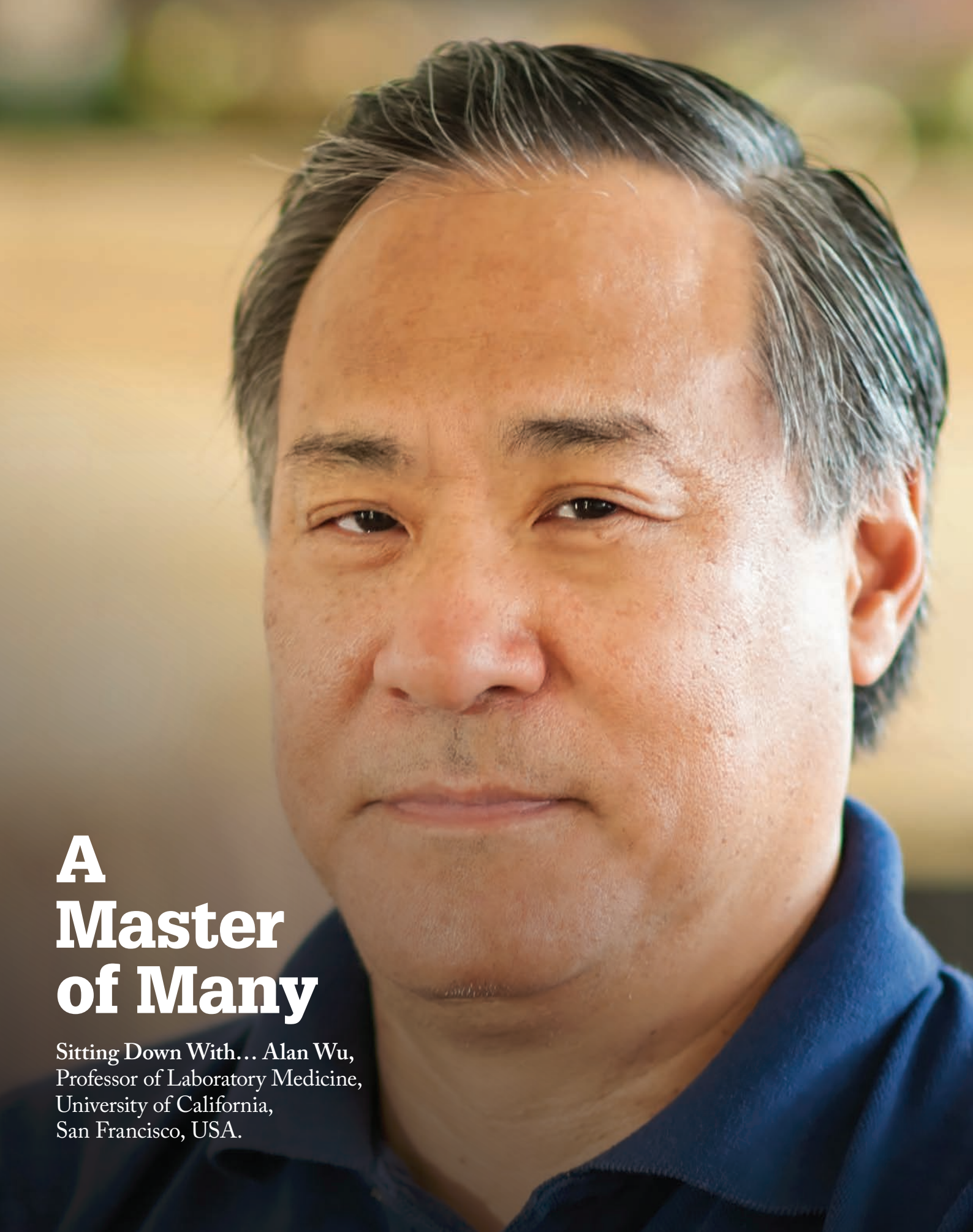
See references online at: tp.txp.to/0823/eliminate-cancer

Tackling Inequalities

Alongside innovation, reaching the elimination target requires us to provide equal access to screening – specifically by tackling the inequalities and barriers that prevent women from attending.

Though our Global Women's Health Index showed that cancer screening rates for women had improved. Our additional research found that i) health inequalities still exist in the UK, and ii) women from ethnic minority backgrounds reported lower attendance for cervical cancer screening attendance compared with white women – 31 percent versus 65 percent (11, 12).

Tackling these inequalities through education, national screening programs, and new approaches is key to ensuring better health outcomes for more women. Alongside fully inclusive screening campaigns that represent and resonate with all women.



A Master of Many

Sitting Down With… Alan Wu,
Professor of Laboratory Medicine,
University of California,
San Francisco, USA.

Before we delve into your writing, could you share your research into biomarkers for traumatic brain injuries?

This is an emerging area of laboratory diagnostics. We have many cases of traumatic brain injury (TBI) that come into our emergency department, but we don't really have tools to determine a mild TBI, such as Glasgow Coma Scores between 13 and 15. Today, the predominant tool for diagnosis is a head CT scan, which is not only expensive, but also exposes the individual to radiation. If we can diagnose mild TBI with blood tests, medical care will be improved overall. In addition to TBI biomarkers, I'd also like to mention my involvement in clinical toxicology, as well as my research into cardiac biomarkers, such as CK-MB and cardiac troponin.

What inspired you to start writing laboratory fiction?

I started writing these stories simply for my friends and colleagues to read. When I realized how much people were enjoying them, I distributed them via Amazon. I don't have an agent or a publisher. As a college and graduate student, I was a poor writer! I had to learn how to write and communicate clearly for my academic career in pathology and lab medicine. And so, in the process of my career, I have become proficient at writing and putting concepts together. But that has always been for medical and scientific purposes. I only became interested in writing for a non-specialist audience about 10 years ago. In many of my publications, I have written case reports of unusual medical findings , and over time these unique reports have morphed into short stories. I had to simplify the science of medicine – most people aren't interested in heavy duty chemistry!

Please give us a quick synopsis of *The Hidden Assassin*…

I have eight books that cover different disciplines in laboratory medicine. *The Hidden Assassin* covers clinical chemistry and molecular diagnostics. Some of my other books cover microbiology, toxicology, COVID-19, and performing-enhancing drugs. *The Hidden Assassin* features short stories in which laboratory testing uncovers some unusual findings that either lead to a happy ending – or quite the opposite…

What's the best story you've written – or which is your favorite?

I love "Explosive Blood" in *The Hidden Assassin*. The synopsis is loosely based on a true story. There was a man who came into our hospital cyanotic with blue fingertips, which suggested he had been exposed to a chemical that had caused oxygen desaturation. The attending physicians asked us to conduct an analysis of his blood and we found a chemical that was used to color carpets. We sent investigators to his place of work, thinking that other individuals within his factory might be similarly exposed. But we found no chemicals at his place of work – it was simply a warehouse for carpets. To this day, we don't really know how he was exposed to this chemical. Further investigation showed that it was a metabolite of trinitrotoluene, which most people know as TNT.

In real life, the story ended here but I took this information and sensationalized it. I changed the narrative into a sinister terroristic plot, where the chemical exposure was a result of bomb-making at home…

You plan to turn *Mind Portals* into a movie show – how is the process coming along?

The script is complete, and my screenwriter and I are currently shopping around. The storyline follows a laboratory director who has the power to turn back time, and can implant ideas into the minds of scientists with the aim of changing their future. Specifically, the protagonist selects doctors who he thinks could have an impact on future medical care, with the goal of saving his daughter who died of acute myeloid leukemia.

Do you think lab representation in the media is important?

Awareness has become the major objective of my writing. There have been challenges with the reimbursement of laboratory tests. We are now under siege and are trying to protect the services that maintain the quality of testing that is required for our patients. I sense that this is heading in the wrong direction; we're facing huge budget cuts in America. I'm hoping to help change that with my stories.

My next goal is to create a scripted dramatic television show. Most medical shows feature doctors and nurses, and although they do the lion's share of treating patients, the laboratory component is often incorrectly portrayed. For example, in *House*, the doctors wander to the lab and receive instant diagnoses. Our efforts are underappreciated and underrepresented. I want to change that. I want to show that laboratory professionals provide the crucial information that doctors need – and it isn't instantaneous or easy!

The TV show *CSI* is a perfect example of how the media can evoke change. There was an influx of young people who wanted to become forensic scientists based on the success of that show. Because of the "CSI effect," the public has demanded that we use science to solve crimes, and jurists that sit on cases have a much better knowledge on how to interpret data. I want that same buzz for laboratory medicine. Crime only affects a relatively small number of us, but medicine affects us all. So why should the portrayal of science in medicine be so trivialized?

hybrid

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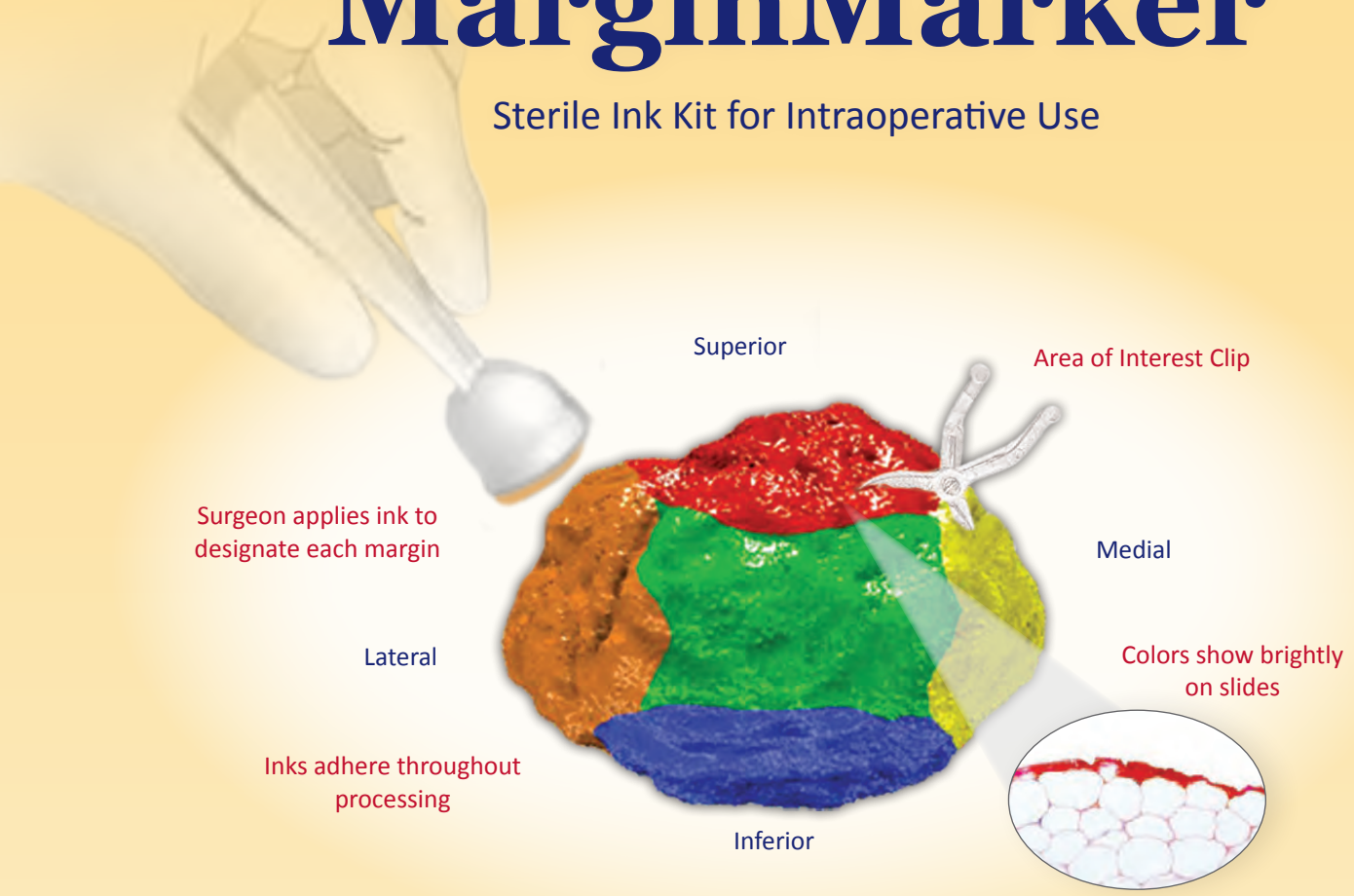

Pathology Receives Specimens With Margins Clearly Marked by the Surgeon

In cancer surgery, the single most important predictor of local recurrence is the tissue margins.[1] Research shows discordance rates as high as 52% in the identification of specimen margins.[2,3] Re-excision rates exceed 20% in breast surgery.[4] Use of Vector Surgical's MarginMarker can result in:

- 50% fewer unnecessary re-excisions[1,5,6]
- Fewer delays of critical adjuvant therapy[7]
- More accurate re-excisions[5,8]
- Lower cancer recurrence[9,10]
- Improved cosmesis[6,8]

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