NOVEMBER/DECEMBER 2022 # 87

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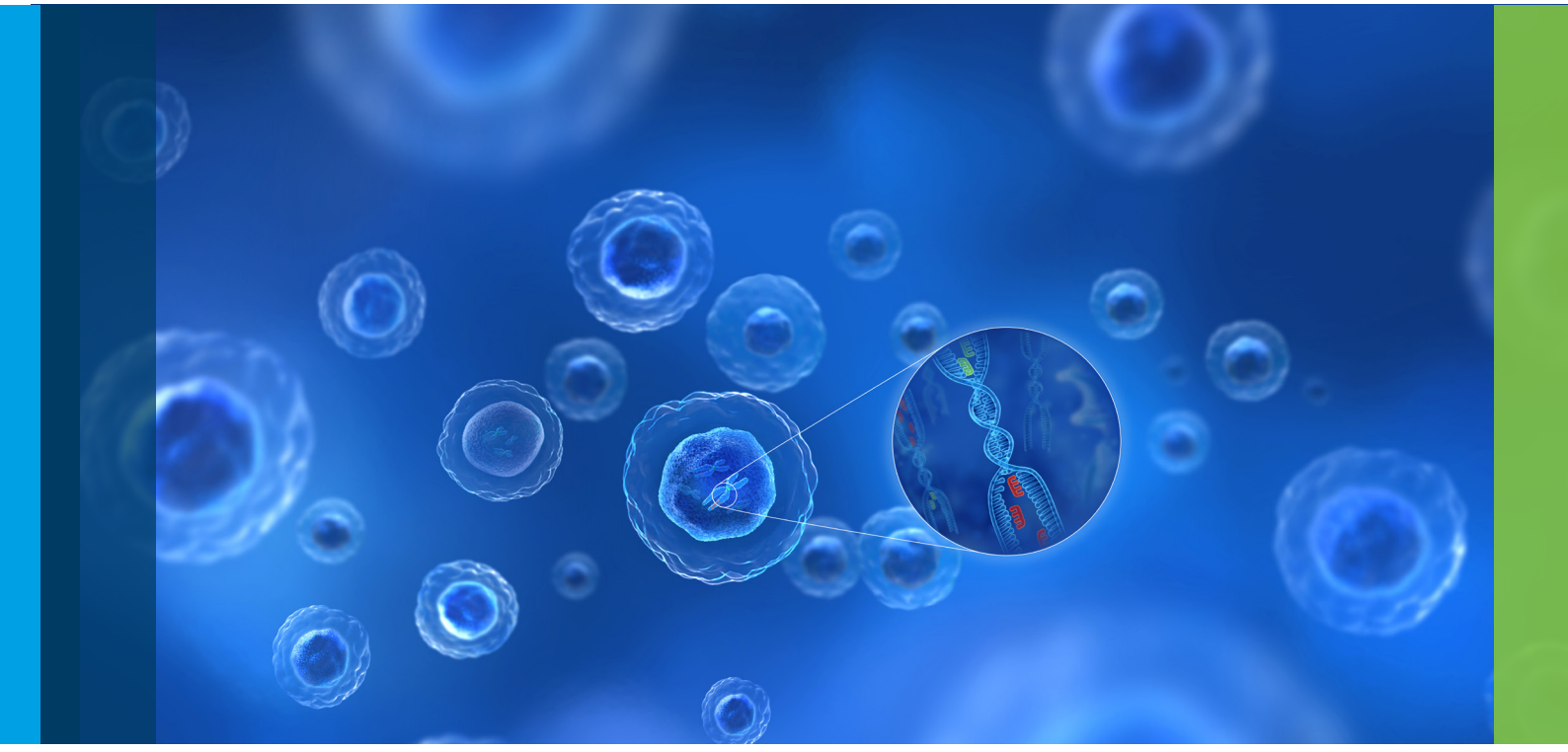
A Rare Disease Revolution

Whole-genome sequencing could simplify the rare disease diagnostic odyssey – but accessibility and awareness issues stand in its way

SureFISH Technology Solves Assay Challenges

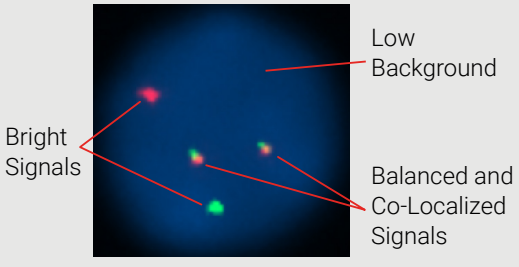
Agilent
Trusted Answers



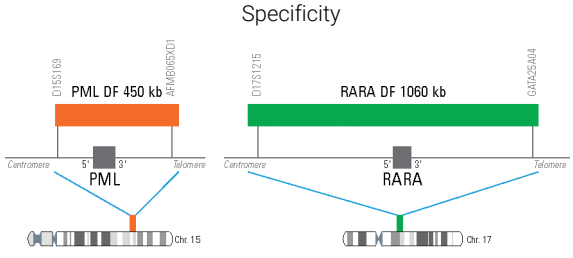
Achieving trusted answers to complex questions requires an assay that consistently delivers high quality results. SureFISH DNA probes are designed in silico and manufactured using Agilent Oligo technology which eliminates the design limitations of BAC FISH probes. SureFISH enables low background and bright signals by eliminating repetitive elements during probe design and manufacturing process. SureFISH oligos can be positioned anywhere in the genome without the need to rely on BAC clone availability. SureFISH offers flexibility with same day or overnight hybridization results to facilitate ease of interpretation.

BAC Assay Challenge		Solved by SureFISH
Probe Design Limitations Custom Probe Design Specificity	→	Oligo Printing
Background	→	Repeat Free
Lot to Lot Consistency	→	Non-biological System

Transformed into a Result



Click or scan to learn more.



PR7001-0130

Assessing Pathology Knowledge

How to ensure that you test your students' knowledge – not their skill at passing tests

When I was still young and full of illusions, I assumed that medical students would be as passionate about pathology as I was and would not need much in terms of incentives to learn the basic characteristics and morphological features of important diseases. It did not take me long to realize that most students are driven by the need to pass exams!

Most exams are presented to medical students in the multiple-choice question (MCQ) format. Students know this and therefore they rapidly develop the skill of efficiently solving MCQs. After some time, they can find the right answer even with minimal real knowledge of the subject at hand, simply by honing their ability to recognize the most likely answer among five possibilities. This raises a question – do MCQ exams test real medical knowledge or just students' capacity to pass a test by choosing the most likely answers?

There are various approaches to solving this conundrum. The good old oral examination may be considered, but it is time-consuming with large student bodies and almost impossible to standardize. Open-ended or essay questions are subject to the same difficulties. This brings us back to questions with a built-in (set of) answers from which students must choose.

The challenge with MCQs is to make distractors whose likelihood of being correct is (to an uninformed student) more or less equal. Many MCQs tend to be of the simple "recall" type so, instead of understanding the issue at stake, students might recognize a verbal configuration that fits with the core of the question. So what can we do instead?

Two similar test formats may work as MCQ alternatives. The first is the "uncued" question (UCQ). Instead of individual questions with a limited set of answer options, UCQ tests provide a list of questions and a long list of potential answers that tends to look like the index of a pathology textbook. During a timed test, students cannot realistically go through the list to find the right answer; instead, they must conceive of the answer, then find it in the list. The main issue with UCQs lies in the length of the answer list; if it becomes too long, students may not find the correct answer in time – or multiple answers might be considered correct.

The model I have used successfully is an MCQ-UCQ hybrid known as "extended matching." The questions are similar to MCQs but, instead of five answers, students receive a set of 10 to 20 possible answers in alphabetical order from which they must choose the most correct one. Intrigued? Why not try your hand at a few examples?

Try the quiz: **tp.txp.to/1222/extended-matching**

Fred Bosman

Fred Bosman is Professor Emeritus at the University Institute of Pathology, University Medical Center of Lausanne, Switzerland

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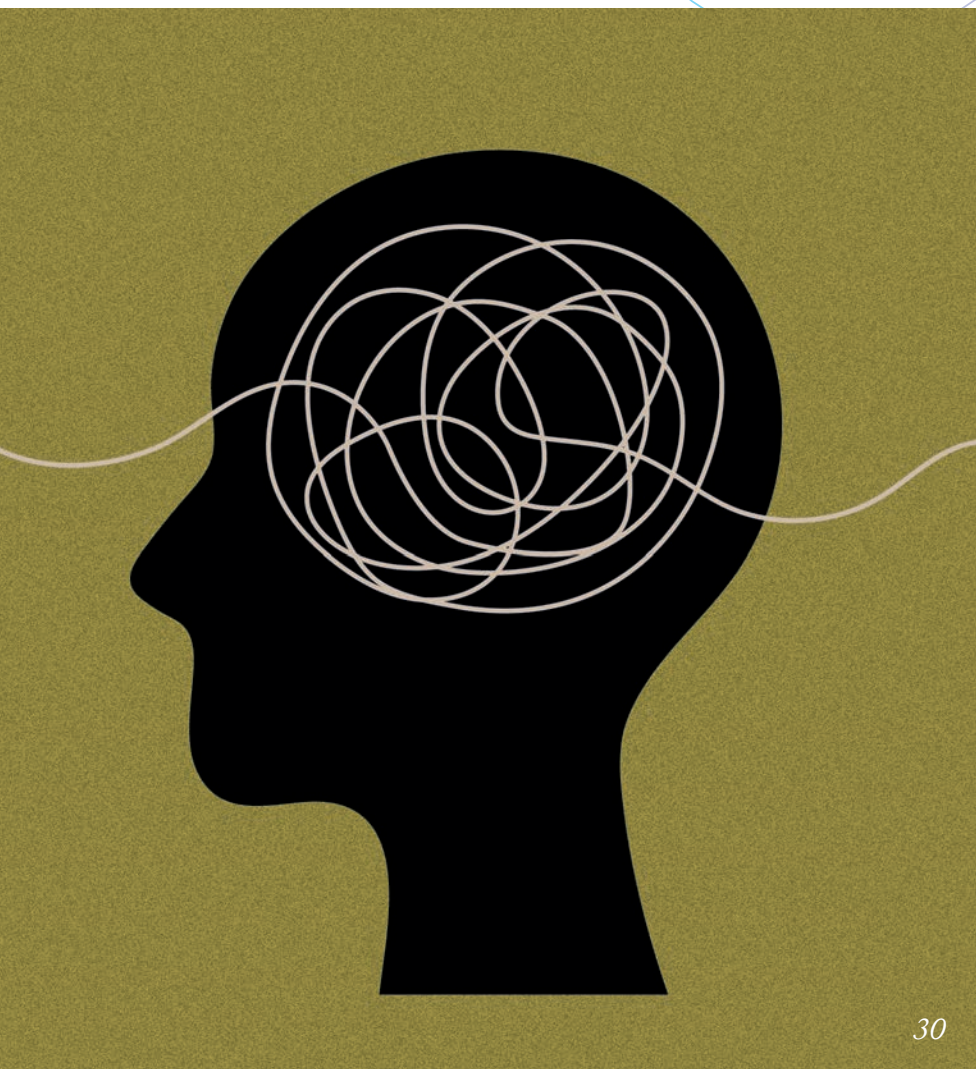

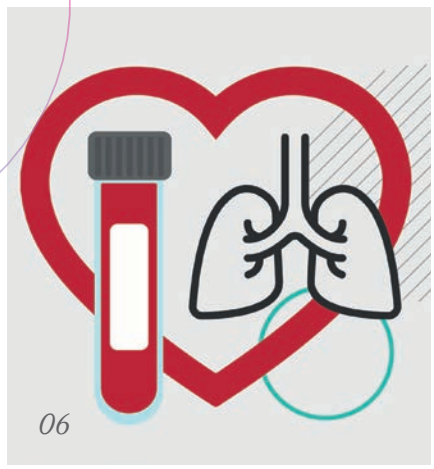

On the Cover

Genomic sequencing for rare diseases at Rady Children's Hospital.

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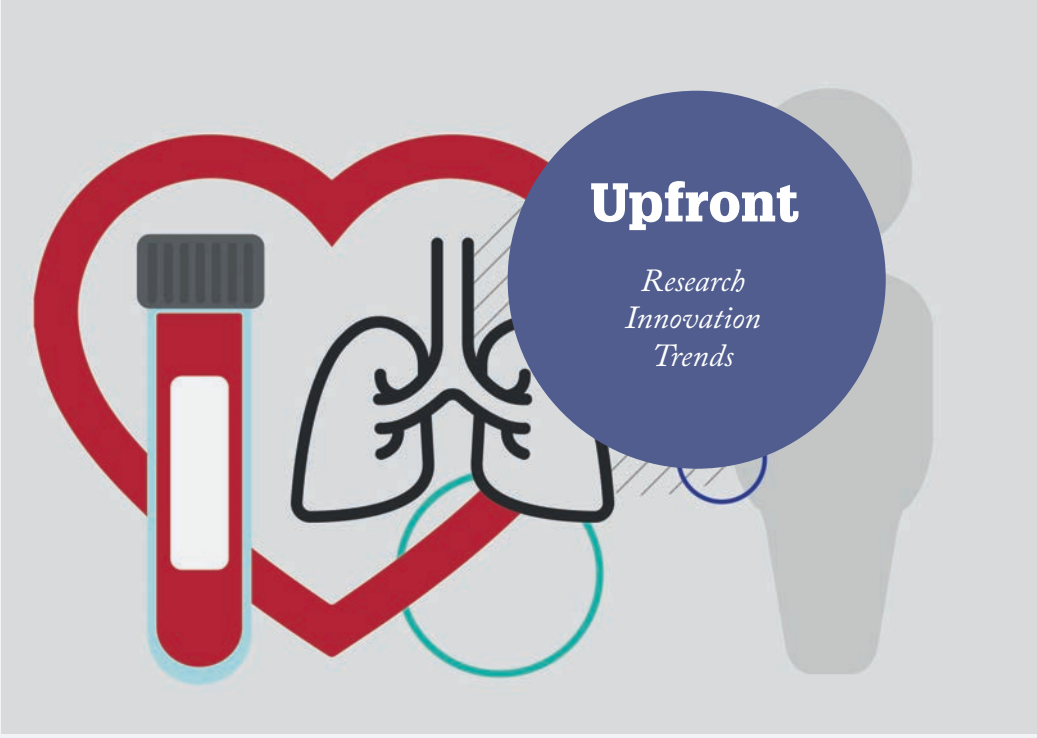

Plasma Mutation Profiling

How plasma cell-free DNA testing could improve therapeutic decision-making for lung cancer

Lung cancer kills more people each year than colon, breast, and prostate cancers combined (1), so there is great incentive to improve testing and better direct treatments – especially for non-small cell lung cancer (NSCLC), which represents 85 percent of all cases (2).

To explore the potential of adding plasma cell-free DNA testing – via an ultrasensitive amplicon-based next-generation sequencing panel (plasma NGS testing) – into the lung cancer workflow, researchers recruited 71 patients with suspected lung cancer and collected both blood and diagnostic tissue samples (3). Ultimately, they showed that plasma NGS offers shorter reporting times, similar specificity and accuracy to standard methods, and higher sample accessibility levels (for the 54 confirmed NSCLC patients, successful tissue samples were acquired from 70.3 percent of participants, whereas 98 percent of participants were able to provide blood samples).

Plasma NGS testing also showed a 26.8 percent additional diagnostic yield in cases where tissue *EGFR* testing was negative or absent, including the detection of five clinically actionable *EGFR* mutations across 16 patients in whom tissue testing was not performed.

Specifically within the group of patients who had NSCLC, the addition of plasma NGS to the standard tests detected actionable mutations in 42.6 percent of cases; standard tissue *EGFR* testing alone led to clinical actionability in only 22.2 percent. As a result, the authors concluded that complementary plasma mutation profiling carries clear clinical utility in lung cancer testing.

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1. *Cancer.org, "Key Statistics for Lung Cancer," (2022). Available at: https://bit.ly/3Cu4qrh.*
2. *JR Molina et al., Mayo Clin Proc, 83, 584 (2008). PMID: 18452692.*
3. *Y Choudhury et al., Front Med, 9, 758464 (2022). PMID: 35223889.*

QUICK HITS

The world of cancer genetics is getting bigger… so we bring you the latest news and research in molecular oncology

Marking Pancreatic Cancer

Pancreatic ductal adenocarcinoma is one of the deadliest cancers – and many patients miss out on FDA-approved treatment. New research has found that *METTL16* overexpression may be a new biomarker of potential susceptibility to PARP inhibitors. Researchers have found that its protein product stymies DNA repair by interrupting the double-strand repair protein MRE11 (1).

(Don't) Dry Those Tears

New research has found that aqueous humor can reliably be used for retinoblastoma diagnosis and prognosis (2). Analyzing DNA methylation profiles in aqueous humor samples linked to the cancer, the researchers noted a particular methylation signature that promotes tumor growth, along with distinct molecular subtypes that may enable treatment success prediction.

Taking Action on FGFR2

New transposon-based screening and tumor modeling has revealed an array of actionable *FGFR2* mutations (3). Genomic alterations that generate stable *FGFR2* ΔE18 variants may be actionable targets for therapy; as a result, cancers exhibiting such mutations should be considered for FGFR inhibitor treatment.

AMP Advice

A paper by the Association for Molecular Pathology (AMP) has laid out guidance in the development and testing of *TPMT* and *NUDT15* genotyping assays for clinical use (5). The goal of the new guidelines is to promote standardization across labs when investigating multiethnic, function-altering *TPMT* and *NUDT15* variant alleles.

See references online at:
tp.txp.to/1222/cancer-growth

Faster Than a Speeding Biopsy

Multi-cancer early detection technology is allowing us to detect undiagnosed cancer earlier than ever before

As our population ages and cancer becomes increasingly prevalent, we require faster (and earlier) ways of detecting the disease. The multi-cancer early detection (MCED) test – capable of detecting 50 types of cancer – can identify the site of origin in tumors of unknown primary, but new research shows that it can also be effective in detecting undiagnosed cancers, too (1).

MCED uses cfDNA and machine learning to locate a cancer signal origin. In this case, researchers tested an early version of the technology on 6,621 individuals and detected cancer in 1.4 percent of participants. The diagnosis was confirmed in 38 percent of those patients, with a further 73 percent receiving diagnostic resolution within three months.

The findings were presented at the 2022 ESMO Congress, where commentators emphasized the tech's potential benefits, but cautioned that fully bringing MCED into the clinic would require a significant boost to both infrastructure and training in upcoming years

See references online at:
tp.txp.to/1222/speeding-biopsy

The Genes of the Spectrum

How is current genetic research helping to map a fuller picture of the autism spectrum?

The role that genetics plays in autism spectrum disorders (ASD) has been investigated for decades, but with our understanding of autism – and neurodivergence as a whole – constantly evolving, what is the current view of genetics and its relationship to ASD?

It's not news that some genes are associated with autism but, so far, many investigations into autism genetics have focused on variants not inherited from parents. To combat this (and to create a much more accurate picture of ASD genetic risk), one team combined both de novo and inherited variants across a wide pool of cases (1). The team used SPARK (Simons Powering Autism Research), an online platform on which individuals across the autism spectrum can offer their genetic data, giving researchers access to a total of 42,607 cases.

The large cohort of autistic individuals led to the identification of five new risk genes – *NAV3, ITSN1, SCAF1, HNRNPUL2*, and *MARK2*. The data show that autistic people who have inherited loss-of-function in the first four of these genes have lower levels of cognitive impairment comorbidities than individuals without such alterations.

Elsewhere, another team has also addressed the focus on de novo variants by exploring mutations rarely observed in non-autistic individuals (2). The team analyzed more than 60,000 cases using joint analysis of protein-truncating variants (PTVs), missense variants, and copy number variants (CNVs) – ultimately leading to the discovery of 72 ASD gene associations. De novo PTVs, damaging missense variants, and CNVs made up 57.5, 21.1, and 8.44 percent of the evidence, respectively. Meanwhile, CNVs conferred greatest relative risk.

The team also conducted meta-analysis alongside individuals who presented with developmental delay. This effort led to the identification of 373 genes associated with both ASD and developmental delay, though relative frequency of these mutations differed between groups. Interestingly, the genes associated with ASD were more enriched in maturing neurons and overlapped with schizophrenia-associated genes. What future research will focus on – and where researchers come to a roadblock – is making sense of the wide overlap between genes associated with ASD and other neurodevelopmental disorders and what pathways exist between them.

References

1. *X Zhou et al., "Integrating de novo and inherited variants in 42,607 autism cases identifies mutations in new moderate-risk genes," Nat Genet, 54, 1305 (2022). PMID: 35982159.*
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The Architecture of ADHD

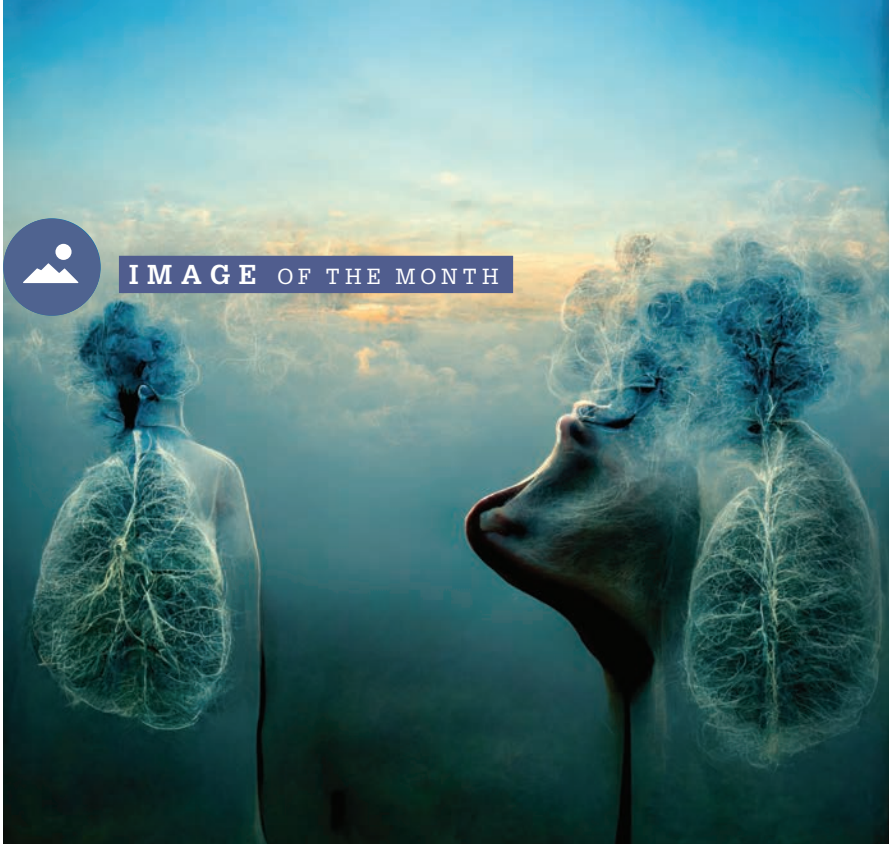
Do ADHD subgroups stem from different genetic etiologies?

ADHD is a neurodevelopmental disorder with childhood onset that can persist into the adult years and can also be diagnosed in later life. Risk factors for ADHD are a complex issue, with both environmental and genetic factors playing a role. Might childhood, persistent, and late-diagnosed ADHD stem from different etiologies?

An international team of researchers has sought to understand whether there are genetic differences between ADHD subgroups (1). A genome-wide association study revealed four genome-wide significant loci for childhood ADHD on chromosomes 1, 5, 18, and 20 and one significant locus on chromosome 7 for late-diagnosed ADHD. None were found for persistent ADHD. The team also found positive genetic correlations between ADHD subgroups and a number of psychiatric disorders, as well as negative correlations with anorexia and obsessive-compulsive disorder.

Reference

1. *VM Rajagopal et al., Nat Genet, 54, 1117 (2022). PMID: 35927488.*



When breath becomes air.

"Artificial intelligence (AI) holds the promise of not only fundamentally changing how we classify, quantify, and measure disease, but also creating and generating novel content. I have explored these possibilities using the beta of Midjourney to generate novel AI-generated, pathology-inspired art."

Matthew J. Cecchini is a Pathologist at London Health Sciences Centre, University Hospital and Assistant Professor at Western University, London, Ontario, Canada.

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

QUOTE OF THE MONTH

"The pandemic has cracked open some doors for laboratory professionals to become a visible part of the front lines. I have always felt that we shouldn't mask our expertise and role by being the behind the scenes heroes. We, as a profession, deserve a space at the front line alongside our colleagues in other health care professions. It is our responsibility to use the trajectory to swing open those doors."

Laura Severs, Director of Clinical Operations, Pathology and Immunology, St. Louis, Missouri, USA

By Our Powers Combined...

Uniting three medical disciplines for non-small cell lung cancer

A number of PD-(L)1 inhibitors have been approved for cancer therapy, but one thing prevents their wider use: treatment resistance. Could a multimodal approach – one that blends pathology, radiology, and genomics – be the solution to this resistance problem?

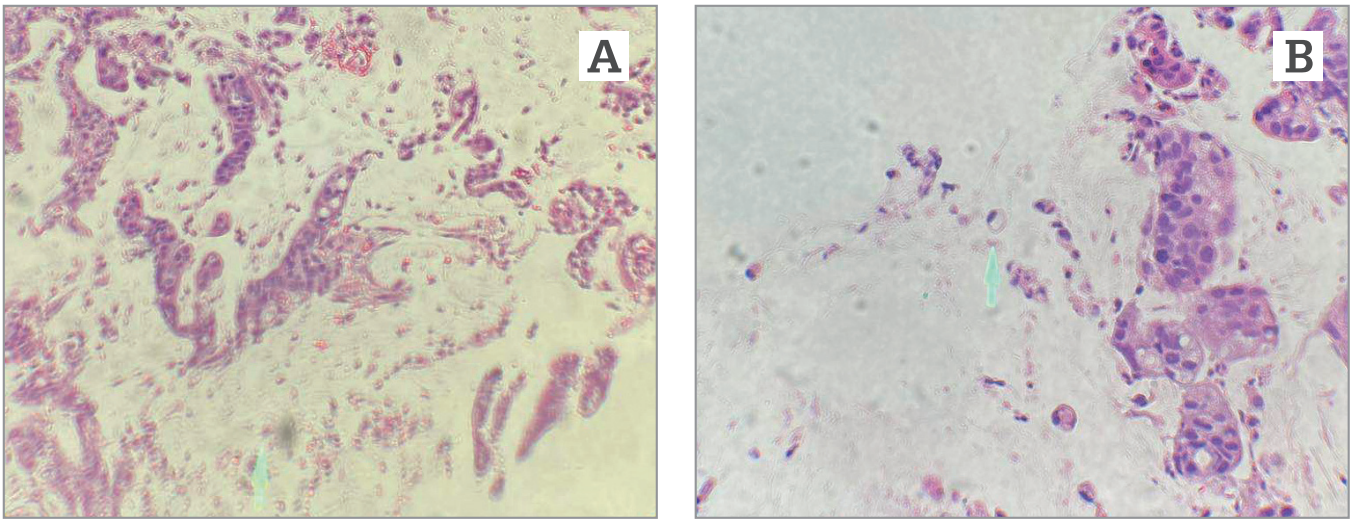
Researchers sought to answer this question through a study involving data from 247 advanced non-small cell lung cancer patients with known outcomes (1). The data were collected from clinical visits and standard-of-care tests – including PD-L1 expression patterns captured in diagnostic tumor biopsies – so that machine learning and analysis tools could compute risk scores for specific patients.

The concept proved effective, and the predictive ability of the multimodal approach was significantly greater than current unimodal standards. The team hopes that these results will encourage others to explore the multimodal method; in light of this, the study's data materials, workflows, and software have been made publicly available to hopefully springboard future research.

Reference

1. *RS Vanguri et al., Nat Cancer, 3, 1151 (2022). PMID: 36038778.*

CASE OF THE MONTH



Colon biopsies. A) Hematoxylin and eosin 10x; B) Hematoxylin and eosin, 40x. Courtesy of Gang He.

Colon adenocarcinoma of rare subtype

The following light microscopic images were obtained from colon specimens. The patient received a diagnosis of signet ring cell adenocarcinoma of the colon. In what organ is this condition most commonly diagnosed?

a) Colon
b) Rectum
c) Stomach
d) Bladder
e) Gallbladder

Answer to September/October's Case of the Month

b) 85 percent of GISTs are associated with KIT mutations

Gastrointestinal stromal tumor (GIST) is the most common mesenchymal tumor of the GI tract. Whereas 85 percent of GISTs are associated with *KIT* mutations, 10 percent are associated with *PDGFRA* mutations and a small proportion are associated with mutations in the succinate dehydrogenase (SDH), *NF1*, or *BRAF* genes.

This case show features diagnostic of GIST arising from the duodenal wall. The tumor comprises fascicles and sheets of spindle cells with focal epithelioid morphology; small intestinal GISTs more commonly show skeinoid fibers. The cytological smears show bland spindle cells and few epithelioid cells. The tumor cells stain positive for c-Kit (CD117) and DOG1 by IHC; Sanger sequencing shows a *KIT* exon 9 mutation, making this tumor less susceptible to imatinib.

Submitted by Vishnu Chandra Kumar Annadurai, Fellowship Trainee in Molecular Pathology; Thomas Alex Kodiatte, Professor; and Rekha Pai, Professor, Christian Medical College, Vellore, India.

To register your guess, please go to http://tp.txp.to/1222/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.

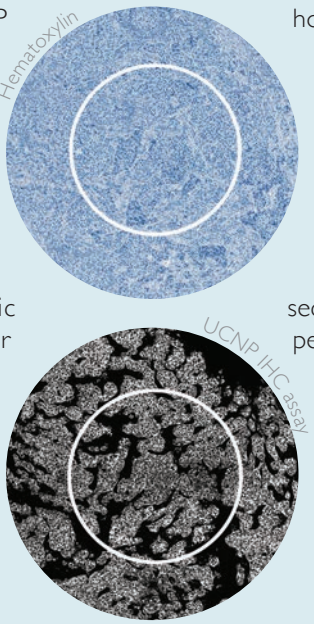
Digital Imaging – Upgraded

How Lumito's innovative labeling system offers fresh insights into tissue diagnostics

The team at Lumito is passionate about presenting an innovative new digital imaging technology. The ultimate driving ambition? To offer powerful tools that meet rapid, safe tissue diagnostics requirements. More specifically, Lumito wants to provide pathologists and researchers with images that form a more comprehensive, histology-based foundation for their analyses and clinical diagnostics. Andreas Johansson, CTO at Lumito, says the company is currently working hard on finalizing its first product for researchers – SCIZYS by Lumito. The plan is to launch during the first part of 2023. This WSI scanner, combined with Lumito's upconverted nanoparticle (UCNP) reagents, provides high-quality immunohistochemistry (IHC) imaging with unique qualities. The SCIZYS offering also enables imaging of tissue traditionally stained with hematoxylin in addition to the UCNP imaging modality.

Better technology means better results

Lumito's technology enables image capture with higher contrast, increased dynamic range, and reduced nonspecific binding. Through higher analysis quality and shorter analysis time, tissue diagnostics can achieve significant improvements. "It is possible to switch between visualizing the morphology or our unique UCNP IHC labeling. The system's flexibility also allows visualization of both readings simultaneously, superimposed on the same image. This will provide more detailed information, but without the issues with overlap that traditional IHC technology provides," says Johansson.



Lumito has recently completed a successful preliminary study with Umeå University under the leadership of assistant university lecturer Daniel Öhlund (1). The research group has mapped how the company's UCNP technology can improve our ability to visualize protein expression in pancreatic cancer. Lumito's imaging technology has provided additional insight by illustrating how specific proteins are secreted by cancer cells and penetrate the tumor stroma, Öhlund reports.

But that's just one study; Lumito has several others underway. For example, a proof-of-concept study is currently exploring the potential of Lumito's UCNP to detect immune complexes and complement deposits in renal biopsies – a collaboration between University Hospitals Coventry and Warwickshire NHS Trust in the UK and a research team led by Kishore Gopalakrishnan. "With Lumito's technique, we hope the problem of background staining can be eliminated by clearer imaging of renal biopsy tissue," says Gopalakrishnan. There will also be the added advantage of being able to preserve the slides for review. In addition, being able to use formalin-fixed, paraffin-embedded tissue would potentially mean an additional biopsy core of fresh tissue will not be required."

If you're excited about the technology's potential, Johansson has an invitation. "We are always interested in getting in touch with more research groups to map out where our product brings the most value."

www.lumito.se/en
For research use only.

Reference

1. *T Lidström et al., "Extracellular galectin 4 drives immune evasion and promotes T-cell apoptosis in pancreatic cancer," [submitted] (2022).*

In My View

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

A Space Waiting to Be Filled

The University of Texas Medical Branch is working to solve dwindling access forbenign hematology patients

By Caitlin Raymond, Paul Young and Christopher Zahner , Department of Pathology, University of Texas Medical Branch, Galveston, Texas, USA..

The term "benign hematology" refers to a variety of non-malignant hematological conditions, including genetic hemoglobinopathies, disorders of coagulation, anemia, and nutritional deficiencies such as iron deficiency. These disorders are often treated by primary care physicians, with more complicated cases referred to hematologists. In the United States, these are predominantly professionals specialized in hematology and oncology – but this means that many benign hematology patients experience long wait times due to a nationwide shortage of available physicians who specialize in hematology (1,2). In American medical training, the pathway to hematological expertise involves completing a combined fellowship that includes both hematology and oncology. A 2019 survey of these fellowship graduates indicated that 62 percent of them had no intention of incorporating benign hematology into their practice (3), further increasing the vacuum of qualified providers. Here at the University of Texas Medical Branch (UTMB), the Department of Pathology is filling that vacuum.

Michael Laposata, chair of the department, has announced plans to open a benign hematology service staffed by a mix of pathologists and other interested, experienced, and available hematology-oncology doctors. The service will act as a traditional consult, capable of not only offering expert advice on the selection of laboratory tests and interpretation of laboratory values, but also delivering direct patient care in both telehealth and in-person formats.

The benefits of staffing benign hematology clinics with pathologists are numerous, particularly for patients. First, pathologists are familiar with using complex laboratory algorithms to diagnose benign hematological disorders, such as bleeding, anemia, and thrombosis; as a consequence, we are adept at interpreting results. Staffing benign hematology clinics with pathologists sets the stage for a reduction in misdiagnoses, as well as in the under- and overutilization of laboratory tests, all of which may decrease the overall cost of care (4,5). At UTMB, we have years of experience with diagnostic management teams and have produced detailed interpretations of laboratory results in patient charts (4,5), working closely with clinicians to advise on the diagnostic evaluation and treatment. Many diagnoses that are predominantly laboratory-based can be communicated through a similar mechanism.

Another benefit is patient appointment times. In this new model of care, pathologists will bill for the patient encounter and are salaried in whole or part for management of laboratory services. This provides the option of spending more time with individual patients, because pathologists will not be dependent on high patient throughput to maintain their salaries. Moreover, pathologists in transfusion medicine and coagulation – who are often most familiar with the required care for benign hematological disorders – will often see patients directly. Additionally, pathologists are experts in the indications, risks, and benefits of transfusion of blood products, which are often indicated for benign hematological disorders.

The benefits of this approach also flow inward. The evolution of this approach to clinical practice opens the door for pathologists to interact more with medical students, improving their understanding of our specialty (and potentially increasing recruitment of students into our discipline). It will increase pathologists' exposure to our clinical colleagues and provide an awareness of the ways in which pathologists can improve diagnostic accuracy. Finally, as this initiative unfolds, it will provide broader training to pathology residents in caring for this class of disorders.

In summary, direct patient care by pathologists in benign hematology is an initiative with many benefits – to the patients, to the field of pathology, and to medicine in general. Several decades ago, transfusion medicine moved into pathology training – and this new initiative bears many similarities. Today, pathologists are uniquely qualified to step into the space of expert physicians in hematology – where we can provide critical services to this often-underserved population of patients. At UTMB, we hope to act as a model for this innovative format for patient care and inspire other pathologists to follow in our footsteps.

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"The evolution of this approach to clinical practice opens the door for pathologists to interact more with medical students, improving their understanding of our specialty."

Pathologists, We Need to Talk About Tech

Technology could help us achieve more effective, equitable cancer care

By Dean Bitan, Co-Founder and Chief Executive Officer of Imagene AI, Tel Aviv, Israel.

"Your biopsy results show you have cancer," says your oncologist. Your heart sinks. "The next step is to wait several weeks for your genomic test results so we can see if you are eligible for any targeted therapies or clinical trials." It's hard to focus as the questions start to fill your head, but a few whys immediately spring to mind. Why me? Why is this happening? Why now? Once this new reality sets in, there's one "why" that drowns out all the others. "Why is the wait so long?"

I hope that you and your loved ones will never hear the words written at the start of this article; in fact, my hope is that no one will need to endure the anxiety of waiting or the frustration of not getting the right treatment for their distinct cancer mutation. But, in 2022 alone, there will be an estimated 1.9 million new cancer cases diagnosed in the US (1) – and every one of those people deserves the best possible diagnostic care.

In recent years, it has become clear that genomic information is crucial for accurate cancer diagnosis and optimal treatment selection – but genomic screening is a long, expensive, and often inaccessible process. We have a growing need for genomic screening – and that calls for change.

My personal cancer journey began when my mother received a diagnosis of aggressive stage IV ovarian cancer. A data-oriented person, I dove in to learn everything I could about her disease and was surprised to realize how many uncertainties and probabilities her diagnosis and treatment process had. As an engineer, I was most comfortable

"AI can also offer insight into which treatments an individual patient will most likely respond to, evaluating genomic data, phenotypic data, proteomics, and spatial mapping to reduce the likelihood of unsuccessful treatment or unnecessary side effects."

when dealing with precision – highly controlled systems with repeatable outcomes. The uncertainty in my mother's treatment showed me that there was a tech-shaped hole in oncology, so I made it my goal to empower physicians with precise, crucial, timely information to change the way cancer is diagnosed and treated.

Today, that goal has become my life's work. My colleagues and I now know that deep learning and artificial intelligence (AI) technologies can allow physicians to receive genomic screening reports in real time, enabling immediate decision-making for additional testing, faster screening for clinical trials, and a well-timed treatment approach. By harnessing the power of AI, we can democratize genomic screening and totally transform patient care. Patients deserve a shift in the healthcare industry to take this change in precision medicine from concept to reality.

Of course, the title of this piece is intentionally confrontational. Pathologists don't need to "talk" with anyone about technology – they use a plethora of different machines, computers, and other gizmos to do their work every day! But the sentiment of my slightly standoffish headline still rings true; why, exactly, aren't pathologists using more tech?

Using only an H&E-stained biopsy image, advanced deep learning algorithms need just a few minutes to provide a report for distinct cancer mutations and novel biomarkers and even to predict whether a patient will respond to specific therapies. Technology can detect patterns in the biopsy image that cannot be seen by the human eye, which can help prioritize the use of biopsy tissue, accelerate clinical trial enrollment, and help physicians optimize treatment protocols.

In addition to reducing the lengthy delays inherent in present-day molecular testing and the high costs of building a next-generation sequencing (NGS) lab, AI-enabled biopsy image analysis can help address other issues that frequently arise in the pathology lab – such as not having enough tissue available, technological challenges with DNA extraction, and difficulty with result interpretation. In lung cancer, for example, less invasive core needle biopsy retrievals mean that up to 20 percent of patients cannot receive the benefit of NGS due to a lack of tissue availability. What's more, technological and interpretational challenges often lead to "inconclusive results."

The use of technology can significantly reduce inconclusive results because it is integrated directly into a lab's workflow and does not consume any additional tissue. Providing pathologists with a genomic screening report as soon as a slide is scanned allows them to better prioritize confirmatory molecular testing to conserve tissue. These AI models have been tested using different types of scanners and slide staining methods and my team's results have been reproduced in multiple medical centers. AI can also offer insight into which treatments an individual patient will most likely respond to, evaluating genomic data, phenotypic data, proteomics, and spatial mapping to reduce the likelihood of unsuccessful treatment or unnecessary side effects.

Today, precision oncology is a reality for only a small percentage of patients, but it remains our best option for achieving real breakthroughs and realizing individualized approaches to treatment. If we are going to achieve the goals of precision medicine, we must democratize genomic screening so that all physicians have the best information available to choose the most suitable treatment plan. Furthermore, leveraging AI to reduce testing costs and make genomic screening available to everyone, everywhere, will make a real impact on the quality of patient care – not only by helping to select the most appropriate treatments, but also by speeding up the selection process to reduce wait times and anxiety for patients and families. I know the anxiety of treatment uncertainty all too well – and I know that now is the moment to do something about it.

Reference

1. *American Cancer Society, "Cancer Facts & Figures 2022" (2022). Available at: https://bit.ly/3zq9zim.*

The Ultimate Influencer

The laboratory is a healthcare leader – on social media and in real life

By E. Blair Holladay

Whether you scroll through Twitter, "like" posts on Facebook, double-tap an eye-catching image on Instagram, or comment on a colleague's insights on LinkedIn, it's hard to get away from social media. Some see its pervasiveness as intrusive, whereas others embrace the feeling of community social media can provide, connecting with people near and far. No matter what your feelings, though, the laboratory and social media are inextricably intertwined – and more so than you may think.

I don't just mean in the sense that the pathology and medical laboratory science community is incredibly active on social media, engaging with colleagues and sharing knowledge. Though that is significant within the healthcare community, the connection between social media and the laboratory goes further. Social media influences what we see and hear and can shape how we think and feel about issues. Pathologists and medical laboratory scientists influence what physicians see and hear and how they understand diagnoses, which in turn influences how they treat their patients. We've all seen the power social media can have over people; the laboratory also has that power when it comes to improving patient care.

In fact, when it comes to patients and healthcare, the laboratory is the ultimate influencer. Physicians cannot make an accurate diagnosis or create a treatment plan without the information the laboratory provides. We touch just about every part of a patient's healthcare journey. The knowledge we share, and the way we share it, is instrumental in providing high-quality patient care.

However, to be the empowered influencer that we know the lab can be, we must embrace our power and be pervasive in sharing our knowledge and the impact we have on patient care. Though collaborating with other departments and specialties is critical to ensuring patients receive each piece of care they need, it is up to us to step out of the laboratory to underscore just how critical our role is. Like social media, the lab should be everywhere – and, although we know it is, it's time for everyone else to know it, too. It's time for everyone to see us, hear us, and fully understand how the laboratory is a partner in patient care.

Being an influencer in healthcare is not without its challenges, and it's not an easy road to travel. The laboratory is well-positioned to meet these challenges and traverse the road no matter what bumps (or, in social media-speak, dislikes and angry emojis) we encounter along the way. Harnessing the power we embody and leveraging it to improve patient care is our ultimate goal – and, as the ultimate influencer, the laboratory can be a leader and example for all.

The Hype Over HRD Testing

Homologous recombination deficiency is a crucial predictive biomarker in certain cancer types – and it's time to get on board

WHAT IS HOMOLOGOUS RECOMBINATION DEFICIENCY?

Homologous recombination deficiency (HRD) is a phenotype defined by cells' inability to repair double-strand DNA breaks using the homologous recombination repair (HRR) pathway (1). When the HRR pathway is compromised, genomic alterations and instability can occur – contributing to cancerous tumor growth.

ATM	*CHEK2*	*PTEN*
ATR	*FANCA*	*RAD50*
BARD1	*FANCC*	*RAD51*
BRCA1	*FANCI*	*RAD51C*
BRCA2	*FANCL*	*RAD51D*
BRIP1	*NBN*	*RAD54L*
CHEK1	*PALB2*	*TP53*

Table 1. Genes involved in the HRR pathway (2).

WHY IS HRD TESTING IMPORTANT?

HRD has been associated with various cancer types, such as ovarian, prostate, breast, and pancreatic cancer, and is an important predictive biomarker for cancer patients. When a tumor exhibits HRD, the patient may be eligible for treatment with PARP inhibitors (PARPi) or platinum-based chemotherapy. HRD is also a positive prognostic marker for both progression-free and overall survival (3).

WHY IS HRD A PREDICTIVE BIOMARKER FOR PARPI THERAPY?

HRD status can provide predictive information on the patient's expected benefit from PARPi treatment and inform strategies for optimal maintenance therapy. Blocking the PARP enzyme inhibits DNA single-strand break repair and cell replication can cause double-strand breaks. Because these breaks would typically be repaired via HRR, inhibiting that pathway through PARPi treatment of HRD-positive tumors can result in cancer cell death.

WHICH METHOD SHOULD BE USED FOR HRD TESTING?

Different mechanisms are available to detect gene functionality loss in the HRR pathway. HRR genes can be sequenced to detect mutations or the HRD phenotype can be measured by a so-called "scar test" (see "Testing methods to detect HRD"). There is increasing evidence for the need to assess both the causal genes of the HRR pathway and genomic scarring to maximize detection of HRD-positive cancers (1). Testing methods limited to *BRCA1* and *BRCA2* or HRR gene panel testing might not be sufficient because HRD can be present without such mutations. Therefore, HRD "scar testing" can identify additional cancer patients who may benefit from PARPi treatment.

WHICH CANCER TYPES ARE RELEVANT FOR HRD TESTING – AND WHO SHOULD BE TESTED?

HRD has been associated with various cancer types; so far, clinical utility has been demonstrated with PARPi in ovarian (HRD, germline and somatic *BRCA1/BRCA2*), prostate (germline and somatic *BRCA1/BRCA2*, HRR genes), breast (germline *BRCA1/BRCA2*), and pancreatic cancer (germline *BRCA1/BRCA2*). Beyond *BRCA*, HRR genes, and HRD, genomic signatures such as microsatellite instability may be associated with different ovarian cancer subtypes. Although these genomic alterations are rarer, it is valuable to assess the genome in a comprehensive manner because of not only these changes, but also the various types of alterations caused by HRD.

ARE BOTH GERMLINE AND SOMATIC TESTING NEEDED?

Both germline and somatic mutations are associated with HRD in cancer patients. In a 2020 study, researchers characterized the *BRCA1/BRCA2* mutation spectrum in a consecutive series of ovarian carcinomas and observed a frequency of 19.3 percent deleterious, 13.3 percent germline, and 5.9 percent somatic variants (4). Germline and somatic BRCA mutation testing is a routine first-line clinical recommendation for high-grade serous carcinoma (HGSC) patients who should receive a PARP inhibitor (5). However, HRD tests do not distinguish between somatic and germline mutations; if a relevant mutation is detected, a genetic counselor should be consulted for germline testing to identify potential familial risk.

TESTING METHODS TO DETECT HRD

HRD status can be measured by "cause" through mutations in the HRR pathway (e.g., *BRCA1* and *BRCA2*) and by the "effect" of the presence of genomic scars at a given threshold or functional assay.

Patients with an HRD-positive tumor may be eligible for targeted PARPi treatments. In the case of ovarian cancer, a composite genomic instability score (GIS) versus a measurement of an individual scar (TAI, LST, or LOH) status may be a better predictor of outcomes for PARPi or platinum-based treatment than the individual components alone (6).

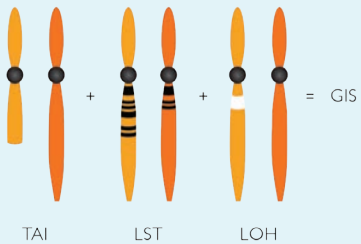

Figure 1: Genomic scars are indicators of genomic instability. TAI: telomeric-allelic imbalance; LST: large-scale state transitions; LOH: loss of heterozygosity.

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A RARE DISEASE REVOLUTION

Genomic medicine is on the upswing – and rapid, reliable, accessible sequencing could significantly shorten the diagnostic odyssey for many rare disease patients

By Stephen Kingsmore

Genomics started off as a purely research exercise – but, over the last decade, it has increasingly come to the fore in medicine. Scientific advances have led to significant improvements in the diagnosis and management of rare diseases with genetic causes. Most of the burden of such illness is pediatric and many of these diseases are fatal in childhood. In fact, they are the leading cause of infant mortality in the first world – and therefore the biggest determinant of childhood health. People don't realize that because genetic disease is like an iceberg; we see the patients who are diagnosed early or survive long enough to receive treatment, but not those who don't.

The (pediatric) rare disease landscape

Currently, there are over 7,200 known genetic diseases – and that number increases by about one a day. We have had some spectacular success in identifying some relatively common diseases, such as sickle cell anemia, thalassemia, or cystic fibrosis. However, the vast majority of rare diseases affect fewer than one in 10,000 individuals and are massively underdiagnosed. Why? Because until recently, we had no way to diagnose these diseases other than by family history.

That all changed when we gained the ability to sequence and decode the entire genome. That's when we realized just how much we had been operating in the dark. We hadn't even known that many of these diseases were genetic; we had theorized that they might be environmental or simply labeled them as "unknown etiology." For example, there are well over 1,000 different genetic diseases that cause seizures in children. The same is true of deafness or intellectual disability. We had always believed that patients with these phenotypes had complex disease affected by environmental factors – when, in fact, most of the conditions were rooted in genetics all along. This meant that many of our patients had been receiving ineffective treatments because they were being treated for non-genetic causes.

Nowadays, we can diagnose a genetic disease in under a day from delivery of a blood sample to result. What proportion of children benefit from this technology? I would estimate about 0.01 percent. The tragedy is that it will take years – hopefully not decades – for children around the world to have access to these diagnostics. There are so many barriers: infrastructure, reimbursement, and training. The vast majority of physicians were never trained in genomics and therefore don't know how to practice genomic medicine. So it's a complex issue – not just a matter of legislation or evidence, but also one of upskilling the medical workforce.

The diagnostic odyssey

Rady Children's Hospital is unique in our approach to whole genome sequencing for all patients. If your child is seen in our autism clinic, for example, genome sequencing is available on the first visit because there are so many genetic causes underlying autism spectrum conditions. If your child is admitted to our neonatal intensive care unit, genome sequencing is immediately available to diagnose

any potential genetic conditions. Even at Rady, doctors still underrecognize genetic disease, but we're getting there. We also have 81 partner children's hospitals across North America who send us medical records and DNA samples from children who may benefit from whole genome sequencing. Genomics is becoming increasingly recognized and democratized, but the need still vastly outweighs the provision – or the reimbursement.

For patients who don't have access to whole genome sequencing, the diagnostic journey can be disheartening, painful, or even dangerous. It can take decades of going from physician to physician, specialist to specialist, subspecialist to subspecialist, until finally the penny drops, genomic testing is ordered, and we get an answer. Families who travel this road go through years of suffering, being misunderstood, and having their children dismissed as having emotional or psychological problems. Many experience organ failure before diagnosis – and that cannot be remedied, especially in neurological conditions. The tragedy today is that we have treatable illnesses that are under- or misdiagnosed, leading to outcomes that are needlessly bad. My patients and their families often ask, "How can this happen in the 21st century?" – and I sympathize with their frustration.

A story of success

We had a five-week-old patient whose mother brought him into our emergency department late on a Sunday night. She explained that her baby – who had no previous health issues – was irritable and couldn't be consoled. Fortunately, the pediatrician on call noticed that his eye movement was not quite normal and ordered a stat CT scan that showed white lesions all over the patient's brain.

He was immediately admitted to our neonatal intensive care unit and, by lunchtime the next day, a decision had been made to perform whole genome sequencing. The patient's blood sample arrived at our institute at 5:00 pm. By 7:30 am, we had a diagnosis – thiamine metabolism dysfunction syndrome 2 (1). Without treatment, the disease is rapidly fatal; in fact, in the short time between admission and diagnosis, the patient had already experienced a seizure, was lethargic, and couldn't feed. We immediately administered treatment – large doses of biotin and thiamine – and, within six hours, he was back to normal. He was alert, happy, peaceful, and feeding from a bottle. A couple of days later, he went home. One year later, he's an affectionate, loving little toddler hitting many of his developmental milestones.

A decade earlier, the patient's sister had presented with similar symptoms. Undiagnosed, she was treated with every antiepileptic drug available – but none controlled her seizures and she died in infancy of profound neurological devastation. Whole genome sequencing was the difference between a premature death and a couple of days in the hospital. Our patient will be on high-dose biotin and thiamine supplementation for life, but that life will probably last 80 to 90 healthy, happy years. Everyone wins.

The Rare Disease Revolution: AI

The biggest challenge in rare disease diagnosis – and how AI can help overcome it

By Venky Soundararajan

The phenotypes clinicians describe are largely encoded in the form of text-based clinical notes, often for months or years before the patient receives a definitive rare disease diagnosis. This means that the greatest impediment to advancing lifesaving rare disease research lies in synthesizing each patient's longitudinal journey to understand their condition's natural history – and, once diagnosed, the outcome of each treatment option they explore.

The ongoing artificial intelligence (AI) revolution is enabling machine-augmented curation of tens of millions of patients' electronic health records – a total of billions of clinical notes from over a century of care. This synthesized institutional biomedical knowledge is revealing, for the first time, the natural history of each rare disease, from the first observable phenotypes through many years of missed or incorrect diagnoses, eventual correct diagnoses, and treatments. In many rare diseases, AI is also making connections to more common conditions whose FDA-approved treatments may offer a glimmer of hope in treating related rare diseases.

Bringing pathology into the digital era at scale by digitizing billions of pathology slides and creating the world's largest digital knowledge base of pathological and normal tissues will be a game-changer in the AI revolution – but realizing this promise to transform biomedical research will not materialize unless these digital images are tied meaningfully to curated health records, including disease phenotypes, attempted treatments, and patient outcomes.

Venky Soundararajan is Co-Founder and Chief Scientific Officer at nference, Cambridge, Massachusetts, USA.

The Rare Disease Revolution: Awareness

To simplify the diagnostic odyssey, we must collect and use all of the information available to us – from genetic sequences to literature review

By Mark Kiel

The biggest challenge facing rare disease diagnosis is the awareness and recognition of each of these diseases – each of which individual clinicians very rarely encounter – and the challenge associated with interpreting genetic testing results.

The widespread adoption of next-generation sequencing has led to rapid whole genome and whole exome sequencing, in turn increasing the rate at which rare diseases – often not present on limited gene panels – are diagnosed. In addition, result interpretation has been accelerated by the increased use of automated pipelines for secondary and tertiary analytics, meaning that the time from sequencing to diagnosis can be as little as a day. In the future, I anticipate that these advances will result in whole genome and whole exome sequencing as a standard of care – and that next-generation sequencing will be universally applied to newborn screening to increase early diagnosis of genetic disease.

The medical literature, which contains millions of articles and is continually expanding, is extremely difficult to navigate – especially for rare diseases – but holds valuable clinical and functional evidence that can impact patients' diagnostic journeys. To ensure accurate and efficient diagnoses, we need a way to automatically aggregate and annotate evidence from the literature.

In addition, patient advocacy groups often collect clinical and genetic information from their patients that could be instrumental in better understanding individual diseases and their causes – but organizing and widely sharing that information with the clinicians, researchers, and pharmaceutical companies that could benefit from it presents a challenge. These groups need a more efficient way to gather, standardize, and share information to maximize its value for continued research.

Collectively, rare diseases are not all that rare, and so must always be considered in the diagnostic process. Genetic testing will be crucial in ensuring that this process is both efficient and sensitive; this is especially true when using whole genome or whole exome sequencing, because these approaches offer the highest likelihood of identifying a causative mutation. In addition, establishing more efficient ways to aggregate and use clinical and genetic information from the literature, patient advocacy groups, and other sources will be necessary to ensure that all patients are diagnosed rapidly, efficiently, and appropriately.

Mark Kiel is Founder and Chief Scientific Officer at Genomenon, Ann Arbor, Michigan, USA.

The future of rare disease

Our hospital has committed to decoding the genomes of 10,000 children in families of need over the next three years. I think of us as an "icebreaker" – somebody has to go through that ice first and create the knowledge base for the entire medical establishment so that other centers follow suit. We began with our most critically ill patients – those in intensive care – because they have the highest incidence of genetic disease. Now, though, we're broadening our focus to our outpatient clinics.

At the same time, we're working on more affordable testing options, because diagnostic whole genome sequencing – especially if it's done in one day – is very expensive. We're planning to introduce newborn screening by whole genome sequencing so that, over the next decade, every newborn baby is fully screened for genetic diseases. The ideal solution is to diagnose every child at birth, before onset of symptoms, and start them on effective treatment immediately (where available). That, in turn, will spur massive pipeline development by pharmaceutical companies – because a diagnosis without a treatment is better than no diagnosis at all, but what we really want are effective therapies for our patients so that they can live full, healthy, normal lives.

That's the journey that we're on – breaking the ice, focusing applications of whole genome sequencing, developing affordable testing, and partnering with the pharmaceutical industry to accelerate drug development pipelines. It sounds like a lot, but it's not just us; there's an ever-growing community of people who are pushing to make these dreams a reality.

Genomic science has evolved very quickly, so traditional pathology is now playing catch-up. Genomics was originally part of clinical pathology, but it's fast becoming a standalone specialty. At Rady, we have conventional pathologists, molecular pathologists, and laboratory directors who have PhDs rather than MDs. The division of duties and expertise is in flux – it feels a little bit like, "Who's on first?" I would say that traditional pathology hasn't yet fully entered the molecular era for rare, inherited genetic disease, so we need to democratize knowledge and make it mainstream for every pediatric subspecialty. If you're a pediatric nephrologist, you need to know the genetic disorders of the kidney – but not necessarily the liver or the brain. The idea that a singular person will cover this space is a fallacy; there are far too many of these diseases and they're highly variable in terms of the organ systems that they affect. The key is to work collaboratively.

> "Whole genome sequencing was the difference between a premature death and a couple of days in the hospital."

Children with rare diseases tend to be medically complex patients who require care from a coordinated team. Those whose diagnoses don't come with effective treatments will need a team-based care approach throughout their lives. Historically, these patients often died in infancy or early childhood – so now, for the first time, adult medicine is encountering the need for this kind of care. Our patients can't continue seeing pediatricians well into their 40s; we need to train adult practitioners and establish adult clinics for rare diseases whose treatment and survival rates are improving.

Record-breaking diagnoses

The first time we set the Guinness world record for fastest whole genome sequence was in 2011 and it took us 56 hours. In 2017, we improved it to 26 hours, then 19 hours in 2019 and 13.5 hours in 2021. Unfortunately, I think we've hit the limit on recertifying the official record – but we're still getting faster!

Why do we do this? Because we're trying to change the world. Researchers don't usually do this kind of publicly visible "fun" – but genomics still has a lot of resistance

The Rare Disease Revolution: Genomics

Bringing whole genome sequencing into rare disease diagnosis, prognosis, and treatment

By Jeanette McCarthy

Rare disease diagnostics using whole genome sequencing (WGS) are essential for many people suffering from unknown illnesses. The greatest challenge with WGS is the myth that sequencing and analysis are too expensive – or too complicated – to implement in a diagnostic setting. There's a perception that WGS requires massive capital outlays and expertise, but this is no longer the case. The cost of sequencing has come down so significantly that many labs can now purchase their own instruments or send out samples for affordable contract sequencing. In addition, customers can now also access cost-effective turnkey solutions – or even full-service support – for help with analysis and interpretation while still delivering turnaround times of 48 hours or less. Even if you don't have genomic experience or technology in-house, you can still provide rare disease patients with rapid whole genome analysis.

Access and equity

With many rare diseases, particularly childhood diseases and time-sensitive medical conditions, reducing the time to diagnosis can significantly improve outcomes and quality of life. Today, we can go from sample to result in just a few days and prioritize high-value diagnostic candidates for clinicians so that they can focus their attention on a smaller number of high-value, potentially causative candidate genes identified by artificial intelligence (AI). We've come a long way in the last couple of years; now, our task is to increase awareness of – and access to – techniques and technologies that can alleviate the burden of the diagnostic odyssey.

Many of the challenges with access and equity are tied to overall awareness. There has been so much discussion of things like the "race to the $1,000 genome" that interpretation – making sense of those three billion base pairs – has been overshadowed by hardware discussions. Today, services that provide ready access to whole genome data and AI-powered clinical decision support platforms are making it possible for any hospital anywhere to offer state-of-the-art whole genome diagnosis without requiring genomic infrastructure. And, as reimbursement for WGS continues to expand, that equity will also expand.

Diagnostic support

AI is really what makes genomic analysis at scale possible. There is no way one human can study millions of variants in a whole genome sequence and turn around an answer in a day or two – and, even if there were, without artificial intelligence, the cost becomes unmanageable at scale.

Training AI on large, population-level WGS datasets has paved the way for better interpretation tools that can automate and accelerate what has been a time-consuming – and, in some cases, impossible – task. With AI, instead of looking at the entire genome, pathologists can focus on the variants with the highest likelihood of causing disease at a cost that is increasingly reasonable and at a speed that is feasible for time-sensitive, critical care situations.

And, if that seems like too much, clinics can start with a simpler custom panel based on WGS and consistently test exactly what they're looking for now – with the added ability to go back to the samples and data later if they find other validated genes they want to study. These panels can start small and be expanded as needed because the data are there – and they can be used for research across populations, too.

Ultimately, AI analysis of whole genomes means you can get high accuracy and rapid clinical reporting, allowing laboratories to provide greater access to the lifesaving answers a genome may hold. And, with expanding reimbursement for rare disease sequencing and treatment, we can look forward to a time when all rare diseases are identified early and treated fast – potentially saving many patients' lives.

Jeanette McCarthy is Vice President of Precision Medicine, Fabric Genomics, Oakland, California, USA.

to overcome. To say, "We're going to decode your baby's genome" – that's a big concept for a parent to take in, so we need things like the Guinness world record to get people excited about genomics.

There are still many misunderstandings and misconceptions around genomic medicine, which is why we consider education and engagement one of our most important responsibilities. We need the public to hear about the benefits of genomics and we need scientific and medical professionals to understand the research so that they can communicate it to their patients. We don't want to wait 20 years for a new generation of doctors to emerge; we want the current medical establishment to realize how exciting and fulfilling genomics can be.

If I could say one thing to my colleagues in pathology and laboratory medicine, it would be, "Genomes are good." Always be thinking about the genome. Anytime something is atypical, think genome. Even if whole genome sequencing turns up no results, you've gained valuable information about your patient – we even published studies showing that 72 percent of clinicians found negative results useful (2) and 97 percent of parents agreed that it was useful despite only 23 percent of children receiving genomic diagnoses (3). Diagnoses are valuable, but ruling out genetic causes of disease can be equally important to help focus diagnostic attention elsewhere – and to reassure parents that their child's genome is healthy. So – think genome!

Stephen Kingsmore is President and CEO of Rady Children's Institute for Genomic Medicine, Rady Children's Hospital, San Diego, California, USA.

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Covering All Bases

The need for molecular testing in NSCLC patients is growing – and QIAGEN can help you meet it

Why is it important to test for *EGFR* and *KRAS* in non-small cell lung cancer patients?

EGFR and *KRAS* represent about 40 percent of all driver mutations within non-small cell lung cancer (NSCLC). Multiple therapies are now approved in the US to target specific driver mutations for patients whose tumors harbor these alterations, but molecular testing is required to guide appropriate, targeted use of these drugs.

Why is molecular testing underperformed in NSCLC patients?

A recent publication suggests that about 23 percent of NSCLC patients in western Europe are not tested for the most clinically relevant biomarkers (1), a statement that was consistently reiterated at the 2022 European Society of Medical Oncology (ESMO) conference. Missed opportunities for testing are likely multifactorial, but one key challenge is the turnaround time of results relative to the need to rapidly initiate treatment – causing some patients to miss out on precision therapy due to access issues or lack of relevant information.

Implementing a user-friendly testing platform that offers a wide menu for oncology testing would facilitate efficient workflows and enable rapid turnaround times with certified diagnostic products that require minimal in-house validation.

Increasing knowledge and access by introducing tests that can use either tissue or liquid biopsies could also help overcome some of the challenges. Tissue remains the primary material for testing, but NSCLC guidelines are constantly evolving to include liquid biopsy when tissue sampling is not possible, which would increase the number of patients tested and allow for routine monitoring where appropriate. Recent approvals of new therapies may also provide additional opportunities for patients once tested, such as newly approved drugs that target previously "untargetable mutations." For example, the *KRAS* G12C mutation represents 13 percent of all *KRAS* mutations. Identifying *KRAS* G12C using molecular testing is of paramount importance to guiding treatment – and makes the mutation a key target for precision medicine.

Tell me about QIAGEN's genomic testing solutions…

Our third-generation *therascreen* EGFR Plus RGQ Kit tests for key *EGFR* treatment resistance biomarkers T790M and C797S and supports testing with either FFPE or plasma samples. *therascreen* EGFR Plus is a certified diagnostic tool within the EU and approved as "Research Use Only" in the US. Important clinical trials using the *therascreen* KRAS RGQ PCR Kit have also led to the approval of the kit as a companion diagnostic. Now, the *therascreen* KRAS RGQ PCR Kit has an approved extension for NSCLC, as well as its original indication in colorectal cancer testing. By combining QIAGEN's EGFR Plus and KRAS kits, pathologists can test NSCLC FFPE samples via qPCR for the two most frequently mutated genes in NSCLC.

For customers who wish to conduct deeper testing with next-generation sequencing (NGS), QIAGEN enables comprehensive oncology profiling with a number of targeted library prep solutions. Our QIAseq Targeted NGS portfolio facilitates ultrasensitive variant and fusion detection using integrated unique molecular indices and highly optimized target enrichment technology.

QIAGEN's newly launched QIAseq Targeted DNA Pro Panel allows labs to expand variant analysis to reveal structural variants with breakpoints defined at the nucleotide level across multiple exons. Another QIAGEN product – the QIAseq RNA Fusion XP – enables the combined analysis of RNA fusion with single-nucleotide variants and gene expression from a single sample, allowing customers to gain complex RNA-seq insights.

Finally, QIAseq Multimodal Panels enable the simultaneous enrichment and profiling of DNA variants, RNA fusions, and gene expression levels from one sample input. Our NGS solutions are molecular biologic

applications that are not certified for diagnostic use.

How do clinical and research labs benefit from these solutions?

Our *therascreen* kits are accredited as diagnostic tests, having been both analytically and clinically validated; therefore, a clinical lab can use them confidently without the need for additional validation. EGFR Plus is validated with QIAsymphony extraction and Rotor-Gene AssayManager software to allow the user to automate sample extraction and data analysis. Furthermore, *therascreen* KRAS and EGFR are part of a much wider portfolio of oncology biomarker testing kits that run on the QIAGEN Rotor-Gene Q platform. Any lab adopting this platform can therefore test for multiple indications in both solid tumors and oncohematology.

Users can easily automate our NGS panels, which come with various levels of automated analysis to reduce the need for costly or time-consuming bioinformatics. The new QIAseq Targeted DNA Pro Panel reduces library preparation time to as little as six hours and requires only two hours of hands-on operator time – allowing highly trained staff to repurpose their time for other tasks.

What sets QIAGEN's genomic testing solutions apart from competitors?

QIAGEN has been providing products in this space for many years and is a trusted supplier of both qPCR and NGS testing solutions. The *therascreen* EGFR and KRAS kits have both been thoroughly validated and registered as in vitro diagnostics – inspiring user confidence that third-party clinical trials have produced reliable data. The sheer breadth of QIAGEN's portfolio is attractive and allows labs to set up for multiple indications with a single, small-footprint system. With EGFR Plus, labs can test liquid biopsy samples for resistance biomarkers T790M and C797S – one of the only qPCR kits on the market to enable this.

"The sheer breadth of QIAGEN's portfolio is attractive and allows labs to set up for multiple indications with a single, small-footprint system."

Due to the fragmented and modified nature of FFPE DNA samples, many NGS library construction workflows have a low recovery rate from FFPE DNA, but the QIAseq Targeted DNA Pro incorporates a seamless FFPE DNA repair step before library construction. The specially formulated chemistry achieves highly efficient enrichment even in GC-rich regions. In addition, QIAseq Targeted DNA Pro libraries can be sequenced with Illumina default sequencing primers and are compatible with most mid- to high-throughput sequencers. Alternative targeted DNA library construction methods have multiple bead cleanup steps that are labor-intensive and result in inconsistent library yield; by replacing the bead cleanup steps with enzymatic processes after ligation and target enrichment, QIAseq Targeted DNA Pro enables an efficient, automation-friendly workflow.

The QIAseq Targeted NGS portfolio comes with a number of catalog panels that have preconfigured workflows for seamless variant calling; however, QIAGEN also offers its customers the flexibility to customize their NGS panels without compromising on data quality.

What's your one key message to laboratory medicine professionals about molecular testing in NSCLC?

"Test your patients" – which was also the main message running throughout ESMO 2022. Molecular diagnosis is required to identify specific alterations that can inform the clinician and enable the initiation of targeted therapy. Genomic testing for NSCLC has provided huge benefits in the past decade and improved patient outcomes by allowing more targeted therapies for their individual disease. I believe the importance of genomic testing will increase alongside our understanding of disease drivers and resistance mechanisms within cancer cells. There will be many opportunities for labs of all sizes to continue to test patients for optimal therapies with qPCR and NGS solutions – and with QIAGEN's comprehensive portfolio in qPCR, dPCR, and NGS, customers can easily access relevant genomic information in a faster, simpler, and more efficient manner.

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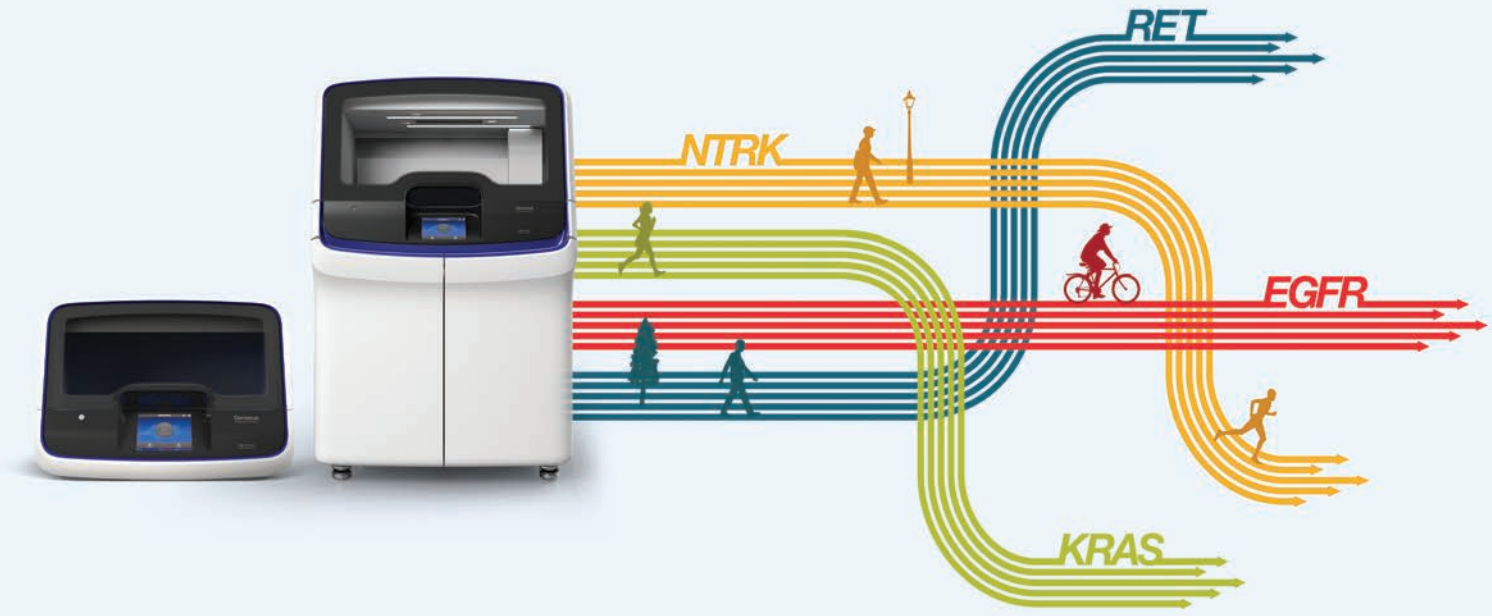

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Foundation
Molecular Pathology

Relapse or Relax. Between 20 and 30 percent of patients with breast cancer experience relapse or recurrence. A new study in 124 patients aims to improve predictive power by using circulatory microRNAs as biomarkers for early-stage breast cancer outcomes. Researchers found that increased miR-145 expression at T2 was associated with improved relapse-free survival (1).

Screening Inequalities. An investigation into newborn screening programs for different cystic fibrosis transmembrane conductance regulator *(CFTR)* variants shows discrepancy over racial and ethnic lines. Detection of at least one *CFTR* variant was highest in the White cohort and lowest in Black, Asian, and Hispanic cohorts, which were also overrepresented in delayed diagnosis and false negative newborn screening (2).

(Non)-Occupational Hazard. PHS290, a polygenic hazard score based on 290 genetic variants, has been used to measure the risk of any, metastatic, and fatal prostate cancer in nearly 600,000 Million Veteran Program participants. PHS290 was a strong independent predictor of prostate cancer and was associated with fatal prostate cancer across the entire cohort and in every racial and ethnic group (3).

The Littlest Library. A team has created a phosphoproteomics library of human-derived, phosphoserine-containing phosphopeptides at proteome scale. The Iterative Synthetically Phosphorylated Isomers library may have potential as a tool to evaluate and optimize phosphorylation-site localization algorithms and as a benchmark to compare performance across data analysis pipelines (4).

Security Breach. An investigation into the medical privacy associated with forensic genetics has shown that CODIS profiles – a series of 20 short tandem repeats – can be used for more than just identification. Information on gene expression levels may also be revealed, which can then be connected to medical phenotypes – a potential privacy issue for individuals and their genetic relatives (5)..

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IN OTHER NEWS

Analyzing autism. *Research suggests chromosome 16p has the greatest influence on polygenic risk for autism spectrum conditions; the region hosts a concentration of genes specifically expressed in the brain and an autism-associated 16p11.2 copy number variant (6).*

AML alterations. *A study of acute myeloid leukemia (AML) identifies recurrent and subtype-specific changes to 3D chromosome structure. Repressive loops were abundant and contributed to AML cell growth – but reducing DNA methylation could revert disruptions (7).*

GRN and bear it. *Lower levels of the frontotemporal dementia gene* GRN *leads to gangliosidosis. Ganglioside or bis(monoacylglycero) phosphate levels may be useful biomarkers (8).*

Not so sweet. *Noncoding variants cause a loss of repression of* HK1 *gene in pancreatic beta cells, resulting in inappropriate expression – leading to insulin secretion and congenital hyperinsulinism (9).*

This Time, It's Personal

Overcoming lung cancer treatment resistance will require predictive biomarkers that take into account significant patient variability

By Ofer Sharon

Since the introduction of immunotherapy almost a decade ago and the development of new targeted therapies, we have seen significant progress in lung cancer management, particularly non-small cell lung cancer (NSCLC). This progress is, in part, thanks to the introduction of precision medicine solutions that allow the selective use of targeted therapies. Nonetheless, response rates for metastatic NSCLC still barely reach 30 percent – meaning that, on average, only around three every 10 patients will benefit from treatment over time. Treatment resistance is still a huge problem and, though commendable progress has been made, we are still far from realizing true success.

"The future of biomarker testing heavily depends on pharmaceutical companies' approach."

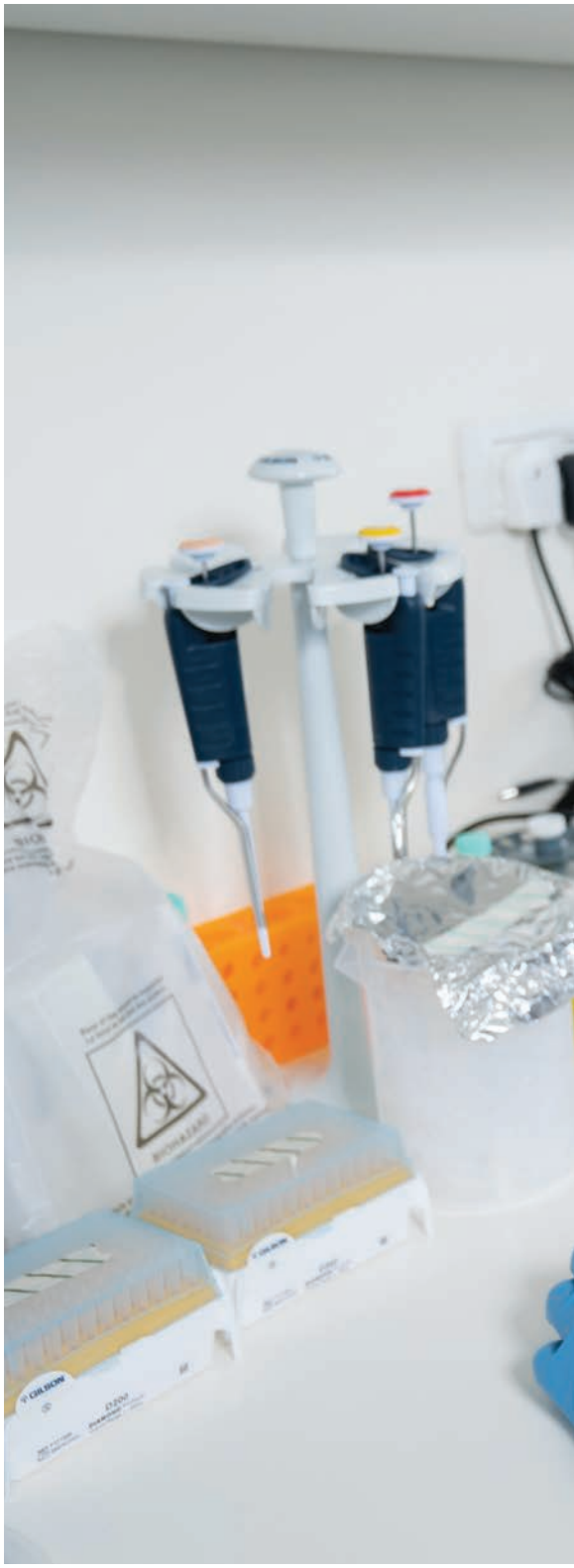
Statistically, there are about 230,000 new cases of NSCLC in the US each year, resulting in around 120,000 deaths. When considering targeted therapies, we look for specific driver mutations to decide whether we should use specific drugs, but this is relevant to only about 14 percent of patients. For immunotherapy, which is relevant for 85 percent of patients, the situation is far worse. We have some biomarkers that we use mainly as prognostic tools, but this is a very limited arsenal to test for resistance and the accuracy of these biomarkers is unimpressive. The bottom line? For most patients, there are no good biomarkers.

Patients enter treatment with multiple therapeutic options – but, if we don't have a way to identify which patients will benefit from specific options, all we can do is start treatment and hope for the best. Almost by definition, we will waste time for some (if not most) of our patients by having to treat them with therapies that may not work. Therefore, if we can discover biomarkers that tell us beforehand what the right treatment might be and what response trajectories might look like, clinicians can make informed decisions, identify resistance, intervene sooner, and choose next-line therapies based on patient and cancer biology, rather than relying on one-size-fits-all protocols.

There are currently hundreds of clinical trials investigating different combinations of lung cancer treatments. If even a fraction of these are successful, two to three years from now, clinicians could have the choice of 10–15 potential combinations of first-line treatments. But, to choose appropriately, we desperately need appropriate biomarkers to support clinical decision-making in first-line treatment and to help identify the best combination for each patient.

Standing in the way

Cancer is a very complex disease. There is a continuous interaction between the patient, tumor, and therapy – so, during



biomarker discovery, we need to consider a complex dynamic system that differs both between patients and within the same patient and changes over time. This is not ideal when trying to identify and develop robust biomarkers. Access to tissue is also a challenge; tumor tissue is not always available or usable, limiting lab professionals' ability to look for new biomarkers.

"We desperately need appropriate biomarkers to support clinical decision-making in first-line treatment and to help identify the best combination for each patient."

Although biomarker development is far from simple, we shouldn't shy away from its complexity. Instead, we should broaden our understanding of cancer biology and tumor–patient–therapy interplay. We should use new bioinformatics and machine learning tools that can make sense out of all the signals, patterns, and markers that play a role in disease dynamics. And we should understand that cancer is not just one snapshot in time; rather, we should think about it as an almost continuous process and try to divide our biomarker search into different stages of the disease – before, during, and immediately after treatment – for continuous monitoring.

The earlier the better

I believe the two areas that require the most focus and investment right now are early detection and controlled or guided treatment planning to help clinicians make more informed decisions. There is a huge need in this area because we must gather a holistic picture of our patients over time. We are not just looking for snapshots of the disease; we are building a dynamic monitoring system. Early detection is one of the most important efforts we can make in cancer management because the earlier you catch it, the higher the chance of better outcomes for the patient. Many companies are focusing resources in this area, but most patients (especially those with lung or ovarian cancers) are still diagnosed late in their journey. In these cases, the tumor is already metastatic and the focus shifts from early detection to optimizing the patient's treatment plan.

Where to next?

Right now, biomarker testing is going in all different directions. Many companies are trying to innovate in this area; that's good news but having so many different players may also make it difficult to find one good solution. The future of biomarker testing heavily depends on pharmaceutical companies' approach. If they continue to search for cancer drugs to treat "all-comers" populations – ignoring the fact that there is huge variability between patients – we will see more drugs doing excellent work, but for only a small percentage of patients.

We understand that we won't find the be-all and end-all answers in DNA – genetics and genomics won't provide us with the "silver bullet" we are looking for – but we do understand the issue of sheer complexity that cancer brings. That's why companies are now attempting to combine biomarkers, bringing together genomics, proteomics, the immune system, and the microbiome to provide a deeper understanding of disease dynamics. By combining biomarkers, disease monitoring approaches, multi-omics, and AI-based systems that generate insights beyond what human pathologists can see under a microscope, we can revolutionize the field of precision oncology and do better for our patients – now and in the future.

Ofer Sharon is CEO of OncoHost, Binyamina, Israel.

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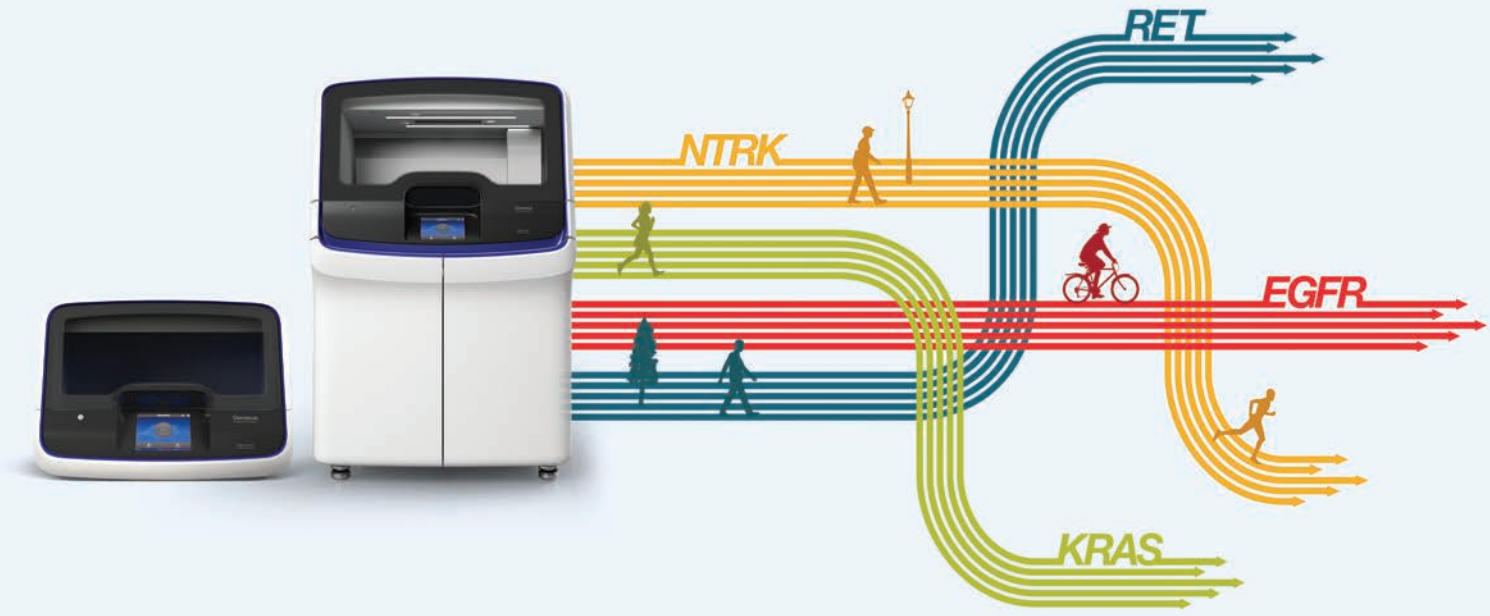

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Resisting the Resistance

Could rapid phenotypic testing help avert the drug resistance crisis?

When COVID-19 turned the world upside down, we were already on a troubling trajectory with drug-resistant superbugs – but the pandemic spurred doctors around the world to prescribe more broad-spectrum antibiotics to prevent and treat secondary bacterial infections, accelerating the potential for resistance. The long-term solution to this growing problem goes well beyond developing new antibiotics; what the global healthcare community desperately needs is access to rapid, reliable data about each patient's infection to rein in the unnecessary use of broad-spectrum antibiotics and help reverse the drug-resistance trajectory.

This concept require profiling each pathogen's antibiotic susceptibility to rule out treatments – or, more importantly, rule in targeted options. However, current tests cannot provide comprehensive antibiotic susceptibility profiles rapidly enough to guide initial antibiotic selection. Culture-based tests provide the necessary data, but can take days; genotypic tests are much faster, but do not provide definitive guidance about which antibiotics will work.

The need is clear – a test that offers phenotypic results at the speed of a rapid genotypic test. Ideally, such a test would expose the collected pathogen(s) to a variety of antibiotics and measure response to guide patient-specific treatment selection.

The crisis at hand

The rise of drug-resistant superbugs is no secret in healthcare – but how bad is it? In 2019 alone, 1.27 million deaths were attributable to drug-resistant bacteria (1). And even before COVID-19, experts believed this would rise significantly in the coming years (2). The crisis is largely fueled by standard treatment protocols in hospitals; because there no commercially available test can identify the bacterial strain and profile its antibiotic susceptibility within a few hours, physicians often prescribe a cocktail of broad-spectrum antibiotics to patients with a presumed bacterial infection.

Resistance to key drugs used for empiric treatment in hospitalized patients has crept up and recent studies indicate that a large proportion of all antibiotic treatment decisions in the hospital are incorrect or inappropriate (3). It's also more common to find superbugs resistant to all available classes of antibiotics. Scientists are aware of the need to develop new antibiotics but, though this would help for a time, it would not address the root cause of the issue. We must curb unnecessary antibiotic use to conserve the effectiveness of the treatments we have today and give future treatments a better chance of remaining effective.

The testing gap

Many physicians would use narrow-spectrum antibiotics if they were confident of their efficacy – but that requires rapid, reliable diagnostics to demonstrate which treatments would be effective for each patient. With turnaround times of days or more, culture-based testing is often only useful for auditing treatments patients are already taking. Meanwhile, critically ill patients with drug-resistant infections are significantly more likely to die with even a 24-hour delay in receiving effective antibiotics (4).

Rapid genotypic tests are marketed as a solution to the slow culture process. However, though they do produce faster results, they are limited by their reliance on genetic resistance markers. I think of this as the "MRSA illusion." Methicillin-resistant *Staphylococcus aureus* (MRSA) has one prevailing resistance mechanism – the *mecA* gene. Because there is only one thing to test for (and PCR does it well), genotypic testing for MRSA has become commonplace, leading to the misconception that resistance testing for all pathogens is equally straightforward. In fact, there are thousands of resistance genes across bacterial pathogens with complex interactions, and the constant evolution and gene-sharing that give bacterial strains new modes of resistance further complicate things. Genotypic testing cannot keep up with the speed at which drug resistance evolves.

A phenotypic approach

The ideal test would identify a pathogen's species and antibiotic susceptibility in just a few hours, guiding treatment selection as early as possible in the patient care journey. For optimal results, these tests would expose the pathogen to an array of antibiotics so physicians could clearly see which treatments would work. Each patient's treatment plan could then be tailored to their infection, allowing physicians to prescribe the most narrow-spectrum antibiotics possible.

This kind of approach has not been possible before but, thanks to recent advances in cell partitioning, single-cell analysis, and artificial intelligence, we have finally reached a point where rapid phenotypic testing should soon be a realistic option.

Nick Arab is the CEO and co-founder of Pattern Bioscience, Austin, Texas, USA.

See references online at: tp.txp.to/1222/resist-resistance

Fail to Prepare, Prepare to Fail

Are global health systems ready for another pandemic?

Emma Hannay, Karishma Saran

Healthcare workers were among the first respondents to the COVID-19 pandemic. Because their occupations required them to be on the frontlines, many lost their lives during the early days and others still suffer from post-viral symptoms or from the psychological aftereffects of the pandemic. The situation highlighted just how unprepared the world was to provide equitable access to medical countermeasures such as tests, vaccines, personal protective equipment, and therapeutics. However, we saw a triumph of science in the diagnostic landscape – accurate PCR tests for confirming SARS-CoV-2 infection were available in laboratories within eight days of the World Health Organization (WHO)'s declaring COVID-19 a Public Health Emergency of International Concern. But when it came to making these tests available to all of the healthcare centers and hospitals that urgently needed them, especially during the early phases of the pandemic, this victory was over as quickly as it came.

A changing world

Test manufacturing and supply has traditionally been very centralized; before COVID-19, research, development, and demand for diagnostic tests left the world with limited manufacturing capacity, unstable supply chains, and poor distribution and use of tests globally. Now, key industry players are coming forward to develop and grow local manufacturing capacities coupled with enhanced technology transfer. However, the same cannot be said for many other disease diagnostics. COVID-19 demonstrated what can be achieved when public and private partners work together; now, we need to develop these partnerships further so that new testing technologies can be rapidly introduced in most, if not all, countries. The pandemic triggered the largest-ever global expansion of genomic surveillance capacity and demonstrated the powerful potential of next-generation sequencing technologies to transform disease surveillance and public health readiness for epidemics and pandemics. However, this expansion exposed existing inequities in disease surveillance systems, marked by uneven distribution and gaps in diagnostic testing and genome sequencing capacities in low- and middle-income countries (LMICs).

After almost three years of battling COVID-19, governments must see the value in systematically building diagnostic capacity, prioritizing testing in national health strategies, investing in local manufacturing, and ensuring that effective mechanisms for real-time disease surveillance are in place. Although this need is clear, a survey by the World Innovation Summit for Health revealed that lack of access to equipment is a key threat facing national health systems (1). We feel strongly about improving access to accurate and affordable diagnostics simply because no tests exist for 60 percent of the "Blueprint" pathogens identified by the WHO as having the greatest outbreak potential (2). This lack of availability and access to reliable, high-quality tests threatens our ability to respond to health emergencies and jeopardizes the achievement of universal health coverage.

Lessons learned

The next pandemic is always just around the corner, but countries have learned some tough lessons from COVID-19 that will help them going forward. Speaking at the World Innovation Summit

for Health 2022, Commonwealth Secretary-General Patricia Scotland said, "We were all in the same storm, but we were definitely not in the same boat" (3). The virus doesn't respect borders and we must work hand-in-hand to ensure that nobody – no matter where they are in the world – is left behind. To combat this, one of the early partnerships formed was the ACT-Accelerator, a global collaboration to accelerate the development, production, and equitable access to COVID-19 tests, treatments, and vaccines. From research to rollout, the ACT-Accelerator remains the world's only end-to-end solution aimed at ending the COVID-19 pandemic.

With inequitable access to vaccines, therapeutics, and tests, many LMICs in the global south were largely left out in the cold during the pandemic. Groups such as the United Nations, European Commission, and WHO need to invest in data-enabled health systems for all on an ongoing basis, not only in the time of a crisis or pandemic. These institutions came together to form the ACT-Accelerator, the learnings from which continue to inform our thinking about new pandemic instruments, financing, and core capacities needed for future countermeasures. However, although monkeypox has been prevalent in certain regions for decades now, it only became an issue of global concern once its effects reached high-income nations. Clearly, existing health inequities are not only a matter of preparedness, but also one of prioritization.

COVID-19 taught us that nothing is impossible when there's a combination of funding and political will. We have seen research and development occur on extremely accelerated timelines because it affected everyone, everywhere. Investing in laboratories and strengthening national surveillance systems has better prepared countries for new waves of COVID-19 and served as a strong foundation for resilient pandemic preparedness.

From a supply chain perspective, we learned that centralized manufacturing does not lead to resilience – revealing how convoluted and fragile our supply chains are. The first few rapid COVID-19 tests were produced from one country, which proved extremely stressful because the whole world depended on a single supply source. All COVID-19 tests require a swab for sampling but, at the start of the pandemic, most swabs were produced in just two factories – one in Lombardi, Italy, and one in the US. The US put export restrictions on those swabs and, when it came down to country equity issues, high-income countries were able to move quickly, not only on the procurement and supply of diagnostic tests, but also on understanding how to use those tests in different circumstances. This meant that LMICs were already falling behind in their testing rates due to a lack of steady supply. Overwhelmed health systems also caused competition for funding and a grave neglect of diseases such as tuberculosis, HIV, and malaria, which then suffered significant setbacks as health systems shifted testing priorities.

Now, many countries around the world rapidly manufacture tests themselves, but this must continue to be an integral part of future pandemic preparedness to ensure supply chain resiliency. Manufacturing hubs and their partners must have a strong access plan to make sure people can get their hands on the necessary tools to keep themselves safe.

Barriers to success

Despite many diagnostic successes during the pandemic, the global testing effort still had many shortcomings. Significant challenges remain to be understood and addressed, particularly the global inequity of accessing tests, treatments, and vaccines – especially in remote areas and LMICs.

Testing is the essential first step in any pandemic preparedness plan – identifying the enemy and directing the development of vaccines and treatments. Like many others involved in diagnostic preparedness, we are now working closely with the Coalition for Epidemic Preparedness Innovations (CEPI) on the 100 Days Mission in five key areas (4):

- Developing diagnostic test kits for high-priority pathogens that can be quickly adapted to any emerging pathogen.
- Normalizing regular diagnostic testing.
- Ensuring global access to diagnostic testing through reliable local manufacturing capacity and investments in LMIC testing networks.
- Global surveillance systems to detect and monitor emerging and re-emerging pandemic threats.
- Global cooperation and coordination in areas such as testing policy, emergency regulatory authorization, and global data sharing.

Most importantly, pathologists and lab medicine professionals are our gatekeepers; we rely on their warning signals and identification of future threats that may have pandemic potential.Looking ahead, we are interested in exploring the potential of multiplex testing rather than binary testing – a world in which patients and healthcare providers find a quick answer to the question, "What disease does the patient have?" rather than, "Does the patient have X disease?" It sounds futuristic, but we believe it's an achievable vision within the next few years – as long as diagnostics need to remain high on our collective agenda.

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Karishma Saran isSenior Manager of Advocacy and Communications at FIND, Geneva, Switzerland.

See references online at: tp.txp.to/1222/fail-to-prepare

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Core Topic
Digital Pathology

The Bigger Picture. Multiplexed imaging and spatial transcriptomics allow us to understand the morphology and interactions of individual cells, but even these powerful tools struggle to reveal higher-order anatomical organization. A new approach – unsupervised discovery of tissue architecture with graphs (UTAG) – combines information about individual cells with data on their physical proximity to identify tissue architecture domains (1).

Deep Learning on Disease. After applying techniques such as multiplexed immunofluorescence, how can pathologists parse massive datasets and determine which cellular microenvironments are disease-related? A graph neural network can simultaneously model tumor microenvironments and spot specific cellular interactions linked with patient outcomes. Applying this strategy to head, neck, and colon cancers identified spatial motifs associated with recurrence and survival, offering more accurate outcome prediction than other deep learning tools (2).

A Little Help. A recent study assessed an AI model's ability to evaluate breast density on a dataset containing 214,158 mammography exams from 61,177 patients – and found that the AI model's assessments were more consistent over time than those given by human radiologists. The researchers conclude that AI support for diagnosticians could yield more consistent patient care (3).

This One, But in Blue. Pathology databases can contain hundreds of images – or hundreds of thousands. How can users easily and confidently find the right ones when searching through databases of that size? A new bimodal image retrieval system, DenseBert4Ret, can learn image and text features concurrently, allowing users to ask the system for images resembling a specific input image, but also request modifications to the image via text input (4).

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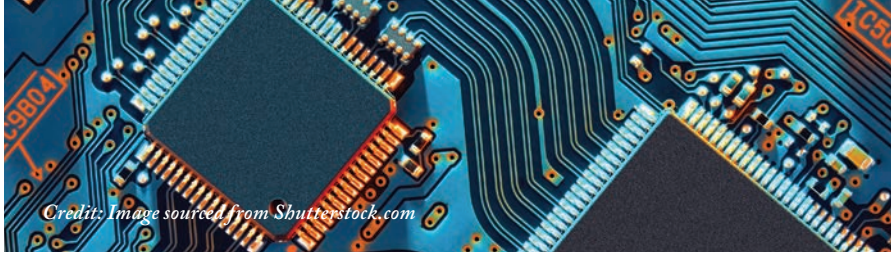
IN OTHER NEWS

Placental prognostics. *Application of digital imaging and AI in placenta pathology increases pathologists' ability to spot diagnostic or prognostic features and reduces interobserver variability (5).*

Digital meets molecular. *Integrating AI and web elements into preparation for molecular tumor boards enables faster, more thorough meeting prep. Adding retrospective patient material ensures ongoing learning for humans and algorithms (6).*

Automated assistance. *A new deep learning–assisted approach to measuring metabolic tumor volume can offer insights into lymphoma patient outcomes with much lower time and labor requirements than traditional methods (7).*

Rationalizing resolution. *Rationalized deep learning approaches to microscopy improve super-resolution information by more than 10-fold, allowing researchers to sensitively image motile cilia kinetics, nucleolar protein condensation, and organelle interactions (8).*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The AI You've Never Considered

AI-powered process automation solutions may not be making headlines, but they are already delivering benefits

By Nathan Buchbinder

There's a whole suite of artificial intelligence (AI) solutions delivering meaningful benefits to pathologists and laboratories. But it's likely you haven't heard about them – despite the conversation around AI in pathology growing ever louder.

So what are these mystery applications? Well, they fall under the umbrella of process automation, and they use AI to streamline many of the manual and repetitive tasks that slow down your routine workflow.

Unleashing the power of AI

To be clear, process automation itself is not new. It dates back to at least 1785, when Oliver Evans developed the automated flour mill – more than a century before Henry Ford cemented himself in history books with the advent of the automated assembly line. These solutions have left their mark on nearly every industry, including diagnostic medicine. The auto stainer in your laboratory is a perfect example of process automation; it is programmed to take over the manual task of staining slides.

So, what is new? Well, following the broad adoption of digital pathology, we are seeing these applications make an unprecedented impact. Process automation solutions rely on data to serve as inputs, and the wealth of data that digitization generates opens up countless opportunities – from applying computer-based rules to automate processes like case creation and case assignment following "if this, then that"' logic, to the use of computational pathology to automate even more complex tasks. Much like the human mind, AI is uniquely able to account for the tremendous variability that exists across pathology slides or images in practice, and this is where the true potential lies.

We can easily see this potential when considering the automation of quality control. There are not only dozens of artifact types – from pen marks to air bubbles – that render slides unusable, but also significant variation within these artifact types. Just as some pen marks are thicker than others, no two air bubbles are identical in size or shape. The difficulty of overcoming this variability is why quality control has remained a manual process, even if it takes hours per day at a high-throughput laboratory.

Object counting is another process that has historically proven difficult to automate. Pathologists might not consciously think about the variability from staining protocols, tissue type, and histomorphology – among many other factors that they encounter when performing a task like mitotic counting. Remember, the human mind is adept at overcoming this diversity. However, as essential as mitotic counting may be for gaining critical clinical information, it is still time-consuming.

What this means for you

Quality control and object counting are just two of the many processes that are ripe for automation with AI, and they both illustrate the same broader trend. Digital transformation isn't just about technology. Rather, it's about using technology to unlock value for users. It's no coincidence that we're also seeing this from the adoption of digital pathology more generally. Just look at how it has streamlined collaboration and improved data accessibility, for example.

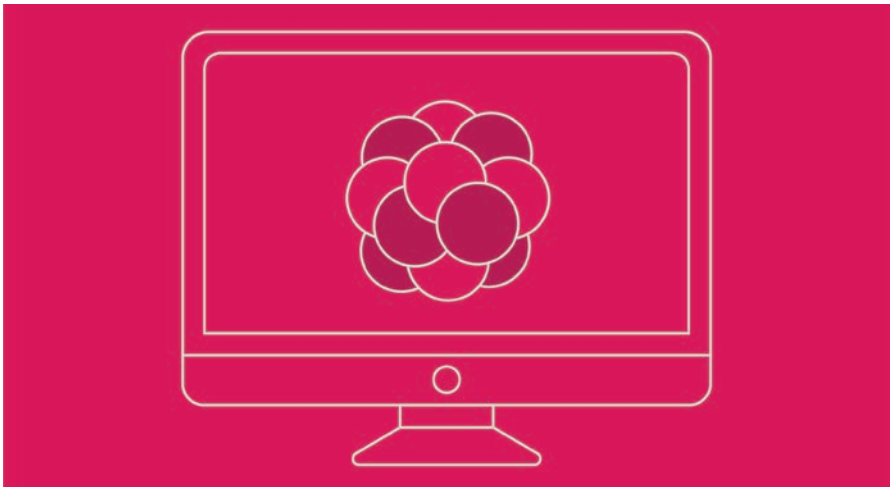
Process automation applications deliver value by ensuring quality and saving time, enabling pathologists to deliver on their commitment to excellent patient care and research. These solutions give you time to focus on generating the best possible results and provide you with the data to make it happen. Process automation applications can also help to improve work-life balance (you could equally use the time saved to catch your child's soccer game or enjoy dinner with your family) – and this becomes even more significant considering that one-third of pathologists already report feeling burnt out (1). New data show that demand for hiring is strengthening amid the ongoing labor shortage, so the need for work-life balance will likely only intensify (2).

I'll leave you with one piece of unsolicited advice. Like all computational applications, AI-powered process automation solutions must be integrated into routine workflows to deliver their full value. Otherwise, you'll spend most of the time that you just saved manually moving data from one application to another or toggling between screens. And that's all the more reason to center your digital pathology practice around an open, interoperable platform that allows you to easily introduce new AI applications – from process automation solutions to detection solutions – into your day-to-day operations. You'll also gain the freedom to incorporate other solutions, including laboratory information systems and whole-slide scanners, creating a connected digital ecosystem that will scale with your laboratory.

The era of computational pathology is upon us. As your lab looks to chart its path, there's a good reason to start with process automation. Though these applications may not get as much attention in the latest research, they are delivering clear return on investment. Implementing AI-powered process automation will enable you to increasingly practice at the top of your license today and ease into adopting additional computational applications as you realize the full promise of pathology's digital transformation.

Nathan Buchbinder is Chief Product Officer at Proscia Inc., Philadelphia, Pennsylvania, USA.

See references online at: tp.txp.to/1222/ai-never-considered



A Personal Touch to Cancer Screening

Recognizing the potential of artificial intelligence to transform cancer screening

By Tim Simpson

There is huge potential for artificial intelligence (AI) to significantly improve women's health care. Over the past few years, we have seen exciting developments in the field, and AI is at the forefront of a digital health revolution. As we try to bounce back stronger from COVID-19 and keep prevention at the heart of healthcare, these developments are more important than ever.

In 2021, the Industrial Strategy AI Mission set a goal to use data, AI, and innovation to transform the prevention, early diagnosis, and treatment of chronic diseases by 2030. It predicts that, within 15 years, better use of AI and data could result in over 50,000 more people receiving an early cancer diagnosis each year (1). Looking ahead to the future of cancer screening, we must harness the power of AI to enable timely results that inspire confidence in our patients.

Personalizing cancer screening

The key to this mission is a shift toward personalized screening. This will require using AI for risk stratification by creating a molecular profile to determine relative risk for each patient and identify those at highest risk. There are certain risk factors in both breast and cervical screening that are well understood; dense breasts, family history, and an elevated body mass index can indicate higher risk of breast cancer (2), whereas persistent human papillomavirus infection – particularly with types 16 and 18 – is associated with higher risk of cervical cancer (3).

AI and machine learning can help identify the most diagnostically relevant information and determine which cases to prioritize for further analysis. This information can also determine screening intervals and test types according to each person's risk.

Easing the burden

On receiving screening results, it is vital for healthcare professionals to be able to rapidly review them for speedy diagnosis and treatment initiation, if needed. How can AI ease this burden? For cervical cancer, implementing AI and advanced imaging can improve the screening process. An advanced algorithm can rapidly review images, assess the cervical cells in the sample, and provide the screener with an image gallery of the most diagnostically relevant cells. This helps medical experts more rapidly identify and accurately diagnose abnormalities because they have fewer cells to analyze.

Challenges to overcome

Although AI offers great potential in cancer screening, it still faces some challenges before it can be truly transformative. A report by Imperial College London highlighted evidence of racial bias in AI and the risk of exacerbating existing health inequalities (4) – indicating that, when it comes to personalized screening, datasets need to be inclusive and consider all risk factors in all demographics. The need for access to diverse datasets is clear; understanding how diseases progress in different populations allows us to ensure accurate and unbiased profiling of patients. The more data points available, the bigger the database and the more accurate the results returned by the AI.

We also need national portals to enable healthcare professionals across the UK to access these data. To ensure widespread AI adoption, our healthcare systems require adequate infrastructure to handle it. For example, networks between different pathology departments would support information sharing and workload. This could allow smaller pathology departments without AI technology to access AI analysis from larger departments or share screening results for a second opinion.

What the future holds

Addressing the challenges outlined here will require close collaboration between regulatory bodies, health systems, innovators, and developers. Only by working together can we unlock the full power of AI, which has the potential to significantly improve cancer screening and aid earlier detection for so many patients. I am excited to see what the future holds and the real-world difference that AI will make to patients, healthcare organizations, and our society.

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

See references online at: tp.txp.to/1222/personal-touch

The Need for Rapid Lung NGS

Speeding up lung cancer NGS so oncologists and NSCLC patients don't have to wait

An interview with Lauren Ritterhouse

How has non-small cell lung cancer biomarker testing evolved in your lab?

Although our laboratory has performed panel-based next-generation sequencing (NGS) testing for quite some time now, we have also run single-gene assays in parallel to provide a faster turnaround time for key actionable alterations in non-small cell lung cancer (NSCLC). Recently, we have been trying to streamline many of our rapid single-gene assays onto a single NGS-based assay that covers the same alterations simultaneously with a quick turnaround time as part of our rapid-lung NGS program.

What's your current lab workflow for NSCLC biomarker testing?

We now use a single fast NGS assay, in some cases from FFPE tissue biopsy, and have also recently piloted an ultra-rapid molecular testing program for certain patients with advanced NSCLC. This is a multidisciplinary program involving oncology, pathology, cytology, interventional radiology, and specialty pharmacy. Ultra-rapid molecular tests are performed using frozen section specimens taken from the diagnostic biopsy – and we often have the genotype report signed out before the diagnostic biopsy result is finalized.

Key components of this program are communication between care teams and early initiation of prior authorization test claims via specialty pharmacy. This integrated diagnostic service improves not only the assay turnaround time, but also the time it takes for a patient to begin receiving the appropriate therapy.

How has in-house NGS improved turnaround times and sample reporting success rates?

By having our molecular testing in-house, we can streamline and optimize workflows all the way from test order, prior authorization, biopsy coordination, and specimen retrieval through to test performance and reporting. With adequate tumor purity (>10 percent), we have very high technical completion rates (well above 95 percent); our turnaround time is 10 days for our routine NGS assays and less than five days for our rapid-lung NGS program.

How does amplicon-based NGS allow you to successfully test small NSCLC samples?

We have a variety of assays on our molecular test menu. With small specimens or those with little tissue remaining, we have very good success using our smaller, hotspot-focused amplicon-based NGS panels. These assays are quite forgiving on specimens with low nucleic acid input, such as those from NSCLC biopsies, as illustrated by the high technical completion rates we achieve.

Why is turnaround time such a critical factor in NSCLC patient management?

The growing list of FDA-approved targeted first-line therapies for NSCLC necessitates that timely genomic profiling results be returned to patients with advanced disease so that they can receive the appropriate therapy as quickly as possible. A recent retrospective study of stage IV NSCLC patients demonstrated that those with actionable oncogenic driver mutations who are placed on TKI therapy as first-line treatment have better clinical outcomes than those treated with immunotherapies, chemotherapies, or combinations (1).

Has rapid NGS allowed you to provide a more complete biomarker profile – including IHC – in a complementary manner to inform clinical decision-making?

Although we do not currently include our genomic profiling results with our surgical pathology reports or with IHC markers such as PD-L1, the availability of those results in a timely manner is important for our oncology colleagues – especially when it takes only a few days for them to receive PD-L1 IHC results. It can be quite challenging when they have the PD-L1 biomarker results, but need to wait several more weeks to receive the additional recommended test results.

Why is this important for the treating oncologists – and what feedback have you received from them?

This is particularly important for patients who are acutely ill and cannot wait weeks before starting therapy. If genomic profiling results are not received quickly, oncologists are forced to make decisions based on an incomplete dataset so that they can provide immediate therapy to patients who need it. With our rapid-lung NGS program, we strive to provide our oncology colleagues with all of the clinically recommended biomarkers in the first-line setting so that they can make these decisions with full information and confidence.

Lauren Ritterhouse is Associate Director of the Center for Integrated Diagnostics and Assistant Professor of Pathology at Massachusetts General Hospital and Assistant Professor at Harvard Medical School, Boston, Massachusetts, USA.

Reference

1. RE Smith et al., "Evaluation of outcomes in patients (pts) with stage 4 non-small cell lung cancer (NSCLC 4) harboring actionable oncogenic drivers (AOD) when treated prior to report of mutation without tyrosine kinase inhibitors (TKI): An Integra Connect Database (ICD) retrospective observational study," J Clin Oncol, 40, 1530 (2022).

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(Blood) Drawing on Experience

How can the patient experience be enhanced during sampling procedures?

An interview with Sandra Merkel, Julie Piazza, and Michele Mitchell

Sandra Merkel
Former Clinical Nurse Specialist for the Pediatric Pain Service at the University of Michigan Health System; now retired.

Julie Piazza
Senior Project Manager, Office of Patient Experience and Certified Child Life Specialist at University of Michigan Health.

Michele Mitchell
Volunteer Patient Advocate for the ASCP and the American Cancer Society; Co-Chair of the University of Michigan Department of Pathology's Patient and Family Advisory Council.

What factors can affect the patient experience during a blood draw?

SM: To name a few, the presence of a needle phobia, history of a traumatic blood draw or an uncaring experience, severe bruising from a prior blood draw, a general dislike for needles, and dehydration can all affect the patient experience. A chronic illness that requires frequent blood draws, long wait times in the waiting room, and a recent serious diagnosis or change in illness can also impact fear and anxiety.

JP: Phlebotomist stress can negatively impact the situation. Sometimes, due to the aforementioned patient factors, the stressful situation becomes heightened for the phlebotomist due to timing requirements of collection, patient fears, and parent or caregiver fears for pediatric patients. Addressing the stress experienced from both sides of the draw with intentional partnership efforts engaging the phlebotomist, patient and family and focusing on comfort strategies was the intent of our research.

What role do phlebotomists and technicians play in ensuring patient comfort?

SM: They play a major role in patient comfort and success of the blood draw. Good skills can make a blood draw faster,

more comfortable, and less stressful.

JP: Phlebotomists are key to a successful experience and future experiences. If we can ensure "comfort competencies" are achieved by phlebotomists, the risk of a negative blood draw experience declines and it supports consistency of experience which can help reduce fear and anxiety – and ultimately enhance the healing environment. The phlebotomist could also get to know the patient and help them become better self-advocates by having an individualized procedure plan to support comfort, relieve stress and anxiety, and reduce unnecessary pain associated with the blood draw.

MM: Phlebotomists and lab professionals are an important part of the multidisciplinary care team. There is no disease diagnosed that didn't start with some type of blood draw and it often provides valuable information on how the disease is progressing and whether treatment is helping. Therefore, phlebotomy, pathology, and laboratory medicine are critical to every diagnosis and treatment plan. Someday, I hope that laboratory professions become an integral part of the patient-facing multidisciplinary care team because behind every test, specimen, and result is an anxious, sick, and tired person wondering what you are looking for – and they're waiting for crucial answers. Phlebotomists play a key role in the process because they are on the front line of this care pathway.

How could interactions between patients, patient-facing providers, and the laboratory be improved?

SM: I have observed phlebotomists and staff who draw blood, start IVs, and administer injected medications. I have also worked with children and advised adults on how to handle their fear and pain associated with needles, developed educational materials, and participated in changing procedures and workflows. Most phlebotomists are skilled in drawing blood and retrieving specimens; however, many do not take the time to establish a caring experience that makes the interaction a positive experience

for the patient. There are five simple steps that healthcare providers can take to build rapport and ease patients into the procedure.

1. Introduce yourself and identify your role.
2. Ask the patient about their needs and expectations.
3. Explain what will happen and work with the patient to outline a plan that includes a specific strategy that incorporates their needs.
4. Proceed with care.
5. Once complete, ask the patient how they thought it went.

JP: The key to enhancing patient interactions is through educating phlebotomists. I have worked alongside phlebotomists for many years, helping to prepare children, parents, and caregivers for the procedure, advocating for comfort positioning, and providing coaching on coping skills that can be used before, during, and following a blood draw. We have worked hard to partner with phlebotomists to improve patient, family, and staff experiences by reducing pain and anxiety and increasing comfort, while being mindful of the timing of collection.

In pediatric practice, it's also important to understand basic child development relating to new experiences, coping strategies, and comfort measures. Implementing simple techniques such as counting, distraction, and positioning can be key to success of current and future procedures. These can also be adapted for adult care.

MM: I believe the interaction between patients and patient-facing providers can be improved if you think of the encounter as a total experience for the patient – beginning with the person who checks them in. People with medical trauma or past bad experiences are full of anxiety when they arrive, but a warm, friendly demeanor goes a long way. However, the patient will have the most interaction with the phlebotomist or technician. After a warm greeting, asking the patient about their past experiences and poke preferences and techniques that have previously worked for them would be helpful. The technician should then inform the patient on what the procedure will entail – a key step in preparing the patient and setting expectations. At Michigan Medicine, the process of asking these questions and documenting the responses is formalized into a questionnaire known as a "poke and procedure plan." As a patient, I can download the information from my portal and take it with me to each appointment. The health system has made the questionnaire and content a permanent part of the patient medical record. It's helpful to know it's there for my future procedures.

Tell us more about the "poke and procedure plan" – what factors affect its implementation?

SM: A poke and procedure plan is

Left and right: Decreasing anxiety with distraction

developed with the patient to outline what can be done to provide support and comfort before, during, and after a procedure. Patients are asked about any past procedures or blood draws, how they went, and what worked to help with pain and fear. A plan can be developed for any procedure – from surgery and physical therapy to going to the dentist or getting blood drawn. A blood draw might not be a simple procedure for the patient, but a poke and procedure plan makes it easier to encourage the patient to speak up and request measures that help with their fear and pain. It's important that phlebotomists and laboratory staff are supported by their work environment to successfully implement these plans.

MM: Education is key for both healthcare professions and patients alike. As a "secret shopper" for the poke and procedure plan at Michigan Medicine, I have found varying degrees of familiarity with the program, so I always take the time to inform staff when I arrive for the procedure or at the blood draw station and ask them if they are aware of the plan. If they are unfamiliar with it, I talk to them about the value of knowing the information it covers ahead of time. I also make sure I have my poke/comfort plan documents readily available for the technicians to access – my hope is while it is a part of the standard medical record, perhaps adding a flag on the patient's record to act as a visual reminder to staff that they have a plan on file. Alternatively, the plan could be attached to the blood draw order or the flag could be added to the receptionist's screen during check-in. If the patient needs a vascular access team to assist with the blood draw, it can then be requested ahead of time. Ultimately, it all starts with awareness – if patients or medical staff are unaware of the poke/comfort plan existing in the first place or do not see the value in having one, then the process breaks down.

If a patient doesn't have a poke and procedure plan, how can phlebotomists make them more comfortable with sampling procedures?

SM: Further to those previously mentioned, comfortable waiting and procedure areas, facilitating workflows to reduce wait times, educating staff, and establishing a strategy for decreasing anxiety and pain can help greatly.

JP: The environment is key. Creating a healing environment from the start begins with intentional efforts to support comfort for all partners in the care experience. It is essential to introduce the phlebotomist and their role and let the patient know that we care about their comfort. Additionally, we have added a distraction mural in the waiting area with nature images and a seek and find to support evidence-based research on the impact of improving wellbeing simply by looking at nature and wildlife.

MM: Listen to what the patient is saying and pay attention to nonverbal cues to create a better experience. It's also important for healthcare professionals to recognize that, when a patient walks through the door, they may have a history of medical or emotional trauma. Of course, this is also true for the technician, who may have just had a difficult time with a prior patient or is experiencing staff shortages, empathy fatigue, and other work environment stressors that can add to the situation, especially if the current patient expresses concern with the procedure. To ease tension on both sides, technicians can ask the patient a number of rapport-building questions, such as:

- Are there any comfort measures that work for you?
- Do you have a preference or specific vein location that works best?
- Would you prefer a butterfly needle?
- How much information do you want during the poke?
- Are there any distractions that might help you?

If possible, creating a calming environment by dimming lights, adding padding or a warm blanket, repositioning, or asking the patient if they would prefer to lay down can help. Making small talk can offer some relief during the procedure; for children, providing a tablet computer for distraction can be helpful.

If the technician has attempted the poke a couple of times without success, the phlebotomist should ask a colleague or supervisor to take over. Many times, I have been forced to advocate for myself and ask for someone else to try, which puts me in an awkward position; however, if I don't speak up, I am often left with a large hematoma. It's not a failure on the phlebotomist's part to recognize when it's time to ask for help – I know the technician doesn't want to cause pain, but some patients may have difficulty advocating for themselves.

What role do laboratory medicine professionals play in supporting and promoting patient- and family-centered care?

SM: They have a role in developing departmental philosophies, procedures, policies, work rules, expectations of performance, and respect of colleagues and patients. They must embrace the work they do and do it caringly.

JP: Work competencies such as supporting comfort, communication, and partnership in care need to be addressed during orientation for each new employee and serve as an ongoing mission and vision for the pathology department. Engaging with patient-family advisors as part of service delivery is essential – whether it be an advisory council encompassing the entire pathology service (including phlebotomy) or focus groups with patient-family advisors and staff to create training, education, and tools to ensure ideal patient- and family-centered care. It also goes beyond pathology to the many different service areas on the care continuum that are served by their important work.

MM: Pathologists and lab medicine professionals should be considered an integral part of the interdisciplinary care team. Professionals who agree should speak up to embrace patient-centered care and redefine their role by creating opportunities to engage with patients and family members. Treating each other with dignity and respect, listening to and honoring patient and family perspectives and choices, sharing information, and collaborating on care can all have a positive impact on both patient and employee perspectives.

What education should patients and families receive regarding the role of pathology and laboratory medicine in their care?

SM: Basic information on the commitment to collect specimens in a respectful and patient-centered manner and a brief explanation of the need for accurate collection, testing, and results that facilitate healthcare plans. Any interesting or quality facts might also be helpful, such as staff certification, highlighting department successes, and materials highlighting the role of pathologists in their care.

JP: I have found that, with both children and adults, understanding the scientific reasons for collecting blood and the ways it can help determine healthcare needs and treatment often reduces many fears associated with the experience. A simple explanation, such as a flowchart or interactive exhibit about what happens to their blood sample after collection and what lab medicine professionals do behind the scenes, would be an excellent waiting area education resource for all ages.

MM: I don't think patients understand that everything starts with laboratory medicine. Written/video materials on the patient portal or a poster in the blood draw stations highlighting the importance of phlebotomy could help. Although these fall upon the healthcare provider, patients must also take more responsibility for their own care and for understanding their lab results. Patients need to engage with their prescribed treatment plan, ask questions, and partner in shared decision-making with their providers. The shift toward patient education and partnership is forward-thinking and can move us toward more personalized medicine – transforming the healthcare system from doing things to or for patients and toward partnering with them instead.

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HER2-low is a new classification of HER2 expression in breast cancer[1,2]

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Score and report HER2-low expression (defined as IHC 1+ or IHC 2+/ISH–).[1]

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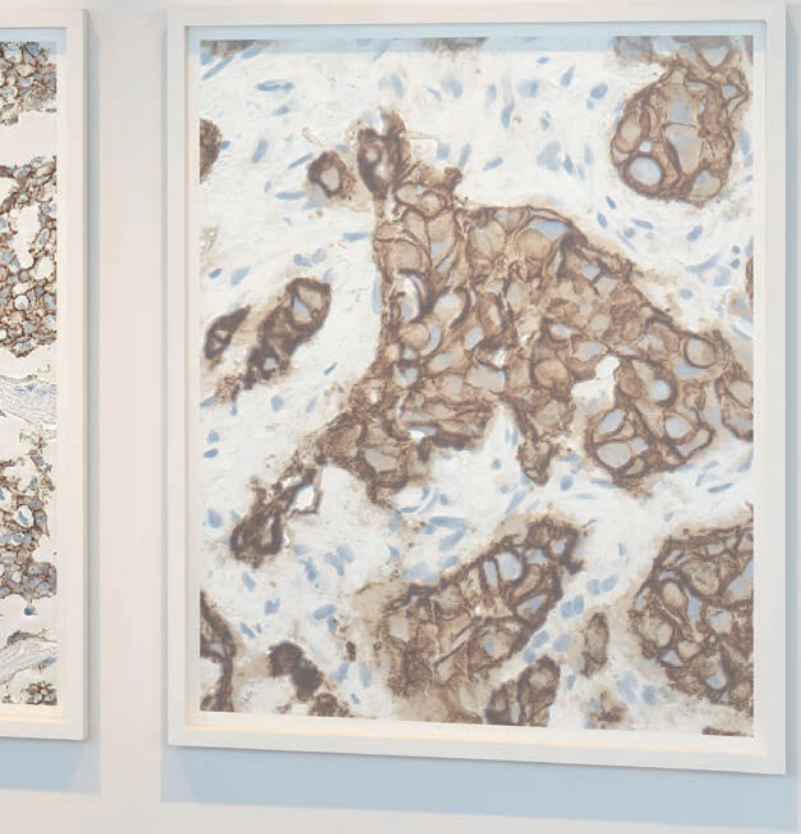

Important Safety Information

Indication

ENHERTU is a HER2-directed antibody and topoisomerase inhibitor conjugate 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

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.**

Contraindications

None.

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 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).

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% 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.

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% and absolute decrease from baseline is 10-20%, continue treatment with ENHERTU. When LVEF is 40-45% and absolute decrease from baseline is <10%, continue treatment with ENHERTU and repeat LVEF assessment within 3 weeks. When LVEF is 40-45% and absolute decrease from baseline is 10-20%, interrupt ENHERTU and repeat LVEF assessment within 3 weeks. If LVEF has not recovered to within 10% from baseline, permanently discontinue ENHERTU. If LVEF recovers to within 10% from baseline, resume treatment with ENHERTU at the same

HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; mBC, metastatic breast cancer.

Please see accompanying Brief Summary of Prescribing Information, including Boxed WARNINGS, and Medication Guide.

Important Safety Information (cont'd)

Warnings and Precautions (cont'd)

dose. When LVEF is <40% or absolute decrease from baseline is >20%, interrupt ENHERTU and repeat LVEF assessment within 3 weeks. If LVEF of <40% or absolute decrease from baseline of >20% 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% 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% of patients, of which 0.4% 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% were exposed for >6 months and 39% were exposed for >1 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%).

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% 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% 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 (76%), decreased white blood cell count (70%), decreased hemoglobin (64%), decreased neutrophil count (64%), decreased lymphocyte count (55%), fatigue (54%), decreased platelet count (44%), alopecia (40%), vomiting (40%), increased aspartate aminotransferase (38%), increased alanine aminotransferase (36%), constipation (34%), increased blood alkaline phosphatase (34%), decreased appetite (32%), musculoskeletal pain (32%), diarrhea (27%), and hypokalemia (25%).

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% were ≥65 years and 3.6% 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%) as compared to younger patients (48%).
- **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 Brief Summary of Prescribing Information, including Boxed WARNINGS, and Medication Guide.

References: 1. ENHERTU. Prescribing Information. Daiichi Sankyo, Inc; 2022. **2.** Modi S, Jacot W, Yamashita T, et al. Trastuzumab deruxtecan in previously treated HER2-low advanced breast cancer. *N Engl J Med*. 2022;387(1):9-20. doi:10.1056/NEJMoa2203690 **3.** Schettini F, Chic N, Brasó-Maristany F, et al. Clinical, pathological, and PAM50 gene expression features of HER2-low breast cancer. Supplementary tables. *NPJ Breast Cancer*. 2021;7(1):1. Accessed August 4, 2022. https://static-content.springer.com/esm/art%3A10.1038%2Fs41523-020-00208-2/MediaObjects/41523_2020_208_MOESM1_ESM.pdf

Daiichi-Sankyo | AstraZeneca

PP-US-ENB-2159 10/22

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 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.

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).

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.

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.

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%).

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
Blood and Lymphatic System Disorders				
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
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

(continued)

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] %
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.

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.

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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From Academia to Industry

Sitting Down With… Julie Feldstein, Chief Pathologist, HistoWiz, New York, New York and Miami, Florida, USA

Tell us about your background in pathology…

I knew by my fourth year of medical school that pathology – specifically hematopathology – was of strong interest to me. I was born and raised in Honolulu, Hawaii, where research opportunities were limited, so I did a Howard Hughes medical student fellowship. That's where I found out about the National Cancer Institute (NCI) residency program, which includes a research component. I chose to do my pathology residency and hematopathology fellowship at the NCI under Elaine Jaffe. My first job was at Sloan Kettering; I spent 15 years there, then was Director of Hematopathology and the Fellowship Training Programs at Mount Sinai for six years before moving to HistoWiz.

What spurred your interest in moving from academia to industry?

I was first approached about moving from academia to industry eight years ago – and then every few years thereafter. Recently, a senior colleague advised me to seriously consider making a move and, if I didn't do it now, I knew I never would. So, after much deliberation, I took the leap.

In academia, I felt we spent a lot of time on platforms without implementation. The unwillingness to move forward was frustrating. Moving from academia to industry was like moving from horseback travel to jet plane travel! Industry focuses on revenue, turnaround time, client satisfaction, metrics, and market analyses, with increased exposure to sales, finance, executive, and board roles. I find it all very interesting.

Have there been any unexpected differences – or similarities?

In academia, I was on the younger side; in industry, the opposite is true. My colleagues in industry tend to be young, flexible, and tech-savvy – it's the only way to survive in such a fast-paced world. But as for the unexpected: the deep appreciation expressed by young colleagues. I'm delighted to be partially back in the lab, the administrative and regulatory layers are simpler than in academia, and working on preclinical therapeutic studies with broad outreach potential has been eye-opening and fascinating.

What do you think lies ahead for pathology?

The need for digital and computational pathology will continue among our clinical, scientific investigator, and industry colleagues. Given the ease of online access and long-distance collaboration, telepathology offers an opportunity to address the ongoing staffing shortages in our field – and the challenges of the pandemic.

There are many grassroots efforts to increase medical students' interest in pathology, but the digital realm offers widespread outreach to colleagues who are interested in helping with those efforts. I hope that our continued progress in digital and computational pathology will make us a highly attractive discipline for future-focused students.

What advice do you have for labs struggling to go digital?

Take the leap. Face your fears, hesitations, and challenges. It's fun and you'll learn a lot.

Initially, browse the web, social media, news, and journals. Major pathology societies, digital pathology societies, and various clinical and scientific meetings have had discussion panels about the status quo and future of digital pathology, as well as platforms and focused sessions to share abstracts. Embedded in these conversations are explorations of computational pathology, artificial or augmented intelligence, and image analysis tools to assist pathologists with integrated reporting. Nevertheless, H&E remains the gold standard.

You have always been deeply invested in education. How does that translate to industry?

I was told by a senior colleague early on that one cannot teach and train unless one has experience. The more time you spend in a role, the more opportunities you get to educate. I am still asked to give lectures and offer opportunities for training and collaboration. These opportunities translate into education for those interested in a change, to hear about the differences, or as career options. I also have daily conversations in the lab in with young colleagues looking for insight, guidance and direction.

If you're considering a move to industry, know that funding – and risk – may vary. There can be a lot of movement, change, acquisitions, and mergers. Expectations, pace, and demands can be high. Projects must be completed in a timely manner. Quality, integrity, communication, and being a strong team player are important. We serve our clients just as our clinical partners serve clinicians and patients. We work hard – and we play hard.

Some say that, once you leave academia, it is harder to return. Others look at it as a spectrum, from preclinical non-human to patient clinical trials. There are strong collaborations between industry and academia. Talk to colleagues in academia and industry about their experiences – at your job, at meetings, during webinars, or on social media. Pay attention to not just medical and scientific news, but also business, finance, and tech to see where investments are being made. Be open-minded, creative, and enjoy!

You're also active on social media. What value do you see in it?

I see tremendous value in social media for support, education, and knowledge-sharing. I don't think there are major differences between social media use in academia, industry, and clinical disciplines. I regularly encounter colleagues from all three online – and they are always actively engaged. I think social media interaction is continually getting stronger and I love the ongoing opportunity to learn from colleagues around the world and across disciplines.

I would like to express my deepest gratitude to those colleagues for their continued support – not just from my mentors, but from collaborators, trainees, patients, friends, and family along the way.

Is systemic mastocytosis showing its hand?

Recognizing hallmark symptoms is just the beginning[1]

Debilitating symptoms of SM can significantly disrupt patients' lives[2*]

Patients reported **professional, psychosocial, and psychological consequences** of living with SM in the TouchStone SM Patient Survey (N=56)—developed by Blueprint Medicines in collaboration with SM physician experts and SM patient advocates.

Explore how to identify signs and symptoms at SuspectSM.com

*US adults with a self-reported SM diagnosis (N=56) completed an online survey of 100 items, including the 12-item Short-Form Health Survey, the ISM Symptom Assessment Form, and the Work Productivity and Activity Impairment Questionnaire, as well as questions about disease impact. The results were analyzed using descriptive statistics.[2]

SM=systemic mastocytosis.

References: 1. Gilreath JA et al. *Clin Pharmacol*. 2019;11:77-92. **2.** Mesa RA et al. *Cancer* (Open Access). Published online August 23, 2022. doi:10.1002/cncr.34420

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