JANUARY / FEBRUARY 2021 # 72

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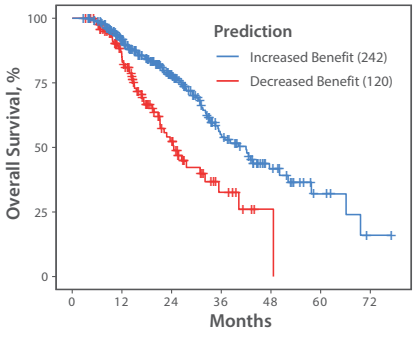
mCRC Real-World Evidence – FOLFOX+BV–FOLFIRI+BV



Median Overall Survival	MI FOLFOXai™ Indicates:	
	FOLFOX+BV 1st → FOLFIRI+BV 2nd (FOLFOX+BV RWE cohort)	FOLFIRI+BV 1st → FOLFOX+BV 2nd (FOLFIRI+BV RWE cohort)
OS When Patient Received: FOLFOX+BV 1st → FOLFIRI+BV 2nd	**42.0 months**	**18.7 months**
OS When Patient Received: FOLFIRI+BV 1st → FOLFOX+BV 2nd	**24.5 months**	**34.4 months**

MI FOLFOXai™ comes standard with every Caris Molecular Intelligence™ colon cancer tumor profile at no additional cost, increased turnaround time or added specimen requirements. Learn more at www.CarisLifeSciences.com/FOLFOXai.

Where Molecular Science Meets Artificial Intelligence.

Decisions on patient care and treatment must be based on the independent medical judgment of the treating physician, taking into consideration all available information concerning the patient's condition.

1. Abraham JP, Korn WM, Spetzler DB, et al. Clinical validation of a machine-learning derived signature predictive of outcomes from first-line oxaliplatin-based chemotherapy in advanced colorectal cancer. Clin Cancer Res. 2020 Dec 8:clincanres.3286.2020. doi: 10.1158/1078-0432.CCR-20-3286. Epub ahead of print. PMID: 33293373.

CARIS® LIFE SCIENCES

2021: A New World

Pandemics, diagnostics, vaccines – a "normal" no one could have predicted this time last year

In the spring of 2020, I was engaged in online science outreach (somewhat presciently, as it turned out!). I hosted regular science chats with school-aged children, fielding questions on everything from "how can a spider bite give you superpowers?" to "how can we cure cancer?"

As March rolled on, though, the questions changed. "What is the pandemic?" "Do we have a cure for the coronavirus?" "Can people die from the coronavirus?" Tough questions to answer for any crowd – let alone schoolchildren.

And the answers to those questions changed, too. Initially, there was a lot of reassurance. The phrase "like a bad cold or a flu" made frequent appearances. Unfortunately, for nearly 2.5 million people that answer has proved fatally wrong – and many more suffer long-term consequences.

This is the "new normal" we move into in 2021 – a world in which we limit our contact with others, wear masks when we venture beyond our thresholds, wash and sanitize our hands every time we touch something unfamiliar, and anxiously track reports on vaccine candidates.

With time, answers to some of our more serious questions have emerged.

Will faster, easier, more accurate diagnostics give us an edge? Yes.

Will a vaccine (whether those already being rolled out or those next in line) change the world? Undoubtedly.

Will we return to our "old normal?" Only time will tell – but the tremendous efforts of scientific, medical, and pharmaceutical professionals globally have not gone unnoticed. As results and regulatory approvals roll in, we'll slowly see the world to come take shape – but it can only happen with appropriate oversight, open conversation, and a culture of shared scientific success. And it will be the diagnostic professionals who take center stage. The big question now is: are you ready for the new world?

Michael Schubert
Editor

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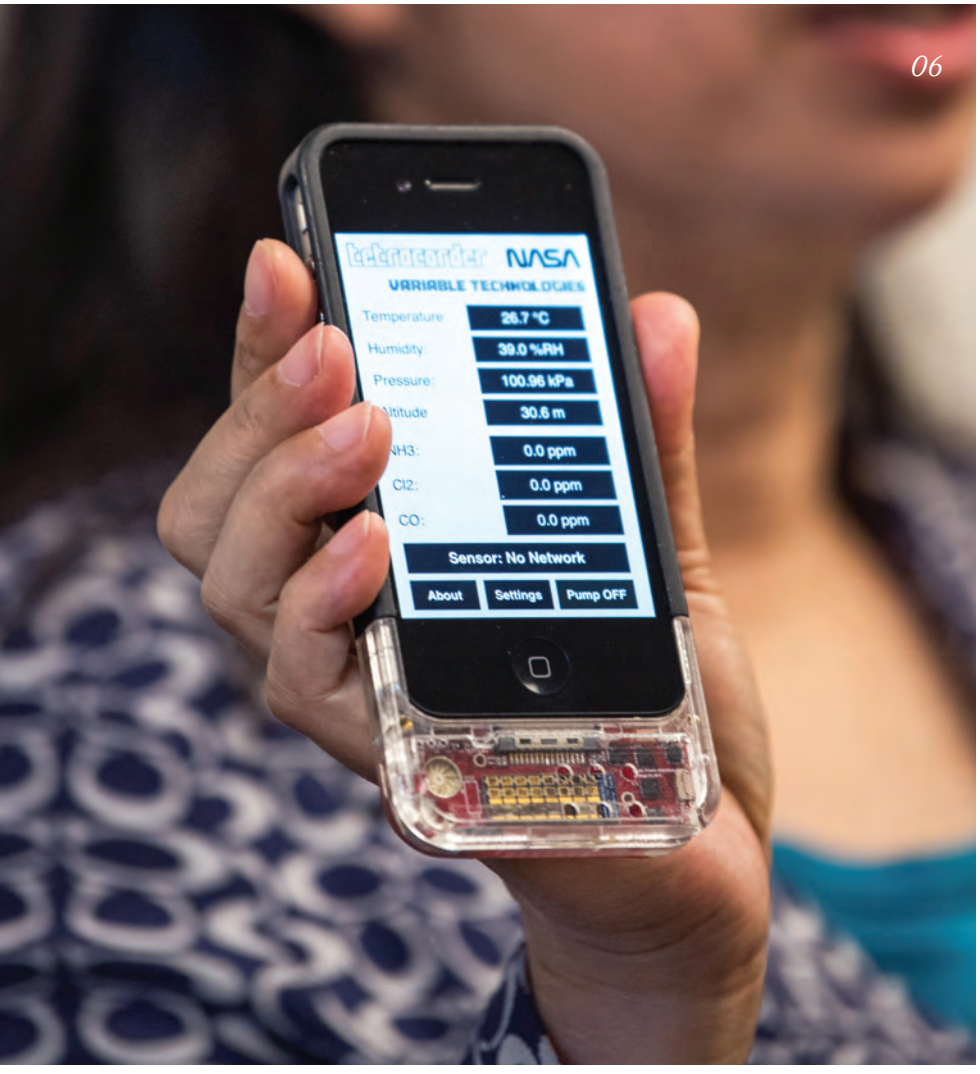

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On The Cover

A piece of Indian-inspired, pathology-themed art

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Upfront

Research
Innovation
Trends

Breathe In, Breathe Out

NASA unveils a new handheld breath analyzer

NASA has unveiled a new diagnostic technology that is out of this world. The NASA E-Nose (electronic nose) breath analyzer is a noninvasive, handheld device that uses breath specimens to detect declining health (1). The tool comprises multiple sensors that measure breath's chemical composition, humidity, pressure, and temperature in real time – detecting any results associated with diseases.

The lack of space (pun intended) in space is not a problem for the device, given its lightweight and portable design. Astronauts can hardly stop by their local doctor's office for a check-up, so the sensor chip connects directly to a smartphone via USB or Bluetooth and transmits the data to clinicians – regardless of distance. "Unlike current point-of-care testing, there will be no 'companion specimens' to be analyzed in the laboratory to confirm the device's results," says David Loftus, a researcher on the E-Nose development team.

"Travel to deep space destinations will expose crew members to harsh environments," Loftus continues, "so, technology for performing medical diagnostics and physiological monitoring is needed to keep astronauts healthy. The noninvasive nature of the NASA E-Nose is an important feature that makes it easier for astronauts to be tested, even when they are wearing a spacesuit."

But the work doesn't stop there – Loftus and his team recognize there is still more to understand in order to develop the device to its full potential. "An ongoing challenge is to expand the number of molecules that the NASA E-Nose can detect, but the development cycle is not fast – each new molecule takes a significant amount of time to formulate a strategy for," says Loftus.

Though the device was designed primarily for space medicine, it could one day be used for civilian point-of-care or home diagnostics – potentially relieving pressure on overworked laboratories and bringing disease diagnosis to underserved areas. Loftus highlights, "Pathologists and laboratory medicine specialists will be integral to the eventual deployment of this novel technology to ensure that accuracy and reproducibility are maintained, appropriate calibration standards are developed, and that measurements can be fully integrated with information systems for other types of clinical laboratory results."

Reference

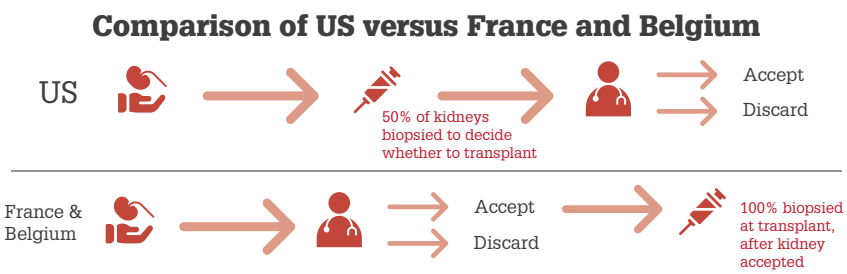
1. *NASA Technical Reports Server (2020). Available at: http://go.nasa.gov/35BuQaY.*

INFOGRAPHIC

Discarded Kidney Donations

Are histologic findings accurate predictors of kidney allograft survival?

Process differences between the US, France, and Belgium



QUICK HITS

The latest research in pathology and laboratory medicine

An Unlikely Connection

Researchers have connected frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS) with the genetic mutation associated with Huntington's disease (1). They found that a small sample of FTD/ALS patients had a repeat expansion mutation of the huntingtin protein, but without clinical symptoms of the disease.

Microscope for All

A collaboration of institutions in Jena, Germany, has developed an optical toolbox – the UC2 – to build cost-effective microscopes with high resolution comparable to their commercial counterparts (2). They hope it will provide an alternative for laboratories that cannot access expensive modern microscopes.

Scientist's Best Friend

Low-cost nanodiamonds improve sensitivity of paper-based diagnostic tests, with the potential to aid early detection of diseases such as HIV (3). The i-sense McKendry group found that the nanodiamonds – thousands of times more sensitive than gold nanoparticles – detected lower viral loads in early disease stages.

Speeding Things Up

A new motorized microsensor seeks to solve the speed versus sensitivity trade-off in biomolecule sensing (4). In motorizing the sensor, the team at Cockrell School of Engineering have increased the speed at which low-concentration molecules collide with each other – improving early disease detection.

Unhealthy Gut, Unhealthy Mind

Major depressive disorder (MDD) has been found to be associated with disturbances in the gut microbiome (5), with significant differences in three bacteriophages, 47 bacterial species, and 50 fecal metabolites compared with healthy controls. This may support development of a biomarker-based tool for improving MDD diagnosis.

References

1. *R Dewan et al., Neuron, [Online ahead of print] (2020). PMID: 33242422.*
2. *B Diederich et al., Nat Commun, 11, 5979 (2020). PMID: 33239615.*
3. *BS Miller et al., Nature, 587, 588 (2020). PMID: 33239800.*
4. *J Guo et al., ACS Nano, 14, 15204 (2020). PMID: 33095572.*
5. *J Yang et al., Sci Adv, 6, eaba8555 (2020). PMID: 33268363.*

Reduce the Resistance

A prototype device detects antibiotic-resistant bacteria in five hours

Where would we be without antibiotics? They are a pinnacle of modern medicine – but overprescription and overuse have left the door open for antibiotic-resistant bacteria. With bacterial infections still one of the world's biggest health problems, we need a solution – and fast. Slow turnaround times for identifying these bacteria is just one barrier to that solution, with standard methods taking up to two days – increasing hospital stays, mortality rate, and cost of care. With this in mind, researchers at Binghamton University built a prototype diagnostic device that combines papertronics with biology based on the principle of bacterial electron transfer (1). Their technique eliminates the need to monitor bacterial growth, yielding a turnaround time of only five hours. As a point-of-care diagnostic tool, the device could reduce unnecessary antibiotic prescriptions, especially in resource-limited areas – closing the door on antimicrobial resistance.

Reference

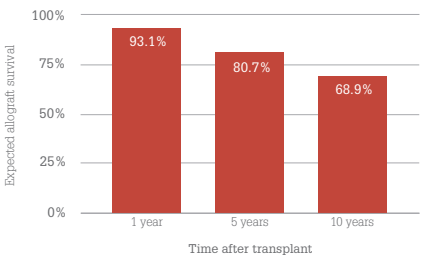
1. *Y Gao et al., Biosens Bioelectron, 168, 112518 (2020). PMID: 32862095.*

Matching discarded kidneys

45%

of discarded kidneys in the US matched histologically to similar kidneys transplanted in France

Expected allograft survival of discarded kidneys



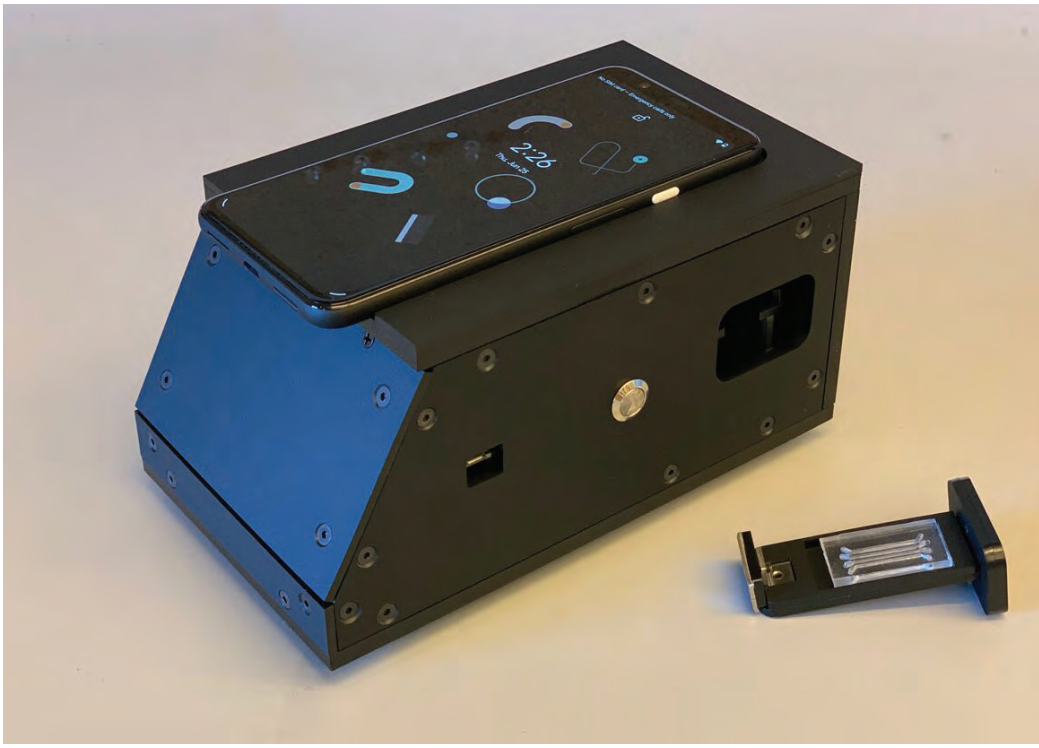
Time to reconsider?

Kidney histology at allocation ≠ organ quality

Many discarded kidneys would have benefited waitlisted patients.

Reference

1. *PP Reese et al., J Am Soc Nephrol, [Online ahead of print] (2020). PMID: 33323474.*



CRISPR Versus COVID-19

A CRISPR-Cas13a-based smartphone test can detect COVID-19 in under 30 minutes

Priorities have continued to shift when it comes to curbing the spread of SARS-CoV-2 – from national lockdowns to mass testing. Recently, rapid mass testing has been proposed as the key to fully reopening communities across the US – but this is easier said than done; rapidly identifying asymptomatic, presymptomatic, and symptomatic carriers still presents a challenge.

Researchers from Gladstone Institutes, the University of California San Francisco, and the University of California Berkeley recognized this need and developed a CRISPR-Cas13a assay that uses a smartphone camera to directly detect SARS-CoV-2 from nasal swab RNA (1). The test avoids the need for amplification, facilitating point-of-care use, and returns accurate results in under 30 minutes.

"One reason we're excited about CRISPR-based diagnostics is the potential for quick, accurate results at the point of need," said Jennifer Doudna (2), a collaborator on the study and winner of the 2020 Nobel Prize in Chemistry for her co-discovery of CRISPR-Cas genome editing. "This is especially helpful in places with limited access to testing or when frequent, rapid testing is needed. It could eliminate a lot of the bottlenecks we've seen with COVID-19."

But the test not only detects the presence of COVID-19, it also measures the viral load of SARS-CoV-2 – as low as ~30 copies/µL. "When coupled with repeated testing, measuring viral load could help determine whether an infection is increasing or decreasing," said UC Berkeley bioengineer Daniel Fletcher (2). "Monitoring the course of a patient's infection could help healthcare professionals estimate the stage of infection and predict, in real time, how long is likely needed for recovery."

References

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2. *Gladstones Institute (2020). Available at: https://bit.ly/2KgOjpD.*

Integrate to Investigate

Integrated anemia and sickle cell disease test yields high sensitivity and accuracy

Effective management of blood disorders – such as anemia and sickle cell disease (SCD) – depend on accurate and rapid diagnosis, but lack of affordable, accessible testing makes this difficult in developing countries. Existing diagnostic technology platforms can already detect SCD, but there's always room for improvement.

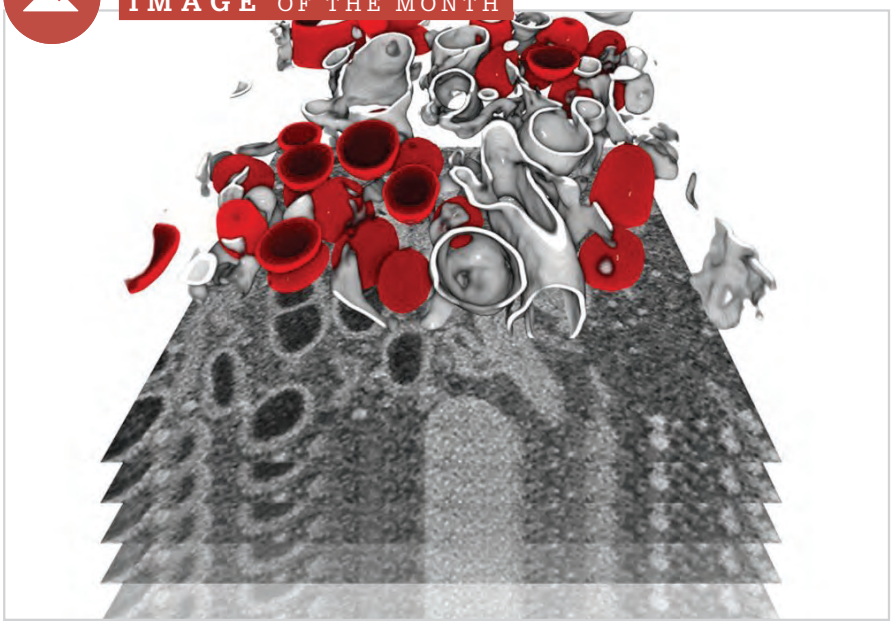
Researchers from Case Western Reserve University recognized this opportunity and integrated an anemia test into the Gazelle platform. They then tested samples from 46 patients studied for anemia and SCD (1). The test yielded 100 percent sensitivity and over 92.3 percent specificity for anemia, and 100 percent accuracy for hemoglobin variants.

"The study from Case Western Reserve demonstrates that a software enhancement […] holds the potential to allow our current sickle cell disease test to also check for anemia, which could help clinicians and patients to optimize disease management through a single, low-cost test," said Patti White (1), co-founder and CEO of Hemex Health.

Reference

1. *Hemex Health (2020). Available at: https://bit.ly/3mj6yrG.*

IMAGE OF THE MONTH



Infect, Remodel, Replicate

SARS-CoV-2 replication cycle uncovered through subcellular changes in infected cells

Credit: Julian Hennies/EMBL. Segmented subvolume of a cell, showing membrane-bound organelles (grey) and double-membrane vesicles (red).

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

TWEET of the month

"'Asking questions' is a powerful force if you are intelligent, analytic, and have a platform. It's important to choose your questions with an understanding of the consequences. Use this power to cast doubt on the right things, not everything in sight."

Benjamin Mazer
Read the original tweet here: tp.txp.to/bmaz-tw

Chip Off the Old Lab

Silicon lab-on-a-chip may provide cheaper, accessible diagnostic tests

An infectious disease micro-laboratory – not long ago, a concept you might think only possible for a Honey, I Shrunk the Kids reboot. But researchers at Imperial College London have developed a disposable silicon chip that performs point-of-care, micro-qPCR testing for bacterial infection (1). Silicon chips are typically expensive to manufacture and production requires a cleanroom, but this chip can be developed in a standard laboratory – reducing cost and time to produce.

"Rather than sending swabs to the lab or going to a clinic, the lab could come to you on a fingernail-sized chip," said lead researcher Firat Güder (2). "You would use the test much like how people with diabetes use blood sugar tests, by providing a sample and waiting for results – except this time it's for infectious diseases."

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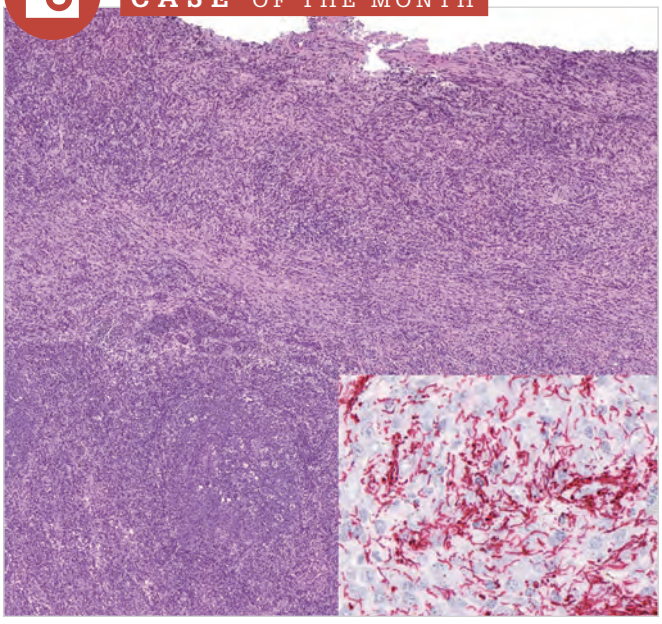
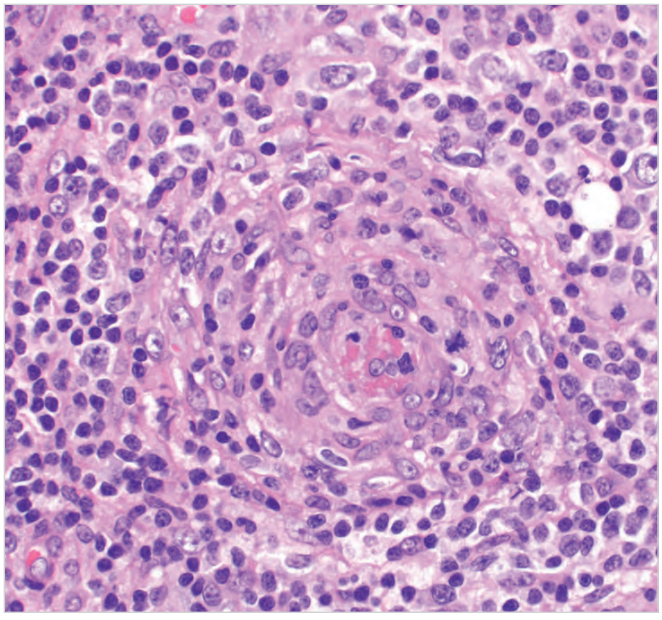
2. *Imperial College London (2020). Available at: https://bit.ly/37i7OHg.*

CASE OF THE MONTH





A 56-year-old female presented with generalized lymphadenopathy. An inguinal lymph node was excised; its histology is shown in the images (inset shows spirochete immunohistochemical stain).

Which of the following microorganisms is the most likely cause of these findings?

a) Chlamydia trachomatis
b) Treponema pallidum
c) Rickettsia rickettsii
d) Mycobacterium avium–intracellulare

Answer to last issue's Case of the Month…

d) Primary cutaneous follicle center lymphoma

The images indicate a diagnosis of primary cutaneous follicle center lymphoma (PCFCL). This disease presents clinically with solitary or grouped erythematous, painless, non-pruritic papules, plaques, or tumors with a predilection for the head, neck, and trunk (1). Despite recurrences (observed in up to 50 percent of cases), prognosis is excellent.

Histopathology reveals nodular-to-diffuse infiltrates within the dermis extending into the subcutaneous fat, sparing the epidermis and papillary dermis. This case shows a follicular pattern with germinal center formation. The neoplastic infiltrate contains centrocytes (small and large cleaved follicle center cells) and centroblasts (large follicle center cells with prominent nucleoli) admixed with variable numbers of small lymphocytes. Virtually all cases express pan B-cell antigens (CD19, CD20, and CD79a) and are always CD5-negative. CD10, CD21, and BCL-6 positivity can be observed more frequently in germinal center lymphomas with a follicular pattern than in cases with a diffuse histologic pattern. The plasma cell marker MUM1/IRF4 is negative. Bcl-2 expression is found only in a minority of cases of PCFCL (2).

Submitted by Muhammad Ahsan, Sahiwal Medical College, Sahiwal, Pakistan.

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2. *H Kerl et al., J Dermatol Sci, 34, 167 (2004). PMID: 15113586.*

To register your guess, please go to http://tp.txp.to/0121/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.

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In My View

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

Unleash Your Superpowers

Digital tools can augment pathologists' molecular medicine powers so they can diagnose and treat more patients

By Nick Lench, Chief Scientific Officer at Congenica Ltd., Cambridge, and Honorary Reader at the UCL Great Ormond Street Institute of Child Health, London, UK

With its potential to revolutionize diagnosis, treatment, and outcomes for patients across multiple clinical indications, demand for next-generation sequencing (NGS) is increasing rapidly. But interpreting sequenced data – complex, lengthy, and costly – presents a bottleneck to widespread routine clinical adoption. To compound the problem, the interpretation of genetic results often still relies heavily on labor-intensive processes that only highly trained clinical scientists can offer.

Initially, we believed that achieving the US$1,000 genome would make whole-genome sequencing a reality in the clinic – but that price point only reflects the cost of generating sequence data, not the staff time, sample processing, or bioinformatic processing and interpretation required to perform this complex task. As NGS accessibility continually increases, we realize that expert interpretation is the new bottleneck. The need to augment the available expertise with automated tools is becoming increasingly apparent.

Across Europe, there are fewer than 400 registered clinical laboratory geneticists (1), a position whose recommended training takes approximately five years. The shortage of clinical geneticists is just as severe in the US, with 71 percent of genomics laboratories already at or near capacity (2). It's easy to see how our ability to generate genomic data has quickly outpaced our ability to analyze and interpret it. And the capacity crunch is likely to increase; the Global Alliance for Genomics and Health predicts that, by 2025, over 60 million people will have had their genomes sequenced in a healthcare context to facilitate a disease diagnosis. Although this influx of data will enrich our datasets and improve diagnostic yield, it will also mean more information for clinical geneticists to filter and review.

To address these challenges, clinical decision support platforms initially simplified complex genomic data workflows so that a 20-hour case analysis and reporting cycle could be completed in a fraction of the time. Increasingly, these platforms are incorporating automation to further expedite the process. For example, many rare and inherited diseases feature recurrent causal variants we can confidently and consistently classify. Clinical users should be able to automatically solve these cases, using the latest data, without needing to repeat analysis; they should only need to provide checks to ensure the quality of the automated interpretation, allowing them to focus on variants of unknown significance or previously unseen variants.

We reviewed the analysis of over 25,000 whole genomes and found that a quality clinical decision support platform could reduce interpretation and reporting time from approximately 20 hours to an average of 30 minutes. By automatically classifying known variants without the need for human intervention, this time can be further reduced to just five minutes – giving us the power to analyze genomic data at scale and enabling widespread clinical use.

But this is just the first step! The ultimate goal is to give clinicians and scientists a range of superpowers so they can help more patients. These superpowers include:

- Perfect memories – providing automatically reported access to all previously known and classified variants
- X-ray vision – using machine learning scoring to predict pathogenicity
- Super-intelligence – through automatic prioritization and access to literature and databases
- Super-speed – automatically applying ACMG classifications

Combined, these superpowers ensure we can make safe, high-quality decisions – fast.

Though some may be looking for a black-box solution that can just make diagnoses on the fly, the field has yet to fully map all the ways genomic variations interact to cause genetic disorders or predict disease susceptibility. Because so much is still unknown, it would be foolhardy to believe we can fully automate every case. However, by providing clinicians and scientists with machine learning and artificial intelligence tools to automate the classification of known variants, we can begin to address bottlenecks and accelerate diagnosis and discovery.

References available online at: tp.txp.to/molec-power

A Circulating Solution?

Liquid biopsy – and appropriate, cell line-derived controls – are essential for improving patient care

By Keith Cannon, Director of Commercial Product Management, Diagnostics at Horizon Discovery, San Diego, California, USA, and Prabha Nagarajan, Senior Research Scientist, Diagnostics at Horizon Discovery, Cambridge, UK

Advances in precision medicine are transforming cancer diagnosis and treatment. The potential to detect and monitor both solid tumors and blood cancers has spurred aggressive research programs around the world. Liquid biopsy – the analysis of short nucleic acid fragments (150–500 bp) in blood – provides researchers with a unique opportunity to identify and define signatures for specific tumor types. These circulating free DNA (cfDNA) fragments not only offer the potential for earlier detection and diagnosis, but can also measure therapeutic effectiveness and inform treatment decisions.

Cancers present complex biological pathways that vary across tumor types and patients, and not all tumors respond equally to treatment. For example, therapies targeting pathways in highly proliferative or resistant tumors are more efficient and effective. Personalized genomics has therefore opened a groundbreaking path for molecular diagnostics in oncology.

With increasing numbers of diagnostic assays entering the lab, our need to evaluate these tests' performance is greater than ever – and appropriate controls are essential to calibration, standardization, and routine quality control.

Reference standards used in molecular tests should be well-characterized, stable, homogenous, and mimic the properties intended for use in analytical measurements. Clinical tests aimed at detecting genetic variations by next-generation sequencing (NGS) can introduce errors at various stages of the workflow, from sample preparation to bioinformatic analysis. To support the use of such comprehensive assays and ensure their accuracy, we must use reference standards that closely represent patient samples at each stage of the process.

That's where cell line-derived controls come in. Cell line-derived materials offer the complexity of the human genome and, when processed into different formats representing a patient sample analyte, serve as a commutable and renewable source of biological controls for assay development and R&D studies. They are comprehensive and, when sufficiently characterized, help establish analytical sensitivity in both quantitative and qualitative measurements.

Every clinical test needs robust controls to ensure reliable results and accurate diagnosis. In lung cancer, for instance, therapeutics tackle at least 10 different disease drivers and elements of the disease pathway – so it's clear that we need new assays to characterize specific cancer types and ensure each patient receives the best possible treatment for their disease. In addition, when studying rare cancers or novel biomarkers, it can be a challenge to obtain reliable, reproducible controls from patient samples. In both cases, cell line-derived reference standards offer a consistent, accurate, affordable way to design these assays.

Tumor DNA shed into blood constitutes a small fraction of the total cfDNA population, but is proving an important noninvasive biomarker in early cancer diagnosis, progression, and remission. However, the variant allele frequencies (VAFs) of tumor-specific mutations can be much lower in the cfDNA population compared to primary tumors – so accurate detection of low-level (1–10 percent) VAFs in cfDNA requires analytical tools with higher sensitivity and specificity. Careful consideration of the preanalytical workflow, which includes sample collection, storage, and nucleic acid isolation, is also critical to cfDNA quality and quantity. Appropriate quality controls for each step of the workflow reduce errors, aid in calibration to achieve higher purity and quality of extracted cfDNA, and facilitate accurate detection of low-frequency alleles.

Cell line-derived DNA, like patient samples, is genomically complex and thus offers an advantage over synthetic reference materials. It's also preferable to non-renewable, non-reproducible patient-derived samples. DNA from cell lines can be processed into smaller fragments corresponding to cfDNA fragment profiles and, when well-characterized for physical properties like quality, purity, quantity, and average size, can be used as controls for preanalytical workflows. Genetic profiling of cell line-derived cfDNA can be useful for developing quality controls to validate mutations and their respective allele frequencies in analytical assays. As the medical community increasingly uses NGS assays to inform diagnosis, prognosis, and treatment, cell line-derived controls will be essential to maximizing their utility and effectiveness in improving patient care.

After the Virus

Looking ahead to a post-COVID-19 world

By E. Blair Holladay

A year ago, SARS-CoV-2 was just starting to make headlines. As scientists and healthcare professionals, we carefully watched the news coming out of Wuhan, China, with the understanding that this virus could have a major detrimental impact on the world as we knew it. Over the ensuing 12 months, as the virus gripped countries around the globe, our worst fears were realized. The laboratory was thrust into the spotlight like never before; patient care weighed heavily in our hands as we tested millions for COVID-19 and pursued research that would help those with the virus recover safely and quickly.

One year on, we are hopeful to be turning a corner on COVID-19, with multiple vaccines available. So now we ask ourselves: what next?

There is no simple answer. It starts, however, with understanding how we function in a post-COVID-19 world. As pathologists and medical laboratory scientists, our job is – in many ways – just beginning. Our essential role in testing for COVID-19 over the past year, and in the months and years going forward, cannot be underscored enough. It is now up to us to drive public education on the available vaccines – and to champion the continued need for testing.

Despite the availability of COVID-19 vaccines, we cannot give up on the need for coordinated testing. It is estimated that nearly 27 million Americans have been infected and, on average, 117,000 new cases are diagnosed each day in the United States alone (1). As we usher in a new administration under Joe Biden and Kamala Harris, the American Society for Clinical Pathology is committed to continuing its push for a national testing strategy. There are major gaps in our current response to COVID-19 that must be addressed, or we risk setbacks to the progress we have already made. We know that the lack of a comprehensive national COVID-19 testing strategy has resulted in poor coordination, disjointed testing patterns, and – more importantly – chronic laboratory supply shortages that ultimately slow not only COVID-19 testing, but other essential laboratory work as well.

The fight against SARS-CoV-2 is far from over. As leaders in health care, we are responsible for ensuring that leaders outside health care understand what patients need to get back to a place of health. We have the knowledge and the expertise to help shape the post-COVID-19 world and establish a foundation on which we can build efficient and effective patient care.

"The fight against SARS-CoV-2 is far from over."

Reference

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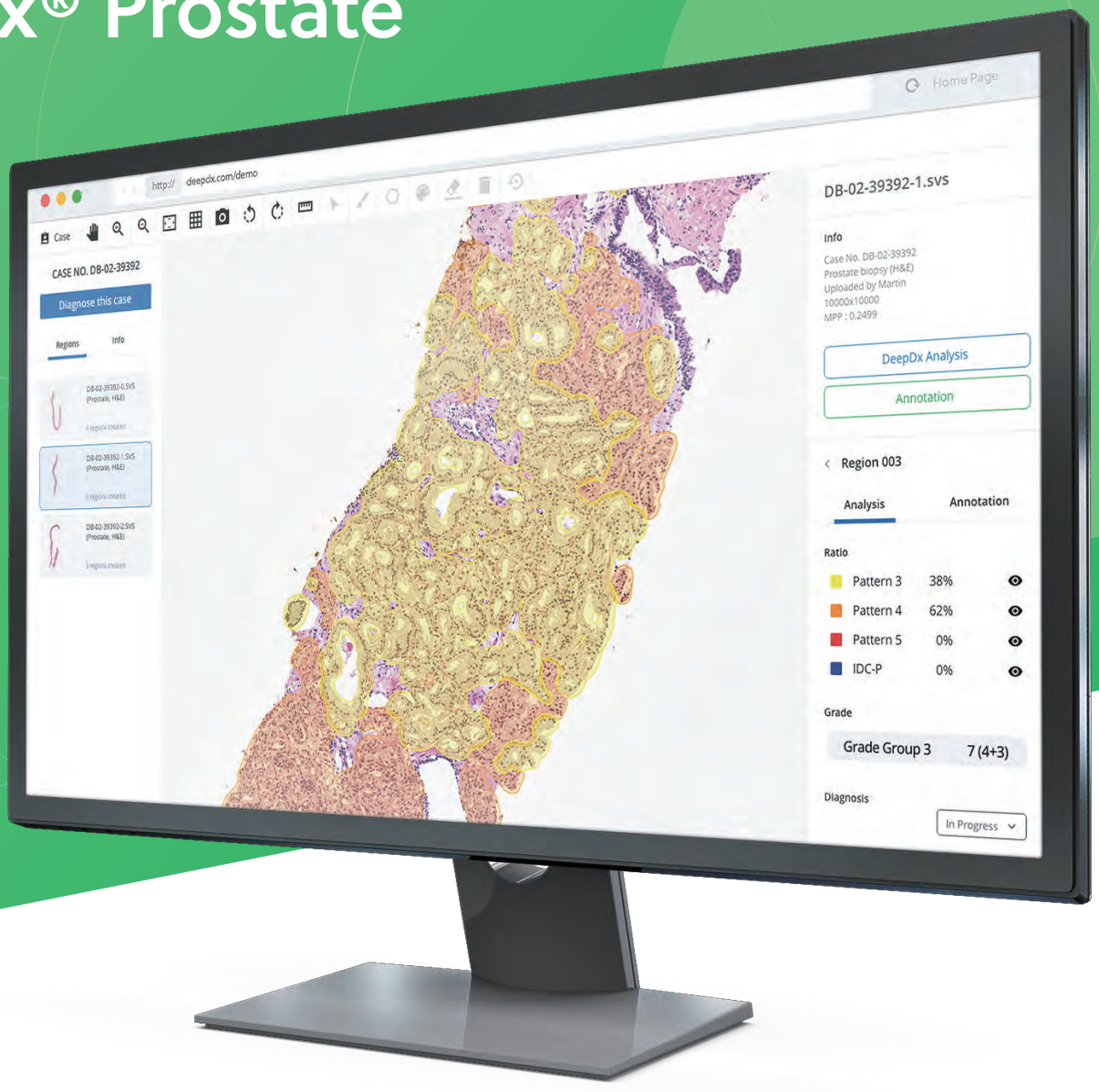

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Biomarker Tests for Precision Oncology: DIY or Pay-for-Service?

Cancer patient management of is increasingly driven by biomarker assays – but how should we manage the assays?

When testing for cancer biomarkers, hospitals and healthcare systems must choose between developing in-house capabilities or purchasing outsourced services. But what's best for the system – and what's best for patients? To discuss this, we convened a panel of oncologists and pathologists with broad expertise in precision oncology biomarkers: Carl Morrison (Roswell Park Comprehensive Cancer Center, Buffalo, New York); Kojo Elenitoba-Johnson (Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania); Alain Mita (Samuel Oschin Cancer Center, Cedars Sinai, Los Angeles, California); and Wei Song (Englander Institute for Precision Medicine, Weill Cornell Medicine, New York, New York). Moderated by Michael Schubert (Editor of The Pathologist) and Amy Carroll (Director of North America Medical Affairs, Next-Generation Sequencing and Oncology Division, Thermo Fisher Scientific), the panel explored the current state of biomarker testing – and the merits of keeping such testing in-house.

How does your institute organize precision oncology tests?

Carl Morrison: At Roswell Park, we perform mosts tests for our own patients; some are for outside parties, mainly local doctors.

Kojo Elenitoba-Johnson: At the University of Pennsylvania Health System, we also focus mainly on our own patients. We opt for in-house testing wherever possible; that said, some tests must be outsourced.

Alain Mita: At Cedars Sinai, we use both in-house and outsourced testing.

Wei Song: At Weill Cornell, in-house is the default.

What are your thoughts on centralized versus in-house testing?

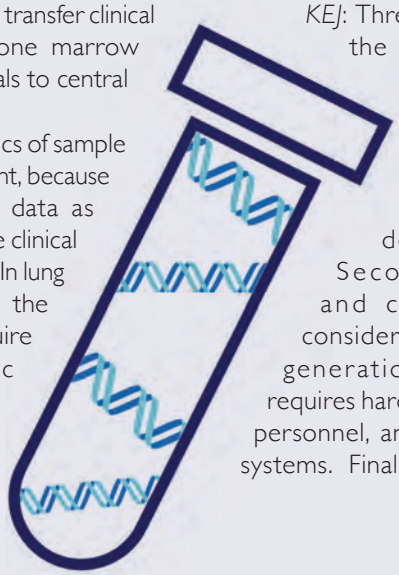
WS: I believe that in-house molecular diagnostics capability is indispensable – no pathology practice is complete without it. Furthermore, in-house expertise is vital for educating future residents. Finally, in-house facilities better meet oncologists' needs regarding type and size of assay panel – and, in particular, turnaround time. Our clinicians' top priority is rapid assay of 20–30 variants for immediate input into clinical management. Speed is key!

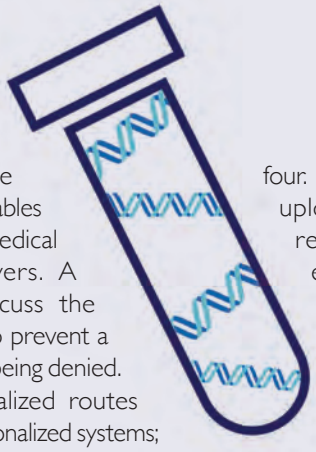
CM: Agreed; up to 98 percent of clinical decisions are based on a small subset of biomarkers. Doctors want fast results for that subset, not slowly delivered data for every single marker of potential interest. It's true that in-house laboratories may not be able to duplicate the infrastructure found in a commercial institution performing thousands of tests annually – but, when turnaround time is key, in-house is better. Remember, it can be time-consuming to transfer clinical samples, such as bone marrow biopsies, from hospitals to central laboratories.

AM: Yes – the logistics of sample transfer is a critical point, because doctors need assay data as early as possible in the clinical management process. In lung cancer, for example, the best outcomes require mutation-specific therapy. And initial therapy choices may have big impacts – immunotherapy followed by mutation-targeted therapy gives more severe side effects than the converse. Rapid decision-making also helps patients psychologically. After diagnosis, they want to start treatment as fast as possible, so turnaround time is of the utmost importance. Another advantage of in-house testing is that physicians can access their molecular pathology departments for expert advice. Because assay interpretation can be difficult, even for those familiar with molecular testing, this is an important advantage that centralized laboratories cannot offer.

KEJ: Three parameters influence the in-house versus out-sourcing decision. First, the nature of the institute's patients; why invest in a test if its patients don't need that test? Second, infrastructure and capital expenditure considerations; building next-generation (NGS) capability requires hardware, software, trained personnel, and regulator-acceptable systems. Finally, bottom-line factors

> *"I believe that in-house molecular diagnostics capability is indispensable – no pathology practice is complete without it."*





such as reimbursement also influence an institution's precision diagnostics strategy. In some cases, outsourcing may alleviate patients' cost burden. In others, patient volumes may affect the bottom line; if few patients need a given test, offering it may not be cost-effective. That said, there are often trade-offs between the cost advantages of outsourcing and its slower turnaround time.

WS: Another point: in-house facilities help oncologists to better serve patients. For example, if we have insufficient material for the assay – which does happen – we can simply ask for more.

Can in-house testing promote team-based coordination of patient care?

AM: Yes. A key advantage of in-house testing is collaborative decision-making. As a clinician, I place a high value on interactions with molecular pathologists. These range from phone calls and emails regarding urgent decisions to molecular tumor boards where we discuss complex cases that benefit from a variety of expertise.

WS: I agree. I regularly discuss data interpretation with my oncologist colleagues. For example, in complex cases – such as patients with two targetable molecular drivers – we employ methods to identify the dominant driver and design more effective care. It's all about patient benefit.

"A key advantage of in-house testing is collaborative decision-making."

CM: The in-house environment also enables interactions with medical directors and payers. A phone call to discuss the situation can help to prevent a patient's treatment being denied. By contrast, centralized routes involve large, impersonalized systems; interaction is difficult and patients may be denied out-of-pocket costs.

KEJ: These discussions also benefit primary care providers, not just those at the tertiary center.

Are all tumor boards becoming molecular tumor boards?

KEJ: In our center, yes. And, in my experience, the molecular tumor board often extends across institutional boundaries. For example, the referring institution or academic institutions may be included, often via telemedicine systems. I believe the reach of the molecular tumor board will continue to grow. After all, there is a natural synergy between oncologists, pathologists, and genomicists.

WS: I'm not so positive about separate, dedicated molecular tumor boards – but I do like the idea of integrating genomic profiling into routine tumor boards. Outlining translation pathways and available targeted therapies is very helpful for oncologists.

AM: Identification of clinical trials that may address a patient's mutation profile is also extremely helpful; molecular tumor boards can provide this information as well. The only problem is that you can't have such meetings in real time; they can take a couple of weeks to set up. But, in the future, I anticipate that most discussions will be integrated into these tumor boards.

What should we aim for in terms of communication speed?

CM: Molecular pathology laboratories should get reports back to oncologists within six days – preferably three or four. Ideally, structured data should be uploaded into the electronic health record as it becomes available, even if the complete report is not ready. And the lab should answer queries very rapidly – certainly within 24 hours.

KEJ: I completely agree. We must deliver accurate, clinically relevant results on a timescale that is relevant to the patient's treatment. But turnaround speed depends on a large number of factors, many of which are somewhat institute-specific. The ability for clinicians to follow-up is also important.

How is precision oncology testing evolving?

CM: Molecular pathology in Roswell Park began about 15 years ago with single-gene tests and advanced to NGS in 2012. Our in-house panels became the basis of a spinout venture in 2015 – and now we are broadening our in-house capabilities again, including new NGS tests.

KEJ: We have gone from classical cytogenetics to NGS. For the last six years, all such tests have been performed in a single division comprising both scientists and clinicians with subspecialty certification from the American Board of Pathology and Molecular Genetic Pathology. The test volumes rise each year, as does the range of assays – it only takes one peer-reviewed publication to add to the list of genes relevant to precision oncology! At the same time, we vary the tests we perform according to the nature of the patients we treat and the turnaround times of the platforms we use. Accordingly, we remain dynamically reactive to the changing biomarker assay environment. More broadly, we expect that, in the near future, any pathology lab will be able to profile the key subset of predictive biomarkers. After all, WHO guidelines now recommend molecular testing to support diagnosis of many cancers. The future is molecular!

PATHOLOGY IN THE EAST AND THE WEST

Two pathologists who have practiced internationally explore the differences – and the similarities – between distant regions

Michael Schubert interviews Shivayogi Bhusnurmath and Dhaneshwar Lanjewar

MEET THE EXPERTS

SHIVAYOGI BHUSNURMATH

is Dean of Academic Affairs and Co-Chair, Course Director, and Professor of Pathology at St. George's University, St. George's, Grenada, West Indies.

DHANESHWAR LANJEWAR

is Professor of Pathology at the Gujarat Adani Institute of Medical Sciences, Bhuj, India, and Overseas Advisor to the Indian College of Pathologists.

In January 2017, we spoke to pathologists from Europe and North America, asking them to compare their regional approaches to pathology. The result? A wealth of discoveries about how lab medicine is different on both sides of the ocean, how it is the same – and what lessons each continent can learn from the other.

But what of labs in other parts of the world? The similarities and differences stretch from early education all the way to routine pathology practice – and there is much to be gained from a better understanding of our peers across the globe. To that end, two pathologists who have trained in India and practiced both there and elsewhere share their experiences, contrast the different regions in which they have practiced, and explore what can be gained from adopting one another's approaches to the discipline.

WHAT INSPIRED YOU TO BECOME A PATHOLOGIST?

Shivayogi Bhusnurmath: I trained in medicine at Bangalore Medical College during the late 1960s and early 1970s. At that time in India, the only "reasonable" options for high-performing students were engineering and medicine – and parental pressure played a major role in career decisions. Because of my academic successes, I had the option of direct admission to either medical school or the Indian Institute of Technology. I opted for medicine because that's what my friends chose, and I wanted to stay with them. At the time, I was too young to consider the broader ramifications of my choice.

In my second year of medical school, I was bored; I was tired after 18 months of anatomy study; the faculty seemed more interested in torturing than inspiring us. Then I read The Final Diagnosis, by Arthur Hailey – and it was a major turning point in my life. The book's central character was a chief of pathology and I was impressed by the role he played in critical decisions. A young nurse's limb amputation due to suspected osteosarcoma; an epidemic of enteric fever; the autopsy that revealed unexpected incidental tuberculosis and prompted the screening of an entire family… These examples are still etched in my mind after five decades. Like the pathologist in the novel, I wanted to be a central figure in clinical decision-making. My intrigue only deepened as I read more pathology texts and learned more about the mysteries of the human body – but the final strike came when I met our head of pathology, Krishna Bhargava, who taught the subject with abundant real-life stories and encouraged active discussion about specimens in the pathology museum. In those days, many clinical questions ended with "maybe, maybe not" – so my drive to eliminate medical uncertainties made pathology a natural choice.

When I finished my internship, I wanted to pursue a pathology postgraduate program. At the time, candidates had to do one year as a house surgeon in medicine and surgery first – but I was fortunate to have Krishna Bhargava as hospital director. He created a new position at Bangalore's Victoria Hospital – house surgeon in pathology – and I was the first inductee.

In June of 1974, I learned about the Postgraduate Institute of Medical Education and Research in Chandigarh, which had a great pathology training program. One of my friends had procured an application form (not an easy thing those days due to poor communication facilities), but the deadline had passed. As I read the application out of interest, I discovered that there was still one deadline I could meet: direct admission into a PhD program in pathology. The application asked me to explain how I qualified as an "exceptional candidate." My naïve response? "Please consider me exceptional because I am greatly interested in pathology and nothing else." Little did I know then that the Dean in charge of admission exams and interviews was Basant Kumar Aikat, who was also the chair of pathology. He saw my interest for the subject and sent me a telegram that stated, "We regret that we have stopped direct intakes into the PhD program. If interested in the MD Pathology program, we could transfer your application to that pool." I immediately replied, "Please do."

The next month, I traveled to Chandigarh, an arduous three-day journey by train and bus, to appear for an entrance exam. My high performance in the entrance examination earned me an interview the next morning. That's when I lost all hope; India's culture of favoritism at that time meant that selections were rarely merit-based, and I had no "connections" in this unfamiliar place. When I arrived, all the candidates were seated in a lecture hall, facing two serious-looking senior professors. They called the candidate with the highest merit rank, asked him which discipline he wanted, and directed him to pay his admission fees at the door. That was it. No subject questions at all. I had never seen such fairness!

When my turn came, I said I had applied for pathology. One of the professors (who I later learned was Pran

Nath Chuttani, the director of the institute and a professor of medicine) reminded me that, because of my exam score, I could choose any discipline I wanted. When I told him I wanted pathology, he thought I hadn't understood. Slowly and deliberately, he repeated, "I know you applied for pathology but, because your score is high, you can take any subject. You don't have to choose pathology." I said, "I applied for pathology because I am interested in it. Why are you forcing me to join some other program?" He gave up, thinking me a hopeless case. I did not realize then that the gentleman sitting next to him was B.K. Aikat himself – and that he was impressed with my determination to pursue his discipline!

My career has afforded me many opportunities to work outside India. I worked as a lecturer-consultant at Ahmadu Bello University in Zaria, Nigeria, from 1982 to 1985. The HIV/AIDS epidemic was just beginning, and we knew nothing about it – but I remember, while introducing fine needle aspiration cytology, experiencing accidental needlestick wounds and living in fear for many years because there were no diagnostic tests and no treatments available. Fortunately, I escaped infection. I also worked in both the United Kingdom and Japan in the late 1980s and in Canada and Oman in the early 1990s. My final move (so far) was in 1996, when I arrived at St. George's University in Grenada, West Indies. In India, I had the good fortune to attend almost all of the annual pathology conferences, become secretary of the Indian Association of Pathology and Microbiology, and establish the Indian College of Pathology (becoming its founder fellow and founder secretary) during my tenure.

Dhaneshwar Lanjewar: I was born into a lower-class labor family in Pulgaon, Maharashtra, India. Life in Pulgaon was difficult and there were high rates of poverty and illiteracy. My parents were uneducated and my father had married my mother when they were 15 and 12, respectively. My father died when I was one year old and, because my mother did not remarry, she bore full responsibility for her three sons. She worked very hard – first on the farms and later in the textile industry – so that all of her children could receive a good education.

I matriculated in science in 1969 and wanted to attend a science college. Pulgaon had no such institution and the college in nearby Wardha had a 200-rupee admission fee – too much for my mother. Instead, I traveled hundreds of kilometers to Aurangabad, where a science college for socially and economically disadvantaged students charged me a single rupee to study biology (and to teach me about my social responsibilities and obligations). Eight years later, I held degrees in both biology and medicine, had just married, and was planning to set up a general practice in Pulgaon. I had never imagined taking a postgraduate position – but, when I went to Aurangabad to collect my medical degree, I spotted a notice on the wall advertising a one-year resident pathologist post. I have no idea what came over me, but I applied – and I got the job. From there, my path was set.

In 1985, I accepted my first position at Grant Medical College in Mumbai. Founded in 1845, the school is one of the oldest institutions in Asia. The pathology department,

CASE 1

A 25-year-old female complained of a lump in her right breast at seven months of gestation. Fine needle aspiration cytology showed features of benign phyllodes tumor. She delivered a baby boy at term; six days after delivery, there was massive enlargement of the right breast and the skin showed cellulitis, resulting in simple mastectomy. The gross examination showed enlarged breast (25x15x15 cm). The nipple was normal and the skin around the nipple was congested. Cut sections showed multiple yellow infarcts surrounded by zones of hyperemia and red, nodular, polypoid tumors. The histology of the polypoid tumor showed infarction of phyllodes tumor. The histology of peripheral normal breast showed features of lactating breast. This is a case of coexistent multifocal infarction of breast with infarction of phyllodes tumor. Breast infarction is a rare condition seen with physiological breast hyperplasia and is associated with pregnancy and lactation. To date, only 18 cases of breast infarcts and only one case of phyllodes tumor infarction are described in the literature. This is the first case of coexistent infarction of breast and phyllodes tumor.

now 140 years old, has housed many of the country's pre-eminent laboratorians and has contributed significantly to the discipline's growth in India. When I joined Grant Medical College, Ulhas Laxman Wagholikar was chair of the department; his extensive experience in clinical autopsy and gross pathology made him an excellent teacher and inspired my interest in autopsy.

> "I had never imagined taking a postgraduate position – but [...] I spotted a notice on the wall advertising a one-year resident pathologist post. I have no idea what came over me, but I applied – and I got the job. From there, my path was set."

In June 1988, I performed my first autopsy on a patient with AIDS. The histopathological findings showed opportunistic infections in 18 organ systems – something none of us had witnessed before. That case was the start of a 22-year career in autopsy. My fascination spurred me to work 10 or more hours a day – and that eventually resulted in my promotion to chair of the department, as well as a number of leadership positions in the Indian Association of Pathologists and Microbiologists and the Indian College of Pathologists. Although I retired in 2016, I still serve as overseas advisor to the Indian College of Pathologists.

WHAT DOES THE AVERAGE WORKDAY LOOK LIKE FOR YOU?

SB: For the past 25 years, the bulk of my work has involved teaching medical students. With my wife, Bharti Bhusnurmath (also a professor of pathology), I created a unique program called the International Clinical Tutor Teaching Fellowship Program. It started with four recent medical graduates who lived locally, but we now recruit recent medical graduates from across the globe to help us run small groups in our teaching lab. Our course is taught twice a year – involving over 900 students each time – and students come from over 130 countries to join us. We are lucky to have them; although my wife and I (the only full-time pathology professors here for most of our 25 years) could handle lectures for a class of any size, we need high-quality preceptors when we split the class into groups of eight to 10 students for applied clinical learning in the laboratory sessions.

My morning begins with two hours spent training these clinical tutors on the lab exercises for the day, followed by two hour-long pathology lectures for the second-

CASE 2

A 27-year-old female presented with fever, vomiting, and pain in the right iliac fossa of two days' duration. She was diagnosed with acute appendicitis and appendectomy was performed. The distal end of the appendix showed a well-circumscribed, yellow tumor measuring 2x0.5 cm in size. Histology showed small, uniform tumor cells arranged in solid nests and trabeculae with peripheral palisading. The nuclei of these cells were round, with finely granular chromatin. The cytoplasm showed numerous small, round, clear vacuoles. Immunohistochemistry showed intracytoplasmic positivity for chromogranin A and synaptophysin. A diagnosis of lipid-rich carcinoid of the appendix was made. The literature describes only 24 cases of lipid-rich carcinoid; this was the first in India. The electron microscopy of lipid-rich carcinoid shows lipid droplets in the cytoplasm. The clinical behavior is similar to that of classic carcinoid tumor of the appendix.

CASE 3

A 63-year-old female presented with three months of fullness and pain in the left upper quadrant of her abdomen. Clinical examination revealed massive splenomegaly. The CT scan showed splenomegaly and well-defined cysts of varying sizes with rims of calcification. A clinical diagnosis of hydatid cyst of the spleen was made and splenectomy performed. The spleen measured 28x16x9 cm in size and weighed 1,800 g. The capsular surface of the spleen was irregular due to numerous cysts. The cut surface revealed replacement of splenic parenchyma with well-defined cysts ranging from 0.3 to 3.5 cm in diameter. The cystic spaces contained blood, serous, or hemorrhagic fluid, and the cyst wall showed calcification. Microscopic examination showed small and large cystic spaces containing red blood cells and lined by a single layer of flattened cells. The lining was strongly CD31-positive and was D2-40-negative. A diagnosis of splenic hemangiomatosis was made. Splenic hemangiomatosis with diffuse involvement of splenic parenchyma is a rare condition. Only 37 cases are described in the English literature; this was the first in Indian literature.

"I saw a case of Budd-Chiari syndrome in a bear owned by His Majesty the Sultan of Oman and cardiomyopathy with granulomatous lesions in his ostriches!"

year medical students (which the clinical tutors also attend). After a lunch break, we have four hours of teaching lab sessions, whose preceptors are the clinical tutors we have trained. My wife and I move between small groups, overseeing discussions and assisting if needed. Finally, we meet informally with the tutors at the end of the day to tackle any unresolved issues they have faced in their groups.

I also have administrative duties during the day: faculty and staff recruitment, budget, faculty development, performance assessments, curriculum development, test item generation, item banking, administration of tests, item analysis, and more. I sit on the School of Medicine's curriculum committee, the committee on academic progress and professional standards, the committee for technology in teaching, the graduation assessment board, the council of deans, and handle tasks including self-study documentation for accreditation, site visits to various international campuses, and one-on-one advising for students who are experiencing difficulties. The diagnostic services work comes later in the day! We process 60 to 80 patient samples per day – mainly in clinical chemistry and hematology, but we also perform fine needle aspiration cytology and sign out surgical biopsies. Where do we fit this work in? Some of it during our lunch break; the rest after our educational duties are finished for the day.

The cases I see here in Grenada are different to those common in India. Here, I see a lot of sickle cell disease, diabetes, hypertension, human T-lymphotropic virus-related lymph node pathology, prostate and breast carcinoma, dengue, thyroid problems, and seasonal flu following the carnival in August (which brings in a lot of international visitors). In Chandigarh, I saw a lot of liver disease – Indian childhood cirrhosis, Budd-Chiari syndrome, veno-occlusive disease of the liver, non-cirrhotic portal fibrosis, Wegener's granulomatosis, and alcoholic liver disease (many cases of which may in retrospect have been non-alcoholic fatty liver disease, which was at the time unknown). In Muscat, I saw a lot of *Helicobacter pylori*, systemic lupus erythematosus, lupus nephritis, and gastric carcinoma.

I also saw a case of Budd-Chiari syndrome in a bear owned by His Majesty the Sultan of Oman and cardiomyopathy with granulomatous lesions in his ostriches!

DL: After my retirement, I joined the Gujarat Adani Institute of Medical Sciences as Professor and Head of Pathology. My workday starts with postgraduate teaching –

slide seminars, subject seminars, journal clubs, and discussions over surgical specimens. The rest of my morning is spent signing out surgical pathology cases and discussing thesis projects with residents. After a lunch break, I host lectures and practical classes for second-year medical students two afternoons per week and guide residents as they assist with practical teaching. Every day also features a wealth of administrative work!

The most common cases I see are thyroidectomy, appendicitis, cholecystitis, mastectomy, gastrointestinal resections, splenectomy, hysterectomy specimens, ovarian tumors, placenta, and limb amputations. I have seen a few unusual cases, though…

HOW DOES THE DAY-TO-DAY WORK OF A PATHOLOGIST IN INDIA DIFFER FROM THAT OF A PATHOLOGIST IN NORTH AMERICA?

SB: It seems to me that there is much less emphasis on quality control in India, especially in private laboratories. In academic institutions, there is less emphasis on research; although publications matter, their reliability is questionable because of the pressure for promotions and the lack of reliable data. The teaching commitments in India in academic institutions tend to be greater, but – unlike in the US – India has no requirements for recertification or continuing medical education.

There is also much less fear of litigation in India. Many private pathology labs participate in "cut practice" – otherwise known as kickbacks. Referring physicians request more tests than the labs perform, and the overpayment is split between the two. It is difficult to determine the extent of this practice, of course, because it is done under the table and no records are kept. Such practices are rare in North America – perhaps because computerized reporting and shared records are common. This also means that India has fewer consultations by extramural experts, fewer referrals to specialized laboratories, and less use of "checklist"-style reports with ICD and billing codes. Most Indian pathology reports are descriptive and contain few or no codes.

DL: In teaching institutes in India, pathologists manage the clinical laboratory, surgical pathology, cytopathology, frozen section, and autopsy – as well as training and examining undergraduate and postgraduate medical students and those studying to become laboratory technicians. We also have administrative responsibilities.

In private practice, things look a little different. There is no registration or regulation of private pathology laboratories in India – so although some are run by qualified pathologists, many more are led by technicians without medical qualifications. Most laboratories in the country are illegal – by which I mean that the reports they generate do not bear the signature of a qualified pathologist. In private laboratories, 95 percent of the workload is clinical pathology and clinical chemistry; only 5 percent is histopathology – a stark contrast to the US, where most private pathology practice is focused on histopathology.

HOW DOES TRAINING DIFFER BETWEEN THE TWO REGIONS?

SB: Training in India is not uniform, but there are three main pathways. The most common is to register as a postgraduate trainee at a medical school. This involves paying tuition fees, attending lectures, and sometimes supervising medical students in labs – but not participating in daily sign-outs. After three years, the program concludes with exams and a dissertation. The second route is through a postgraduate residency program, available only in a few high-end institutions. The (paid) residents rotate through different sections, do grossing, and sign out cases with the faculty. This program is intensive, and residents are involved in the routine management of patients. To finish, they must write a dissertation. The third route involves working in the pathology department of a recognized hospital and taking a national examination conducted by the National Academy of Medical Sciences.

The first two routes result in a medical doctorate in pathology; the third results in the title of Diplomate of the National Board. Nonetheless, all three are considered equivalent for employment purposes.

The quality of training and exams varies considerably among institutions but tends to be better in residency programs. Personal bias and favoritism plague private institutions and university departments, making it easier for popular trainees to do well in their exams and have their dissertations approved. Postgraduate programs also have little national oversight to ensure uniform training and exam standards. Several departments lack facilities for molecular pathology,

immunopathology, electron microscopy, medical autopsies, flow cell cytometry, and more – so trainees advance with no experience in those fields. Many departments receive very few representative biopsies from various subspecialties because clinicians send them to private labs for better diagnostic help (or kickbacks), so trainees have limited exposure to cases. There is also little effort to teach laboratory quality control, quality assurance process, and accreditation. Ultimately, the exit exams are poor indicators of readiness to function as a consultant or attending. Most training has one goal: to enable students to attach diagnostic labels to slides.

Unfortunately, there is little impetus to ensure equal opportunity for trainees across India. Leaders in academic pathology have a fair idea of which institutions offer the best training and which are unreliable training facilities; however, there are few concentrated efforts to improve national standards so that all trainees have reasonable access to broad-based, high-quality training. Such a goal could be easily accomplished by cooperation between institutions, national oversight committees, tapping of interested academics in India and abroad who want to contribute to education, and making use of online platforms for education – so I often question why matters have not yet improved.

In North America, the system is very structured. Pathology training is residency-based, overseen by national boards, and involves stringent requirements for the length and breadth of training. There are mandatory sessions for journal article reviews, tumor boards, in-service exams, and final national exams that are well-supervised, well-audited, and completely objective. That is not to say that these programs are perfect; variability remains in the quality of faculty and residents, in entry requirements, and in the emphasis on research and academic activities.

Both regions share four major deficiencies:

1. There are no learning objectives related to professional behavior and communication skills. We try to emphasize this in the training of medical students; it is worthwhile to consider in resident training as well.
2. Little attention is paid to training and testing in the general principles of pathology – a crucial pillar of both our work and medicine.
3. There is little training in how to select laboratory investigations in different clinical scenarios and in intelligent interpretation of test results. Many physicians today are comfortable just clicking on a battery of investigations available on the computer screen without critically reasoning why each one is needed and how the results will aid diagnosis. This increases healthcare costs and can result in unnecessary treatment of asymptomatic patients based solely on abnormal lab values.
4. Both regions must rapidly incorporate digital pathology and artificial intelligence into training programs, lest we be left behind as these trends sweep medicine.

DL: The Medical Council of India regulates the country's postgraduate pathology training. After medical school and a one-year internship, students may take an entrance examination to qualify for postgraduate study. The three-year program takes the form of postings in various assigned sections, 20 lectures per year (delivered by senior faculty), and activities such as slide seminars, symposia, group discussions, and journal clubs. Resident pathologists rotate through surgical pathology and autopsy (12 months), hematology and laboratory medicine (10 months), cytopathology (eight months), transfusion medicine/blood bank (two months), archiving and record management (one month), and immunopathology, electron microscopy, molecular pathology, cytogenetics, and research methodology (two months in total).

Residents must submit a thesis, present at least one poster and one oral paper at a national or state conference, and publish at least one paper during the program to be eligible for the final examination. They must also maintain a logbook, which is periodically assessed, to record their work. Finally, they must teach undergraduate students. The idea behind the program is good, but it has some flaws; for instance, there is no designated person in charge of the program to monitor residents' performance, and most residents don't get adequate autopsy training because many institutes don't conduct clinical autopsies.

> "The salary in teaching institutions cannot compete with private laboratories [...] It is a tragedy; institutions that train residents cannot attract top academic talent, perpetuating issues of quality and inconsistency."

In the US, training requirements are defined by the American Board of Pathology, which examines and certifies pathologists at the end of their training. There is also an official Director of Residency Program in every institution who is responsible for monitoring every candidate's performance based on evaluations from faculty members – and who makes sure that training requirements are satisfied. The training takes four years – two in anatomic pathology and two in clinical pathology. Residents gross surgical specimens, conduct tumor board meetings, and perform a minimum of 50 autopsies prior to board certification. They have a six-month rotation in clinical chemistry and another in the blood bank, where they take calls and handle quality assurance. Even microbiology rotations are a minimum of one to two months.

DO BOTH REGIONS FACE SIMILAR DIFFICULTIES WITH STAFFING AND RECRUITMENT?

SB: It is good for pathologists trained in India to work in North America. It will help address any deficiencies in their training and make them better pathologists. Most Indians never leave India in their hearts and minds even if they move physically to seek out better prospects and working conditions. Almost everyone regularly visits family and friends at home and most feel a strong desire to "give back" – a cost-free feedback loop that enhances education and facilities in India. Some who have moved up the academic ladder in North America even invite trainees from India to observe in their departments as guests. The only drawback is that these individual efforts are spotty and uncoordinated. We have formed the Association of Indian Pathologists in North America to streamline this energy and enthusiasm so that we can help upgrade pathology education, practice, and research in India.

Staffing and recruitment are not major problems in India because of the many certified pathologists who graduate each year. However, the quality of those pathologists is variable due to the lack of national standards. The salary in teaching institutions cannot compete with private laboratories – so, unfortunately, those who choose to teach are usually those who cannot find positions at high-end laboratories (although there are exceptions). It is a tragedy; institutions that train postgraduate residents cannot attract top academic talent, perpetuating issues of quality and inconsistency.

DL: In India, filling the posts of retired faculty is not a priority – and new recruitment also takes time, so many pathologists are overburdened. Although some Indian pathologists move to the US for work or study, that migration doesn't limit the country's ability to train new pathologists. Each year, over 80,000 students are admitted to medical colleges in India – of whom over 1,700 become full-fledged pathologists.

HOW DO LABS IN INDIA DIFFER FROM THOSE IN NORTH AMERICA?

SB: The only Indian laboratory in which I have worked is the Postgraduate Institute of Medical Education and Research in Chandigarh, where I practiced from 1974 to 1992. It is one of the best labs in the country – so perhaps not representative of Indian labs as a whole. However, I have visited many labs in both India and North America

In India, labs in academic institutions (excluding the top few national institutes) generally lack funding, equipment, quality control, and – worst of all – faculty motivation to excel. The quality of testing and reporting is variable, but rarely reliable. As a result, diligent clinicians often send their patient samples to large multinational laboratories that offer better-quality reporting – kickstarting a vicious cycle in which the local labs receive fewer and fewer samples and thus have fewer and fewer opportunities to learn and improve.

DL: At government medical colleges, resources are limited. Even though the technology is modern, we don't have a regular supply of reagents – so we often can't perform necessary tests. Laboratory staff also lack regular training, so their knowledge is often outdated – and, in many institutions, those who retire are not replaced, so laboratories run on skeleton crews. Sadly, it seems that laboratory safety is not always a priority.

Because there is no regulatory agency in India, very few labs are quality-conscious. NABL 15189:2012 accreditation is purely voluntary; less than 1 percent of labs are accredited. Without efficient, credible, and quality-conscious diagnostic reports, the future of healthcare in India will continue to languish. We need a set of binding rules and regulations for pathology labs.

"The practice of kickbacks robs trainees of the opportunity to see interesting samples, whereas the lack of advanced mentoring robs them of potential career opportunities."

In the US, on the other hand, the Centers for Medicare & Medicaid Services regulate all laboratory testing (except research) performed on humans via the Clinical Laboratory Improvement Amendments. All clinical laboratories must be properly certified to receive Medicare or Medicaid payments. Many US labs have state-of-the-art technology and place a high priority on safety.

HOW WIDESPREAD ARE NEWER TECHNOLOGIES LIKE DIGITAL AND MOLECULAR PATHOLOGY IN INDIA?

SB: They are available in only a few select laboratories and institutions.

DL: Awareness of molecular diagnostics is increasing in India, where there are now more than 20 molecular pathology labs. Most are in tertiary care hospitals and research centers. In 2011, a group of enthusiastic Indian experts formed the Molecular Pathology Association of India to promote and cultivate the study and practice of molecular pathology.

Although interest in digital pathology is growing among Indian pathologists, there are still impediments to its adoption. Recently, the Department of Pathology at Mumbai's Tata Memorial Hospital surveyed pathologists' knowledge, attitudes, and practices toward digital pathology. The results will provide a roadmap for digitization in the Indian pathology community. At the moment, only one laboratory in India offers web-based consultations with national and international pathologists using whole-slide images.

WHAT ARE THE BIGGEST CHALLENGES PATHOLOGY FACES IN INDIA? WHAT ARE THE BIGGEST CHALLENGES IT FACES IN NORTH AMERICA?

SB: In India, the main challenge is the variable quality of training, practice, and research. There is also a lack of collaboration between the "haves" and "have-nots" who

could facilitate one another's growth, little oversight of training and quality, and little access to advanced technologies. The practice of kickbacks robs trainees of the opportunity to see interesting samples, whereas the lack of advanced mentoring robs them of potential career opportunities. These things, coupled with the overall lack of uniformity in testing and training, mean that two young Indian pathologists might have completely different backgrounds, educations, and skill sets after completing their training.

In North America, the opposite is true. Pathology is becoming dependent on a "checklist" philosophy that may lead to a lack of independent and creative thinking. Many pathologists are entrenched in subspecialty silos, impacting their ability to be good diagnosticians across the full spectrum of surgical pathology. I feel that some pathologists may even rely too much on adjunct techniques, denying the humble H&E-stained slide the respect it deserves. Most importantly, US pathologists often engage in defensive practice to avoid litigation. Excess caution may seem like a good thing but can lead to unnecessary testing and overtreatment.

DL: In India, the biggest challenge is quality control. How sure are you that your lab results are accurate? Indian pathologists need to organize and make quality a priority across labs, with restrictions on who can start and run a lab. Technology has improved in clinical pathology, but histology lab quality is still largely substandard. Even tests as basic as immunohistochemistry are too expensive for routine use.

The decline of the autopsy has confronted us with the challenge of providing adequate training and experience for new pathologists. Growing administrative duties have increased our workload and responsibilities – including the need to comply with various regulatory bodies. Issues such as accreditation, internal and external quality assurance, continuing professional development, performance indicators, continuous audit activities, revalidation, and participation in clinical governance activities are just a few of the tasks expected of medical professionals nowadays.

In North America, pathologists generally subspecialize, which carries its own set of challenges:

- Decreased staffing flexibility in comparison with more general laboratories.
- Increased operational overheads (every subspecialty operates as a separate unit).
- Difficulty measuring workload equity between staff on different subspecialty teams.
- Difficulty evaluating the efficiency of pathologists' work due to weights and indicators that vary from one subspecialty to another.
- The need for more staffing – still the biggest factor hindering subspecialization.

Technology is also a double-edged sword for North American pathologists; although molecular tests are becoming more readily available, their cost is affecting hospital budgets.

WHAT CAN NORTH AMERICAN AND INDIAN PATHOLOGISTS LEARN FROM ONE ANOTHER?

SB: North American pathologists often think that their Indian colleagues are poorly trained or have had few opportunities for training – when, often, this is not the case. Indian pathologists, on the other hand, believe that all North American pathologists are rich, well-trained, and otherwise superior to their Indian colleagues.

We can both learn from one another. India must adopt North America's focus on lab management, quality control and assurance, accreditation, communication skills, and mandatory continuing medical education or other forms of professional development. In return, India can teach volumes about how far down the diagnostic pathway one can go with just a simple H&E-stained slide and how to be truly selective when ordering additional tests.

DL: The one thing I would like North American pathologists to learn from their Indian counterparts is the skill of making a diagnosis with limited resources. We may have suboptimal sample or stain quality and lack ancillary stains, such as immunohistochemistry, but we still make diagnoses.

In India, there is no culture of laboratory inspections and quality assurance. Therefore, one thing I would like our country to take from North America is the strict adherence to quality assurance protocols and the value of accreditation and regulation.

In Practice

Technologies and techniques
Quality and compliance
Workflow

The Fantastic Four

Key questions to ask yourself about sigma metrics in the lab

By Satish Ramanathan

For two decades, I have been an ardent devotee of sigma metrics – a way of measuring quality and performance in the laboratory. In fact, my lab was the first in India to receive sigma certification from Westgard QC. Ever since, sigma has been one of the essential ingredients in my quality kitchen. I consider it one of the best statistical tools for measuring, monitoring, and improving the quality of testing in the clinical laboratory.

Even though I consider myself to have attained "sigma consciousness," there is always more to learn – a fact that was brought home to me one fine day in Hyderabad. I was taking questions after a presentation when someone asked me a series of questions: the "fantastic four."

1. What was the state of my lab's analytical quality before we implemented sigma?
2. Can the quality kitchen thrive without sigma – even for a single day?
3. Have I ever used sigma as a tool for risk management or financial management?
4. Is sigma a mere publicity stunt? Only a few labs have attempted to bring sigma into routine quality control (QC) practice, but there are over 500 publications on sigma – most written by labs who don't use it themselves.

"I consider [sigma] one of the best statistical tools for measuring, monitoring, and improving the quality of testing."

These insightful questions prompted a deep dive into sigma metrics as a critical aspect of QC – an analysis I think will be useful for any lab using, or considering, the sigma approach.

Sigma metrics are derived from a mathematical calculation involving three components: total allowable error (TeA), bias, and standard deviation. On the sigma grading scale, an analyte with metrics above 6 exhibits "world-class performance," whereas one with sigma less than 3 is considered "not fit for patient use."

And that brings us to the "ugly side" of sigma's perception in the laboratory world. The tool is an industrial standard and the grading system is accordingly designed to improve productivity and reduce defects in industrial processes. Many laboratory medicine specialists may wonder how an industrial standard can fit into a clinical laboratory. If one of our tests shows a sigma of 1.5, are we reporting patient results with poor quality? This need to understand the intersection of sigma metrics and clinical utility drove me to answer the "fantastic four."

What was the state of my lab's analytical quality before we implemented sigma?

Sigma is a statistical quality measurement tool – nothing more. The past, present, and future of analytical quality lies not in the hands of sigma, but in the tight fist of analytical method design. So when an analyte's sigma result is poor, the lab has only two viable options: to switch analytes or to lower its analytical goals. But does this serve the purpose of sigma – that is, to improve quality to meet clinical needs? My answer is no. It's not analyte choice but method selection that is the main ingredient in our signature quality dish; sigma is added to the recipe at a later stage to test the strength of the chosen method.

Can the quality kitchen thrive without sigma – even for a single day?

In my opinion, no. I consider sigma the salt of my quality kitchen. Without salt, a kitchen cannot produce a quality dish – but too much or too little spoils the broth. You can't blame the salt for that; it's the fault of the chef who handles it! Similarly, you can't wield sigma without first mastering the art of its application.

The first skill to learn is how to select an analytical goal. One size does not fit all! Various organizations have designed different sigma goals, but it's the laboratory's job to select the most ideal goal for any given analyte based on its clinical significance and needs. For example, you may want to select a stringent goal for creatinine, but a broader goal for AST, due to the differences in their clinical needs. Serum creatinine is the diagnostic and prognostic marker for chronic kidney disease and acute kidney injury – so even a fractional change affects treatment selection and outcome, meaning that creatinine needs a stringent analytical goal. AST, in contrast, is neither a diagnostic nor prognostic for liver disease – where ALT takes center stage – so a laboratory measurement error is deemed acceptable as long as its magnitude is within the analytical goal (total allowable error).

Have I ever used sigma as a tool for risk management or financial management?

Absolutely not! This question highlights the bitter truth of how sigma is used in clinical laboratory practice – but that's not its true purpose. The metric should act as a whistleblower for a specific analyte's performance quality. For example, if I discover that sigma for my potassium is 3.2, I know I need to search for the root cause of its below-par performance. Three key areas I will focus on are: i) my analytical goal, ii) my inaccuracy, or bias, and iii) my imprecision, or standard deviation. Once I've identified the cause of the low score, I can implement a set of QC rules – for instance, Westgard rules – to improve the performance of that particular analyte. Selecting and implementing appropriate QC rules based on the Ped (probability of error detection) and Pfr (probability of false rejection) paves the way to improving sigma… but at what cost?

The Westgard rules work on numbers (of QC rules, of QC runs, of QC failures…). When I try to fit these numbers into the science of risk management, I encounter a discrepancy – quality controls do not equal patient samples. Westgard sigma science focuses on QC; nowhere do patient results play a role. This prompts a question of my own: How can a lab claim to have improved its quality based on QC tools if it hasn't taken into account medically unreliable results? Any tool whose aim is effective risk management must fit patient results into the puzzle.

And what of financial calculations? In practice, sigma's value proposition is limited to quality improvement. The financial aspect of analytical process (in

terms of cost incurred in QC reruns, calibrations, reagents and consumables, manpower, and even patient result recall costs in the event of QC failure) has been neither included nor explored in current sigma-oriented quality practice. As a result, the field as a whole is still in need of a process improvement tool that offers the golden trio: quality management, risk management, and financial management.

Is sigma a mere publicity stunt?

My one-word answer to this question is "sigma-phobia."

Many laboratories experiment with sigma as an intriguing new "toy" – leading to a host of publications. But when it comes to the hardcore challenge of fully bringing sigma into the gamut of quality management systems, many professionals are hampered by worries about whether ISO 15189 has a place for sigma in quality management.

Many labs wrongly assume that, under ISO 15189:2012, sigma has no place in analytical processes. But look closer – the standard reads, "The laboratory shall design quality control procedures that verify the attainment of the intended quality of results (1)." To benefit clinical labs, the Clinical Laboratory Standards Institute has published their C24 guideline on Statistical Quality Control for Quantitative Measurement Procedures, which provides an evidence-based approach to adopting and implementing sigma metrics in quality practice. Organizations like these are paving the way for clinical laboratories to move toward stronger quality management processes.

The need of the hour is for labs to shed their sigma-phobia and move toward internal quality control practices aimed at maximizing patient safety and customer satisfaction. So I leave you with one final question: are you ready for sigma?

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Algorithmic Assistance

By working with each other – and with carefully designed algorithms – we can improve patient outcomes

By Chaith Kondragunta

AIRA Matrix is a company that builds applications for the life sciences industry. I say life sciences because we focus on two broad aspects of pathology – the pharmaceutical drug discovery space and the medical diagnostic space. For both, we develop deep learning algorithms that analyze pathology samples, automate work processes, and help increase laboratories' workflow efficiency.

Higher accuracy is crucial in laboratory processes that aid critical decision-making – for instance, in discovery pathology or oncopathology. Our deep learning-based algorithms function as more objective and accurate quantitative tools in such applications. In other instances, such as in preclinical toxicology studies, labs may need to improve turnaround times. We have solutions that help reduce the resource requirement for such tasks – which currently take days – to minutes. With our solutions, pathologists have the advantage of increasing accuracy or speed and, quite often, both.

One final hurdle for labs: healthcare costs are growing and pathologists are under constant pressure to reduce costs. Not all tasks are cost-effective when performed by a human pathologist – and we feel artificial intelligence (AI) and automation can help in these instances.

Aiding the big decisions

In addition to solutions that improve the speed and accuracy of diagnosis, we have initiatives underway to aid development of novel prognostic and predictive markers. Our vision is solutions that help pathologists practice precision diagnostics to aid disease stratification, patient risk stratification, and treatment selection. To this end, we are developing predictive and prognostic algorithms in collaboration with a number of research partners and hospital systems. Our goal is to reach a point where we can help caregivers confidently conclude, "This is the patient's personalized therapy recommendation based on their condition, the progress of the disease, and the outcomes seen in patients with similar characteristics."

Consider prostate cancer; one of the first steps in grading the disease is Gleason scoring – which, despite its ubiquity, is not a perfectly applied system. When used by a single pathologist, its accuracy is sometimes lacking; when used by multiple pathologists, Gleason scoring is subject to interobserver variability. In response, we have developed tools that can help score the disease more objectively. Further, important prognostic parameters like tumor volume are currently eyeball assessments. To overcome this shortcoming, our tools offer accuracy and reproducibility, so that every pathologist who looks at the model will have the same objective information to assist their decision-making. Ultimately, this will lead us to the point where we can make predictions about the course of a patient's disease and suggest a treatment approach based on a consensus between the pathologists – and the algorithms.

A platform-based service model

We recognize the complexity of these initiatives and have adopted a platform-based approach to increase the chances of success. Our approach allows us to develop custom solutions faster and more efficiently based on users' needs. We analyze data, respond to the results of analyses, and receive feedback from our users that lets us further improve the platform. Customizability and responsiveness aren't the only reasons we chose a platform-based strategy; another advantage is the ease of collaboration within and across disciplines. Caregivers and pathologists work on complex, often multisystem problems and deal with multimodal data – having a platform for collaboration helps break down silos and facilitates comprehensive solutions.

We are doing exciting work on improving patient outcomes in oncology – primarily in prostate and lung carcinoma. In lung carcinoma, we can analyze transbronchial aspirates and provide assessments in minutes. In current practice, oncologists and pathologists often work separately, need multiple aspirate-gathering attempts, and the overall turnaround time can be a few days! Our solution makes it possible for oncologists and pathologists to work together in real time as procedures are performed on patients. When the oncologist, pathologist, and algorithms are in sync, diagnosis and treatment selection happen faster – with better patient outcomes.

To make a meaningful difference in the diagnostic process, we have adopted the approach of taking what has been developed in conventional pathology – which is often the gold standard, but invasive – and make it multimodal by incorporating technologies such as radiology or genomics. This lets us create meaningful solutions that make a difference to patients. For this approach to be successful, we seek to partner with leading institutions worldwide. With these collaborations across laboratories, clinics, and industry, we aim to create diagnostic solutions that are less invasive, more accurate, and provide better outcomes than current practices.

Chaith Kondragunta is CEO of AIRA Matrix, Mumbai, India.

NextGen

Research advances
New technologies
Future practice

Preventive Genomics in the Clinic

What do preventive genomics clinics mean for patients?

By Luke Turner

Bethany Zettler

Since the turn of the millennium, we have made great progress in understanding how hereditary differences in DNA impact an individual's risk of issues such as cancer, cardiovascular disease, and diabetes. Today, thanks to the recent rise in direct-to-consumer (DTC) genetic testing, it has never been easier to access your own genetic information. It is estimated that, by 2021, 100 million people will have used a DTC genetic test (1), setting the market on track to be worth US$6.36 billion by 2028 (2). But as the number of people who want to discover their own genome increases, so does the need to educate consumers about the implications of their results. This is something that two health systems in Boston are now aiming to address with the introduction of their own preventive gene sequencing clinics.

Brigham and Women's Hospital's Preventive Genomics Clinic provides comprehensive genome sequencing, interpretation, and risk reporting to healthy adults and children. "We discovered that 15–20 percent of apparently healthy people have a strong genetic risk factor for disease – and nearly everyone carries recessive traits that could lead to serious disease in children," says Bethany Zettler, Genetic Counselor and Project Manager. "Preventive genomics is an important milestone in shifting medicine from a reactive, treatment-based model to one where illness can be prevented." More recently, Massachusetts General Hospital (MGH) launched their own Preventive Genomics Clinic, which brings together genetic counselors, clinical geneticists, and physicians to offer personalized testing and treatment plans based on genomic interpretation.

"Despite a growing interest from MGH patients in medical genetics, there were several key questions for us to first consider," says Renée Pelletier, a Genetic Counselor at MGH. "Which tests are most appropriate and clinically valid? What are the implications of genetic testing for disability and life insurance? How do we best craft individualized care plans? And which patients will benefit most from genetic testing?" Although genetic information certainly provides another tool in the physician's armory, the best way to distribute genetic information is less clear. "Some people advocate for a direct-to-consumer model, but others would prefer a 'consumer-initiated, physician-mediated' approach or even a traditional clinical model," explains Zettler. "Like anything in medicine, it is important to have a range of valid options; what is convenient for one person may be inaccessible for another."

But just how accessible are these options for consumers? "In many cases at MGH, we work with patients' insurance companies or commercial testing companies so that the test is covered at minimal or no cost to the patient,"

Renée Pelletier

says Pelletier. "We have both genetic counselors and a dedicated genetic testing assistant to help patients navigate the testing options and costs associated." However, when there are no symptoms or family history of disease, genetic testing is not currently the standard of care – and most insurance companies won't cover the service.

"Genetic sequencing offers clear potential for precision medicine."

Genetic tests can cost as little as $50 or as much as $3,000 – and, for those who cannot afford to shell out, the only option may be to participate in research projects. "Health inequity is a nefarious problem across the entire medical system – and genomics is no different," says Zettler. "Genomes2People is one of our research studies that strives to make genetic testing more accessible to historically underrepresented populations. For example, we recently began the first effort to provide genetic risk information to a large cohort of African Americans in the Jackson Heart Study." MGH offers interested patients the opportunity to participate in nationwide programs such as AllofUs, an NIH-funded initiative to enroll and ultimately sequence at least one million Americans. Although the program is committed to returning genetic data to those who are interested, it can take years to receive sequencing results through this route.

It's clear that our DNA can provide insightful and potentially crucial health information – and the rise of over-the-counter tests has triggered a surge of interest and engagement in personal genetics. "The issue is that many of these tests are not held to the same standard as clinical laboratories to ensure that they are accurate and appropriately addressing the needs of the patient," explains Pelletier. "What's more, the results of these tests are typically not integrated into the healthcare system, leaving patients to understand, communicate, and act upon their results alone." This is where preventive genomics clinics help patients to navigate next steps based on their genetic information, including an in-depth review of results by a clinical laboratory geneticist, genetic counseling, ordering additional testing, and personalized clinical management plans.

One of the classic arguments against DTC testing is that it can cause unnecessary worry for patients who discover potentially harmful genetic risk factors. The Genomes2People research program at Brigham and Women's Hospital has studied the behavioral and economic outcomes of genome sequencing, finding that even those who receive high-risk information don't experience psychological distress or incur significantly higher healthcare costs. "Genetic sequencing offers clear potential for precision medicine," says Zettler. "For example, take cancer or high cholesterol. Someone with a genetic risk factor for colon cancer could have yearly screening colonoscopies to remove polyps, which is 10 times more frequent than population guidelines. Another person might have a genetic risk factor for high cholesterol and start a statin in their 20s to prevent early-onset heart disease."

As the popularity of DTC testing and the prevalence of preventive genomics clinics grows, genetic information is becoming another tool that patients and doctors can use to make personalized predictions about disease risk. Despite early fears over cost, health equality, and accuracy, it seems clear that the future of precision medicine lies in a more proactive approach to healthcare.

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The Other Epidemic

Medical students face high levels of stress and burnout at the best of times – and the pandemic only exacerbates the problem

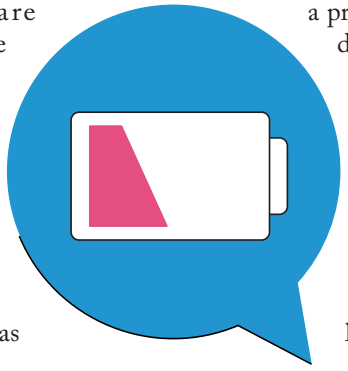
By Ritcha Saxena

Burnout – it's a natural part of medical student life, right?

Unfortunately, that's the mindset of many doctors (and medical students) – and it's only recently that the devastating long-term effects of burnout have come to our attention. The problem is compounded by the fact that many people may not fully understand what burnout is, how it originates, or what can be done to mitigate it.

Slow burn

Burnout often arises from a prolonged, nerve-wracking setting. Medical students are particularly susceptible because of their often-overwhelming academic workload, the pressure to learn vast amounts of information within a limited period, and their intense feelings of obligation to medicine as future physicians.



Students often describe feeling disconnected and lacking the impetus to learn. They walk through life drained, lackadaisical, and emotionally worn out. Some feel inept; others depersonalized. Among the challenges medical students face, burnout is a key concern because of its association with diminished life satisfaction, thoughts of dropping out, and even suicidal ideation. Its negative impacts encompass students' mental health, academic performance, sleep quality, learning capacity, and knowledge and job attainment. Worse yet, it's a vicious cycle; these negative effects lead to ever higher amounts of stress and burnout. Even before COVID-19 struck, medical students were tackling their own epidemic. A meta-analysis in 2016 postulated that 27.2 percent of medical students fit a probable diagnosis of major depressive disorder and a monumental 11.1 percent confessed to suicidal ideation (1). Reports by the American Foundation for Suicide Prevention show that medical students are nearly three times more likely than their peers in other career paths to commit suicide (1,2,3). They are also more likely to succumb to substance abuse; one study found that almost 33 percent of medical students admitted to alcohol abuse, compared with 16 percent of their non-medical peers (4) – and alcohol consumption in medical students is also correlated with higher levels of stress, anxiety, and pressure (5,6).

"Many people may not fully understand what burnout is, how it originates, or what can be done to mitigate it."

Psychological distress advances chronologically. Studies demonstrate that, at the time of enrollment, medical students have similar – if not better – psychological health to their peers (3,7); by the end of their second year, medical students display considerably more precursors to anxiety and burnout (8). Further studies indicate that mental health deteriorates after students

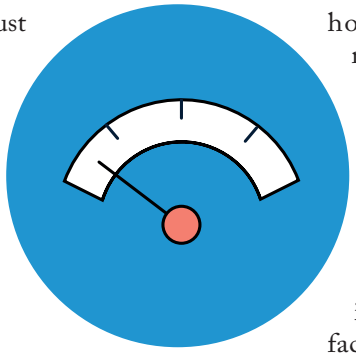
start medical school and continues deteriorating throughout school (9,10). Nearly 50 percent of students have experienced burnout by the time they prepare to enter residency (11). Especially given that these statistics only reference the final stages of burnout, it's clear that the number of medical students suffering its effects is distressingly high.

Pandemic pile-on

COVID-19 is influencing not only students' socioeconomic lives, but also their psychological and mental wellbeing, worsening existing levels of burnout. Higher emotional stress in these difficult times also increases the risk of depression. Even now, the ongoing march of the pandemic brings to the forefront the importance of prioritizing health and wellbeing – particularly for medical students, who face not only changes to their lives, but also a dramatic shift in the medical education landscape.

Tried and tested methods of instruction and assessment, though still useful and relevant, are no longer practical – so they are gradually giving way to new and innovative online teaching methods. Although COVID-19 has brought with it upset and upheaval, it also carries a silver lining: medical curricula, teaching, learning, and assessment methodologies have been forced into the 21st century – and, with them, approaches to the physical and psychological health of staff and students.

With students now pulled out of classrooms to stop the spread of the disease and studying from home instead, the loss of both classroom and in-person cohort experiences has highlighted new challenges. Struggles previously contained at school have been unmasked, underscored by the continued expectations of a demanding medical school curriculum. And, as unexpected changes continue to arise, students must quickly learn adaptability, endurance, and mental resilience – and they need our help. Everyone involved in medical education must foster wellness and stress management for their students. The new stressors brought on by the pandemic are diverse and influential – but, fortunately, so are the potential coping strategies.



Finding the right response

The first step in preventing or ameliorating a burnout situation and emotional stress is to recognize emotional stressors and acknowledge our responses to them. People often tend to feel anxious, embarrassed, or guilty when they encounter strong feelings, such as despair or resentment – and, as a result, they try to hide or suppress those feelings. Unfortunately, a buildup of negative emotions can lead to irritability, agitation, apathy, and emotional fatigue – key signs of burnout. Accepting and reflecting on these feelings – and receiving assistance from others – can be essential in coping. And that's why all staff and students can benefit from fundamental strategies, such as training sessions on how to recognize and reduce signs of distress. It's also worth removing mystery and stigma from professional assistance, such as cognitive behavioral therapy. But beyond that, what are the main issues medical students face – and how can they begin to tackle them?

A new environment

The challenges associated with shifting from school (an ordered environment) to home (almost entirely unordered) can place students under pressure.

Sleep deprivation, detachment, self-criticism, and emotional overload are all likely to arise when students must act as their own peers, tutors, and support systems – and these factors have a proven association with burnout. Structuring and maintaining a regular schedule can help re-establish a sense of normalcy in everyday life. This includes coordinating a routine sleep-wake routine, studying at regular hours, and setting a schedule for meals, recreation, and other activities.

When spending the majority of one's time between the same four walls, it's easy to forget about physical needs: sleep, proper diet, exercise, relaxation, and social activities. It's also easy to succumb to the temptations of unhealthy coping strategies, such as drinking or drug use. Not only do these strategies carry health risks of their own, but they are also counterproductive, often camouflaging dangerous levels of stress, depression, or anxiety that require treatment.

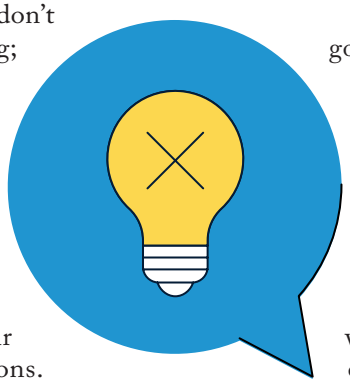
Setting healthy limits

To come to terms with the fact that life as we know it has changed, people need to spend time considering new challenges and brainstorming ideas to overcome them. This thought process can help them acclimatize to the "new normal."

Above all else, students must understand the need for self-care. It may seem as though everyone else is taking on additional projects and activities with the free time they suddenly have – but time doesn't exist purely to be filled. It's important to resist extra commitments rather than risk crumbling under pressure. Excessive demands on self – and the self-criticism resulting from failure to fulfil a commitment – will only hurt, not help. Not every experiment will succeed; not every exam will yield a passing grade; not every new hobby will become a lifelong pursuit. We must acknowledge that we will sometimes fail despite our best efforts – and we must be ready to forgive ourselves and move on.

Lack of in-person contact

Studying without face-to-face faculty or peer support is tough – but traditional study techniques can be adapted to suit our new, socially distanced world. Learning from home does not mean learning in isolation. Why not work with peers via video call or seek out other students on social media? These approaches don't just support learning; they also help people cope with stress. Social media, for instance, allows users to feel connected to one another while at the same time expanding their educational horizons. Peer support groups, even online, can help students manage conflict, improve self-perception, and cultivate empathy. Student-led mentorship programs provide opportunities to communicate and examine feelings. Shared contemplation highlights the fact that no one is alone in their difficulties and may help students discover how their peers solved similar problems – and, when one student's past struggles help another succeed, both experience a self-esteem boost.



Even when face-to-face contact is impossible, human connection remains a vital part of our lives. Sharing our challenges, accomplishments, and the small joys of everyday life can be an effective stress reliever and a powerful weapon in our arsenal against burnout.

Modeling good health

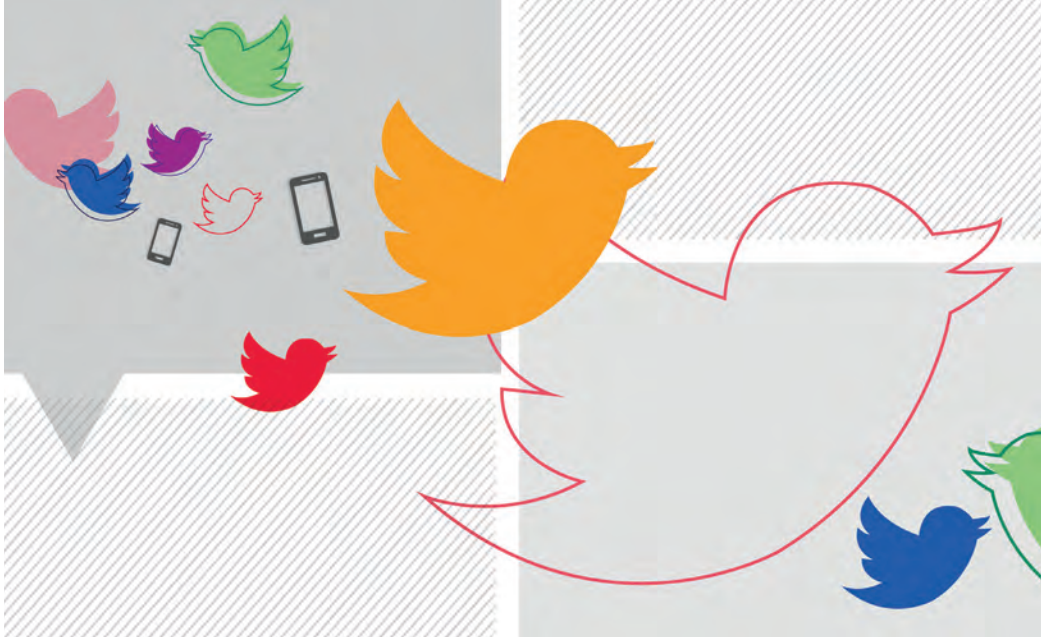
As educators, we can (and must) be good role models for self-care and empathy. We must engage with our students online and offer support where possible, not just in academics, but also career counseling and life coaching. But, above all, we must look after our own wellbeing – and ensure that our students see us "putting on our own oxygen masks" as well.

"Even when face-to-face contact is impossible, human connection remains a vital part of our lives."

These measures can go a long way toward alleviating medical students' stress and reducing burnout. In the long run, they may even enhance the quality of the medical school curriculum by fostering conscientious care and societal engagement among students, leading to a healthier educational environment. Ultimately, I hope we see a new generation of doctors who understand the full picture of health and wellness – both for their students and for themselves.

Ritcha Saxena is Professor of Pathology and Course Director at Medical University of the Americas, Charlestown, Nevis, West Indies.

References available online at: tp.txp.to/burnout



So Much for "Antisocial"

The rise of the social pathology applicant

By Emily Towery, Philip Hurst, Matthew Luo, Brett Kurpiel, and Kamran Mirza

For most students starting medical school, pathology is an unknown – and, even after their introduction to the subject, they view pathologists as "behind the scenes" and fail to see the true beauty of the discipline. Worse yet, despite years of work to combat popular stereotypes, pathologists are still often viewed as solitary, antisocial, basement-dwelling hermits whose best friends are microscopes and glass slides.

These clichés are obviously harmful – perhaps evidenced by the low (and decreasing) numbers of candidates applying for residencies in pathology – but is there a way to fight back against them? Incoming pathology residents Emily Towery, Philip Hurst, Matthew Luo, and Brett Kurpiel think so. Along with mentor Kamran Mirza, they point to social media – and specifically Twitter – as a light at the end of the stereotype tunnel.

The pathology social media community, popularly known as #PathTwitter, has been around for many years, pursuing initiatives as diverse as online consultations, tweet-based journal clubs, live conference reporting, medical school assignments, and even humorous art competitions. How do these offerings help attract medical students to pathology? Not only do they provide access to a friendly and welcoming community of pathologists and laboratory medicine professionals, but they also highlight valuable educational resources and showcase the most fascinating parts of a discipline that deserves more credit than it gets. And, as the world moves increasingly online in response to an ongoing pandemic, such resources will be ever more valuable.

Does Twitter work? The numbers say yes – with 60 percent of pathology residency applicants stating that they felt their social media presence had helped their applications, 86.7 percent recommending social media to upcoming applicants, and 100 percent expressing a desire to see their own programs develop a social media presence. Faculty were not far behind, with 60 percent using social media professionally and, of those, 61 percent using social media to engage medical students. In any interview process, it's important to demonstrate enthusiasm, professionalism, and collegiality – and Twitter provides residency applicants with one more platform on which to do so. The benefits of social media are clear, but – as with any public platform – it's up to users to monitor their behavior and ensure that the picture they paint of themselves is the one they want faculty members to see.

Not everyone will want to engage in social media – but its popularity is growing. From #Path2Path (a Twitter-based introduction to pathology for medical students) to #VirtualPathMatch (a way for newly minted pathologists to celebrate together during a pandemic), social media carries a lot of promise for laboratorians at every career stage – so why not take the plunge and put an end to outdated "antisocial pathologist" stereotypes!

Emily Towery is an incoming pathology resident at Brigham and Women's Hospital, Boston, Massachusetts, USA. She is on Twitter at @pathnoob.
Philip Hurst is an incoming pathology resident at the Mayo Clinic, Rochester, Minnesota, USA. He is on Twitter at @pathophil.
Matthew Luo is an incoming pathology resident at the University of Utah, Salt Lake City, Utah, USA. He is on Twitter at @Mattcrophage.
Brett Kurpiel is an incoming pathology resident at the University of Virginia, Charlottesville, Virginia, USA. He is on Twitter at @basophil_brett.
Kamran Mirza is Associate Professor and Vice-Chair of Education at Loyola University Chicago Stritch School of Medicine, Maywood, Illinois, USA. He is on Twitter at @kmirza.

Read the full article online at: tp.txp.to/pathtwitter

The Rise and Rise of Fine Needle Aspiration Biopsy

Raising nodule diagnostic standards for patients in Puerto Rico

An interview with Guillermo Villarmarzo-García

How did you come to work on fine needle aspiration biopsy?

During my pathology residency at the University of Puerto Rico (UPR), my main interests lay in gynecological pathology and cytopathology. After completing my training, I became assistant professor at UPR and, four years later, I joined the school of cytotechnology at the School of Allied Health Professions. At the time, fine needle aspiration (FNA) was starting to gain momentum in the US – so, after attending a meeting of the American Society of Cytology, I became involved in developing FNA courses and workshops in Puerto Rico. We started a FNA program with physicians from the University District Hospital and San Juan City Hospital, which lasted several years, and we developed a large database of cases showing the correlation between FNA diagnoses and surgical results.

Before the introduction and refinement of FNA, what challenges did pathologists (and patients) face in thyroid nodule diagnosis?

Before FNA, it was difficult to deal with a nodule because, until the patient underwent surgery, the diagnosis was unknown. Many thyroid surgeries could have been avoided with a diagnostic tool that could be administered prior to surgery. In fact, thyroid surgery halved once FNA became established as a diagnostic procedure for nodules – because only the cases that really required surgery went ahead. As much as half of the world's population has a palpable or non-palpable thyroid nodule, so FNA is a valuable tool.

FNA was started in a systematic way in UPR's pathology department, which allowed us to develop our expertise in the procedure. For several years, it was performed by palpating the nodules through insertion and aspiration of the needle without any guidance other than the palpation. Ultrasound later became the most important tool in thyroid FNA, guiding the procedure in real time with visualization of the nodule. It has also helped us develop several ultrasound criteria for separating the chosen nodule to be sampled.

How did HRP Labs establish its FNA clinics and evolve into the medical faculty it is now?

Once we had sufficient experience with FNA, we incorporated it into our clinics at Hato Rey Pathology Associates, Inc., to serve the medical community of Puerto Rico. Starting out, I performed all FNA biopsies until we brought in new associates. Ultrasound eventually became part of the standard procedure and now all FNAs are performed under guidance from the ultrasound. We now have several sites in nine locations on the island – including Ponce, Arecibo, Dorado, Humacao, and San Juan – where HRP Labs staff perform FNA.

How many FNA procedures has HRP Labs performed?

Around 6,000 FNAs are performed every year at HRP Labs; of those, 98 percent are on the thyroid and the remainder on sites such as breast, lymph nodes, salivary glands, and soft tissue. Besides thyroid nodule diagnosis, FNA has become extremely helpful in diagnosing lymph nodes; together with ancillary studies, it allows us to differentiate patients with reactive lymph nodes from those with a lymphoproliferative disorder. This is important for identifying metastasis and finding the primary site of the cancer. FNA's minimally invasive nature enables us to obtain tissue without needing to perform surgery for the sole purpose of diagnosis.

What is the key advantage of FNA over other biopsy methods in thyroid nodule diagnosis?

The advantage of FNA is its capacity to establish a diagnosis with minimal invasiveness – allowing the attending physician to plan the next step in treatment based on the patient's diagnosis.

What does the future hold for FNA biopsy in pathology and laboratory medicine?

The use of FNA is ever-growing and, with more organs being targeted, it is becoming an essential part of the management of not only thyroid nodules, but also salivary gland lesions, breast nodules, and soft tissue tumors. This will decrease the need for major surgical diagnostic procedures – making FNA an essential part of pathology and cytopathology for many years to come.

Guillermo Villarmarzo-García is Co-Founder and President of HRP Labs and Director of Fine Needle Aspiration Clinics, San Juan, Puerto Rico.

RECOMMENDED

Olaparib (LYNPARZA) is the only PARPi included in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) as a Category 1† recommended option for men with HRRm mCRPC adenocarcinoma who have progressed on prior treatment with enzalutamide and/or abiraterone, regardless of prior docetaxel therapy.[6]

†Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

INDICATION

LYNPARZA is a poly (ADP-ribose) polymerase (PARP) inhibitor indicated for the treatment of adult patients with deleterious or suspected deleterious germline or somatic homologous recombination repair (HRR) gene-mutated metastatic castration-resistant prostate cancer (mCRPC) who have progressed following prior treatment with enzalutamide or abiraterone. Select patients for therapy based on an FDA-approved companion diagnostic for LYNPARZA.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

There are no contraindications for LYNPARZA.

WARNINGS AND PRECAUTIONS

Myelodysplastic Syndrome/Acute Myeloid Leukemia (MDS/AML): Occurred in <1.5% of patients exposed to LYNPARZA monotherapy, and the majority of events had a fatal outcome. The duration of therapy in patients who developed secondary MDS/AML varied from <6 months to >2 years. All of these patients had previous chemotherapy with platinum agents and/or other DNA-damaging agents, including radiotherapy, and some also had a history of more than one primary malignancy or of bone marrow dysplasia.

Do not start LYNPARZA until patients have recovered from hematological toxicity caused by previous chemotherapy (≤Grade 1). Monitor complete blood count for cytopenia at baseline and monthly thereafter for clinically significant changes during treatment. For prolonged hematological toxicities, interrupt LYNPARZA and monitor blood count weekly until recovery.

If the levels have not recovered to Grade 1 or less after 4 weeks, refer the patient to a hematologist for further investigations, including bone marrow analysis and blood sample for cytogenetics. Discontinue LYNPARZA if MDS/AML is confirmed.

Pneumonitis: Occurred in <1% of patients exposed to LYNPARZA, and some cases were fatal. If patients present with new or worsening respiratory symptoms such as dyspnea, cough, and fever, or a radiological abnormality occurs, interrupt LYNPARZA treatment and initiate prompt investigation. Discontinue LYNPARZA if pneumonitis is confirmed and treat patient appropriately.

Embryo-Fetal Toxicity: Based on its mechanism of action and findings in animals, LYNPARZA can cause fetal harm. A pregnancy test is recommended for females of reproductive potential prior to initiating treatment.

Females

Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception during treatment and for 6 months following the last dose.

Males

Advise male patients with female partners of reproductive potential or who are pregnant to use effective contraception during treatment and for 3 months following the last dose of LYNPARZA and to not donate sperm during this time.

Venous Thromboembolic Events: Including pulmonary embolism, occurred in 7% of patients with metastatic castration-resistant prostate cancer who received LYNPARZA plus androgen deprivation therapy (ADT) compared to 3.1% of patients receiving enzalutamide or abiraterone plus ADT in the PROfound study. Patients receiving LYNPARZA and ADT had a 6% incidence of pulmonary embolism compared to 0.8% of patients treated with ADT plus either enzalutamide or abiraterone. Monitor patients for signs and symptoms of venous thrombosis and pulmonary embolism, and treat as medically appropriate, which may include long-term anticoagulation as clinically indicated.

ADVERSE REACTIONS—HRR Gene-mutated Metastatic Castration-Resistant Prostate Cancer

Most common adverse reactions (Grades 1-4) in ≥10% of patients in clinical trials of LYNPARZA for **PROfound** were: anemia (46%), fatigue (including asthenia) (41%), nausea (41%), decreased appetite (30%), diarrhea (21%), vomiting (18%), thrombocytopenia (12%), cough (11%), and dyspnea (10%).

Most common laboratory abnormalities (Grades 1-4) in ≥25% of patients in clinical trials of LYNPARZA for **PROfound** were: decrease in hemoglobin (98%), decrease in lymphocytes (62%), decrease in leukocytes (53%), and decrease in absolute neutrophil count (34%).

DRUG INTERACTIONS

Anticancer Agents: Clinical studies of LYNPARZA with other myelosuppressive anticancer agents, including DNA-damaging agents, indicate a potentiation and prolongation of myelosuppressive toxicity.

CYP3A Inhibitors: Avoid coadministration of strong or moderate CYP3A inhibitors when using LYNPARZA. If a strong or moderate CYP3A inhibitor must be coadministered, reduce the dose of LYNPARZA. Advise patients to avoid grapefruit, grapefruit juice, Seville oranges, and Seville orange juice during LYNPARZA treatment.

CYP3A Inducers: Avoid coadministration of strong or moderate CYP3A inducers when using LYNPARZA.

USE IN SPECIFIC POPULATIONS

Lactation: No data are available regarding the presence of olaparib in human milk, its effects on the breastfed infant or on milk production. Because of the potential for serious adverse reactions in the breastfed infant, advise a lactating

Among men with **BRCA1/2- or ATM-mutated mCRPC following progression on enzalutamide or abiraterone**

LYNPARZA more than doubled median rPFS vs retreatment with enzalutamide or abiraterone[1,7]

PROfound: A PHASE 3 trial of a PARPi in mCRPC[1,7]

TRIAL DESIGN[1,7]

- The PROfound trial was a prospective, multicenter, randomized, open-label, phase 3 trial of LYNPARZA in patients with HRRm mCRPC
- Key eligibility criteria: Metastatic castration-resistant prostate cancer; progression on prior enzalutamide or abiraterone treatment for metastatic prostate cancer and/or CRPC; a tumor mutation in at least 1 of 15 genes* involved in the HRR pathway
- Patients were divided by mutation: ***BRCA1/2* or *ATM* gene mutation (Cohort A [n=245][†‡]) and other HRR gene mutations (Cohort B [n=142][‡§])**, and randomization was stratified by prior receipt of taxane chemotherapy and presence of measurable disease by RECIST 1.1
- Each cohort was randomized 2:1 to receive LYNPARZA (tablets, 300 mg per dose, twice daily) or an active comparator (retreatment with investigator's choice of enzalutamide or abiraterone)

*HRR gene mutations (*BRCA1*, *BRCA2*, *ATM*, *BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *PPP2R2A*, *RAD51B*, *RAD51C*, *RAD51D*, and/or *RAD54L*) were identified by tissue-based testing using the Foundation Medicine FoundationOne® clinical trial HRR assay performed at a central laboratory. No patients were enrolled who had mutations in 2 of the 15 prespecified HRR genes: *FANCL* and *RAD51C*.

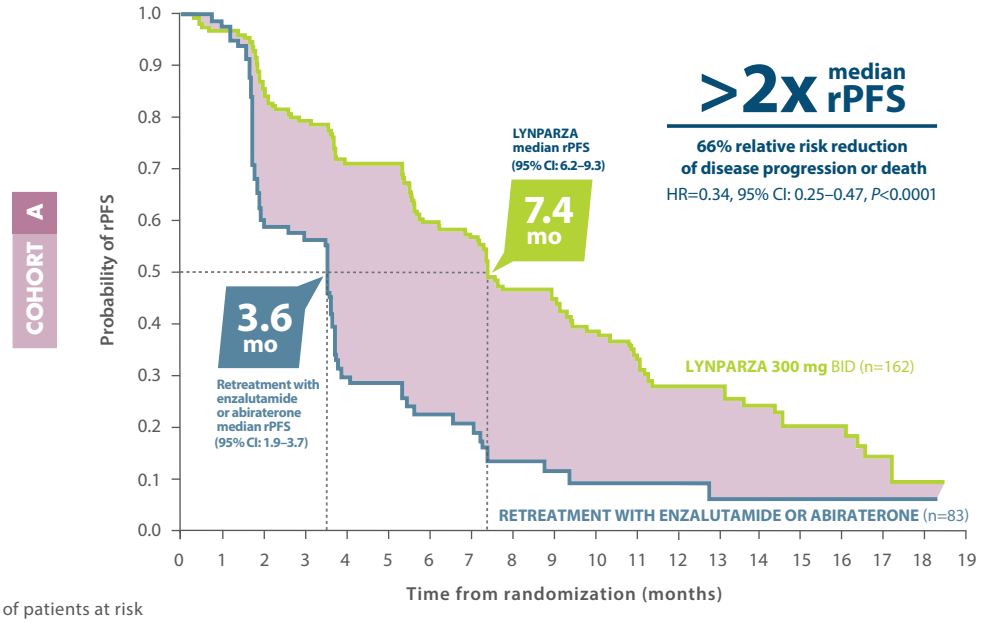
†Patients with co-mutations (*BRCA1*, *BRCA2*, or *ATM* plus a Cohort B gene) were assigned to Cohort A.

‡All patients received a GnRH analog or had prior bilateral orchiectomy.

§*BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *PPP2R2A*, *RAD51B*, *RAD51C*, *RAD51D*, or *RAD54L*.

Although patients with *PPP2R2A* gene mutations were enrolled in the trial, LYNPARZA is not indicated for the treatment of patients with this gene mutation due to unfavorable risk-benefit ratio.

PRIMARY ENDPOINT: RADIOLOGICAL PROGRESSION-FREE SURVIVAL (rPFS)[1,7]



>2x median rPFS

66% relative risk reduction of disease progression or death

HR=0.34, 95% CI: 0.25–0.47, *P*<0.0001

Number of patients at risk

LYNPARZA	**162**	**149**	**126**	**116**	**102**	**101**	**82**	**77**	**56**	**53**	**42**	**37**	**26**	**24**	**18**	**11**	**11**	**3**	**2**	**0**
Retreatment with enzalutamide or abiraterone	83	79	47	44	22	20	13	12	7	6	3	3	3	2	2	1	1	1	1	0

- rPFS in Cohort A was determined by BICR using RECIST version 1.1 and PCWG3 (bone) criteria
- Consistent results were observed in exploratory analyses of rPFS:
  - For patients who received or did not receive prior taxane therapy
  - For those with germline *BRCA* mutations identified using the Myriad BRACAnalysis CDx assay compared with those with *BRCA* mutations identified using the Foundation Medicine F1CDx assay

The PROfound study included additional secondary endpoints not present here.

Explore the data, including secondary endpoints, and testing recommendations at LYNPARZAprchcp.com

From *The New England Journal of Medicine*, de Bono J, Mateo J, Fizazi K, et al. Olaparib for metastatic castration-resistant prostate cancer. *N Engl J Med*. 2020;382(22):2091-2102.

IMPORTANT SAFETY INFORMATION (CONT'D)

USE IN SPECIFIC POPULATIONS (CONT'D)

woman not to breastfeed during treatment with LYNPARZA and for 1 month after receiving the final dose.

Pediatric Use: The safety and efficacy of LYNPARZA have not been established in pediatric patients.

Hepatic Impairment: No adjustment to the starting dose is required in patients with mild or moderate hepatic impairment (Child-Pugh classification A and B). There are no data in patients with severe hepatic impairment (Child-Pugh classification C).

Renal Impairment: No dosage modification is recommended in patients with mild renal impairment (CLcr 51-80 mL/min estimated by Cockcroft-Gault). In patients with moderate renal impairment (CLcr 31-50 mL/min), reduce the dose of LYNPARZA to 200 mg twice daily. There are no data in patients with severe renal impairment or end-stage renal disease (CLcr ≤30 mL/min).

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

Please see accompanying Brief Summary of Prescribing Information on the following pages.

BICR=blinded independent central review; BID=twice a day; CI=confidence interval; CRPC=castration-resistant prostate cancer; GnRH=gonadotropin-releasing hormone; HR=hazard ratio; HRR=homologous recombination repair; HRRm=homologous recombination repair gene–mutated; mCRPC=metastatic castration-resistant prostate cancer; NCCN=National Comprehensive Cancer Network; PARPi=poly (ADP-ribose) polymerase inhibitor; PCWG3=Prostate Cancer Working Group 3; RECIST=Response Evaluation Criteria in Solid Tumors; rPFS=radiological progression-free survival.

References: 1. LYNPARZA® (olaparib) [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2020. **2.** Zejula® (niraparib) [prescribing information]. Waltham, MA: TESARO, Inc.; 2020. **3.** Rubraca® (rucaparib) [prescribing information]. Boulder, CO: Clovis Oncology, Inc.; 2020. **4.** Talzenna® (talazoparib) [prescribing information]. New York, NY: Pfizer Inc.; 2020. **5.** Teo MY, Rathkopf DE, Kantoff P. Treatment of advanced prostate cancer. *Annu Rev Med.* 2019;70:479-499. **6.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Prostate Cancer V.2.2020. © National Comprehensive Cancer Network, Inc. 2020. All rights reserved. Accessed May 21, 2020. To view the most recent and complete version of the guideline, go online to NCCN.org. **7.** de Bono J, Mateo J, Fizazi K, et al. Olaparib for metastatic castration-resistant prostate cancer. *N Engl J Med.* 2020;382(22):2091-2102.

MERCK AstraZeneca

LYNPARZA® (olaparib) tablets, for oral use

Initial U.S. Approval: 2014

Brief Summary of Prescribing Information. For complete prescribing information consult official package insert.

INDICATIONS AND USAGE

HRR Gene-mutated Metastatic Castration-Resistant Prostate Cancer

Lynparza is indicated for the treatment of adult patients with deleterious or suspected deleterious germline or somatic homologous recombination repair (HRR) gene-mutated metastatic castration-resistant prostate cancer (mCRPC) who have progressed following prior treatment with enzalutamide or abiraterone. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza *[see Dosage and Administration (2.1) in the full Prescribing Information]*.

DOSAGE AND ADMINISTRATION

Patient Selection

Information on FDA-approved tests for the detection of genetic mutations is available at http://www.fda.gov/companiondiagnostics.

Select patients for treatment with Lynparza based on the presence of deleterious or suspected deleterious HRR gene mutations, including *BRCA* mutations, or genomic instability based on the indication, biomarker, and sample type (Table 1).

Table 1 Biomarker Testing for Patient Selection*

Indication	Biomarker	Sample type		
		Tumor	Blood	Plasma (ctDNA)
Germline or somatic HRR gene-mutated metastatic castration-resistant prostate cancer	*ATM*m, *BRCA1*m, *BRCA2*m, *BARD1*m, *BRIP1*m, *CDK12*m, *CHEK1*m, *CHEK2*m, *FANCL*m, *PALB2*m, *RAD51B*m, *RAD51C*m, *RAD51D*m, *RAD54L*m	X		
	g*BRCA1*m, g*BRCA2*m		X	
	*ATM*m, *BRCA1*m, *BRCA2*m			X

* Where testing fails or tissue sample is unavailable/insufficient, or when germline testing is negative, consider using an alternative test, if available.

Recommended Dosage

The recommended dosage of Lynparza is 300 mg taken orally twice daily, with or without food.

If a patient misses a dose of Lynparza, instruct patient to take their next dose at its scheduled time. Instruct patients to swallow tablets whole. Do not chew, crush, dissolve, or divide tablet.

HRR Gene-mutated Metastatic Castration-Resistant Prostate Cancer

Continue treatment until disease progression or unacceptable toxicity for:

- HRR gene-mutated metastatic castration-resistant prostate cancer

Patients receiving Lynparza for mCRPC should also receive a gonadotropin-releasing hormone (GnRH) analog concurrently or should have had bilateral orchiectomy.

Dosage Modifications for Adverse Reactions

To manage adverse reactions, consider interruption of treatment or dose reduction. The recommended dose reduction is 250 mg taken twice daily.

If a further dose reduction is required, then reduce to 200 mg taken twice daily.

Dosage Modifications for Concomitant Use with Strong or Moderate CYP3A Inhibitors

Avoid concomitant use of strong or moderate CYP3A inhibitors with Lynparza.

If concomitant use cannot be avoided, reduce Lynparza dosage to:

- 100 mg twice daily when used concomitantly with a strong CYP3A inhibitor.
- 150 mg twice daily when used concomitantly with a moderate CYP3A inhibitor.

After the inhibitor has been discontinued for 3 to 5 elimination half-lives, resume the Lynparza dose taken prior to initiating the CYP3A inhibitor *[see Drug Interactions (7.2) and Clinical Pharmacology (12.3) in the full Prescribing Information]*.

Dosage Modifications for Renal Impairment

Moderate Renal Impairment

In patients with moderate renal impairment (CLcr 31-50 mL/min), reduce the Lynparza dosage to 200 mg orally twice daily *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3) in the full Prescribing Information]*.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Myelodysplastic Syndrome/Acute Myeloid Leukemia

In clinical studies enrolling 2351 patients with various cancers who received Lynparza as a single agent *[see Adverse Reactions (6.1) in the full Prescribing Information]*, the incidence of Myelodysplastic Syndrome/Acute Myeloid Leukemia (MDS/AML) was <1.5% (28/2351) and the majority of events had a fatal outcome. Of these, 25/28 patients had a documented *BRCA* mutation, 2 patients had g*BRCA* wildtype and in 1 patient the *BRCA* mutation status was unknown. Additional cases of MDS/AML have been documented in patients treated with Lynparza in combination studies and in postmarketing reports. The duration of therapy with Lynparza in patients who developed secondary MDS/cancer-therapy related AML varied from <6 months to >2 years. All of these patients had received previous chemotherapy with platinum agents and/or other DNA damaging agents including radiotherapy. Some of these patients also had a history of more than one primary malignancy or of bone marrow dysplasia.

Do not start Lynparza until patients have recovered from hematological toxicity caused by previous chemotherapy (≤Grade 1). Monitor complete blood count for cytopenia at baseline and monthly thereafter for clinically significant changes during treatment. For prolonged hematological toxicities, interrupt Lynparza and monitor blood counts weekly until recovery. If the levels have not recovered to Grade 1 or less after 4 weeks, refer the patient to a hematologist for further investigations, including bone marrow analysis and blood sample for cytogenetics. If MDS/AML is confirmed, discontinue Lynparza.

Pneumonitis

In clinical studies enrolling 2351 patients with various cancers who received Lynparza as a single agent *[see Adverse Reactions (6.1) in the full Prescribing Information]*, the incidence of pneumonitis, including fatal cases, was <1% (20/2351). If patients present with new or worsening respiratory symptoms such as dyspnea, cough and fever, or a radiological abnormality occurs, interrupt Lynparza treatment and promptly assess the source of the symptoms. If pneumonitis is confirmed, discontinue Lynparza treatment and treat the patient appropriately.

Embryo-Fetal Toxicity

Lynparza can cause fetal harm when administered to a pregnant woman based on its mechanism of action and findings in animals. In an animal reproduction study, administration of olaparib to pregnant rats during the period of organogenesis caused teratogenicity and embryo-fetal toxicity at exposures below those in patients receiving the recommended human dose of 300 mg twice daily. Apprise pregnant women of the potential hazard to a fetus and the potential risk for loss of the pregnancy. Advise females of reproductive potential to use effective contraception during treatment and for 6 months following the last dose of Lynparza. Based on findings from genetic toxicity and animal reproduction studies, advise male patients with female partners of reproductive potential or who are pregnant to use effective contraception during treatment and for 3 months following the last dose of Lynparza *[see Use in Specific Populations (8.1, 8.3) in the full Prescribing Information]*.

Venous Thromboembolic Events

Venous thromboembolic events, including pulmonary embolism, occurred in 7% of patients with metastatic castration resistant prostate cancer who received Lynparza plus androgen deprivation therapy (ADT) compared to 3.1% of patients receiving enzalutamide or abiraterone plus ADT in the PROfound study. Patients receiving Lynparza and ADT had a 6% incidence of pulmonary embolism compared to 0.8% of patients treated with ADT plus either enzalutamide or abiraterone. Monitor patients for signs and symptoms of venous thrombosis and pulmonary embolism and treat as medically appropriate, which may include long-term anticoagulation as clinically indicated.

ADVERSE REACTIONS

The following adverse reactions are discussed elsewhere in the labeling:

- Myelodysplastic Syndrome/Acute Myeloid Leukemia *[see Warnings and Precautions (5.1) in the full Prescribing Information]*
- Pneumonitis *[see Warnings and Precautions (5.2) in the full Prescribing Information]*
- Venous Thromboembolic Events *[see Warnings and Precautions (5.4) in the full Prescribing Information]*

Clinical Trial 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.

The data described in the WARNINGS AND PRECAUTIONS reflect exposure to Lynparza as a single agent in 2351 patients; 1585 patients with exposure to 300 mg twice daily tablet dose including five controlled, randomized, trials (SOLO-1, SOLO-2, OlympiAD, POLO, and PROfound) and to 400 mg twice daily capsule dose in 766 patients in other trials that were pooled to conduct safety analyses. In these trials, 55% of patients were exposed for 6 months or longer and 31% were exposed for greater than one year in the Lynparza group.

In this pooled safety population, the most common adverse reactions in ≥10% of patients were nausea (60%), fatigue (55%), anemia (37%), vomiting (34%), diarrhea (25%), decreased appetite (23%), headache (16%), neutropenia (15%), dysgeusia (15%), cough (15%), dyspnea (14%), dizziness (12%), dyspepsia (12%), leukopenia (11%), thrombocytopenia (11%), and abdominal pain upper (10%).

HRR Gene-mutated Metastatic Castration-Resistant Prostate Cancer

PROfound

The safety of Lynparza as monotherapy was evaluated in patients with mCRPC and HRR gene mutations who have progressed following prior treatment with enzalutamide or abiraterone in PROfound *[see Clinical Studies (14.7) in the full Prescribing Information]*. This study was a randomized, open-label, multi-center study in which 386 patients received either Lynparza tablets 300 mg orally twice daily (n=256) or investigator's choice of enzalutamide or abiraterone acetate (n=130) until disease progression or unacceptable toxicity. Among patients receiving Lynparza, 62% were exposed for 6 months or longer and 20% were exposed for greater than one year.

Fatal adverse reactions occurred in 4% of patients treated with Lynparza. These included pneumonia (1.2%), cardiopulmonary failure (0.4%), aspiration pneumonia (0.4%), intestinal diverticulum (0.4%), septic shock (0.4%), Budd-Chiari Syndrome (0.4%), sudden death (0.4%), and acute cardiac failure (0.4%).

Serious adverse reactions occurred in 36% of patients receiving Lynparza. The most frequent serious adverse reactions (≥2%) were anemia (9%), pneumonia (4%), pulmonary embolism (2%), fatigue/asthenia (2%), and urinary tract infection (2%).

Dose interruptions due to an adverse reaction of any grade occurred in 45% of patients receiving Lynparza; dose reductions due to an adverse reaction occurred in 22% of Lynparza patients. The most frequent adverse reactions leading to dose interruption of Lynparza were anemia (25%) and thrombocytopenia (6%) and the most frequent adverse reaction leading to reduction of Lynparza was anemia (16%). Discontinuation due to adverse reactions occurred in 18% of Lynparza. The adverse reaction that most frequently led to discontinuation of Lynparza was anemia (7%).

Tables 16 and 17 summarize the adverse reactions and laboratory abnormalities, respectively, in patients in PROfound.

Table 16 Adverse Reactions* Reported in ≥10% of Patients in PROfound

Adverse Reactions	Lynparza tablets n=256		Enzalutamide or abiraterone n=130	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Blood and lymphatic disorders				
Anemia†	46	21	15	5
Thrombocytopenia‡	12	4	3	0
Gastrointestinal disorders				
Nausea	41	1	19	0
Diarrhea	21	1	7	0
Vomiting	18	2	12	1
General disorders and administration site conditions				
Fatigue (including asthenia)	41	3	32	5
Metabolism and nutrition disorders				
Decreased appetite	30	1	18	1
Respiratory, thoracic, and mediastinal disorders				
Cough	11	0	2	0
Dyspnea	10	2	3	0

* Graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03
† Includes anemia and hemoglobin decreased
‡ Includes platelet count decreased and thrombocytopenia

In addition, adverse reactions of clinical relevance in PROfound that occurred in <10% of patients receiving Lynparza were neutropenia (9%), venous thromboembolic events (7%), dizziness (7%), dysgeusia (7%), dyspepsia (7%), headache (6%), pneumonia (5%), stomatitis (5%), rash (4%), blood creatinine increase (4%), pneumonitis (2%), upper abdominal pain (2%), and hypersensitivity (1%).

Table 17 Laboratory Abnormalities Reported in ≥25% of Patients in PROfound

Laboratory Parameter*	Lynparza tablets n†= 256		Enzalutamide or abiraterone n†=130	
	Grades 1-4 n= 247 (%)	Grades 3-4 n=247 (%)	Grades 1-4 n=124 (%)	Grades 3-4 n=124 (%)
Decrease in hemoglobin	242 (98)	33 (13)	91 (73)	5 (4)
Decrease in lymphocytes	154 (62)	57 (23)	42 (34)	16 (13)
Decrease in leukocytes	130 (53)	9 (4)	26 (21)	0
Decrease in absolute neutrophil count	83 (34)	8 (3)	11 (9)	0

* Patients were allowed to enter clinical studies with laboratory values of CTCAE Grade 1.
† This number represents the safety population. The derived values in the table are based on the total number of evaluable patients for each laboratory parameter.

Postmarketing Experience

The following adverse reactions have been identified during post approval use of Lynparza. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Immune System Disorders: Hypersensitivity (rash/dermatitis/angioedema).

DRUG INTERACTIONS

Use with Anticancer Agents

Clinical studies of Lynparza with other myelosuppressive anticancer agents, including DNA damaging agents, indicate a potentiation and prolongation of myelosuppressive toxicity.

Effect of Other Drugs on Lynparza

Strong and Moderate CYP3A Inhibitors

Coadministration of CYP3A inhibitors can increase olaparib concentrations, which may increase the risk for adverse reactions *[see Clinical Pharmacology (12.3) in the full Prescribing Information]*. Avoid coadministration of strong or moderate CYP3A inhibitors. If the strong or moderate inhibitor must be coadministered, reduce the dose of Lynparza *[see Dosage and Administration (2.4) in the full Prescribing Information]*.

Strong and Moderate CYP3A Inducers

Concomitant use with a strong or moderate CYP3A inducer decreased olaparib exposure, which may reduce Lynparza efficacy *[see Clinical Pharmacology (12.3) in the full Prescribing Information]*. Avoid coadministration of strong or moderate CYP3A inducers.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on findings in animals and its mechanism of action *[see Clinical Pharmacology (12.1) in the full Prescribing Information]*, Lynparza can cause fetal harm when administered to a pregnant woman. There are no available data on Lynparza use in pregnant women to inform the drug-associated risk. In an animal reproduction study, the administration of olaparib to pregnant rats during the period of organogenesis caused teratogenicity and embryo-fetal toxicity at exposures below those in patients receiving the recommended human dose of 300 mg twice daily *(see Data)*. Apprise pregnant women of the potential hazard to the fetus and the potential risk for loss of the pregnancy.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. The estimated background risk in the U.S. general population of major birth defects is 2-4%; and the risk for spontaneous abortion is approximately 15-20% in clinically recognized pregnancies.

Data

Animal Data

In a fertility and early embryonic development study in female rats, olaparib was administered orally for 14 days before mating through to Day 6 of pregnancy, which resulted in increased post-implantation loss at a dose level of 15 mg/kg/day (with maternal systemic exposures approximately 7% of the human exposure ($AUC_{0\text{-}24h}$) at the recommended dose).

In an embryo-fetal development study, pregnant rats received oral doses of 0.05 and 0.5 mg/kg/day olaparib during the period of organogenesis. A dose of 0.5 mg/kg/day (with maternal systemic exposures approximately 0.18% of human exposure ($AUC_{0\text{-}24h}$) at the recommended dose) caused embryo-fetal toxicities including increased post-implantation loss and major malformations of the eyes (anophthalmia, microphthalmia), vertebrae/ribs (extra rib or ossification center; fused or absent neural arches, ribs, and sternebrae), skull (fused exoccipital), and diaphragm (hernia). Additional abnormalities or variants included incomplete or absent ossification (vertebrae/sternebrae, ribs, limbs) and other findings in the vertebrae/sternebrae, pelvic girdle, lung, thymus, liver, ureter, and umbilical artery. Some findings noted above in the eyes, ribs, and ureter were observed at a dose of 0.05 mg/kg/day olaparib at lower incidence.

Lactation

Risk Summary

No data are available regarding the presence of olaparib in human milk, or on its effects on the breastfed infant or on milk production. Because of the potential for serious adverse reactions in the breastfed infants from Lynparza, advise a lactating woman not to breastfeed during treatment with Lynparza and for one month after receiving the last dose.

Females and Males of Reproductive Potential

Pregnancy Testing

Recommend pregnancy testing for females of reproductive potential prior to initiating treatment with Lynparza.

Contraception

Females

Lynparza can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1) in the full Prescribing Information]*. Advise females of reproductive potential to use effective contraception during treatment with Lynparza and for at least 6 months following the last dose.

Males

Based on findings in genetic toxicity and animal reproduction studies, advise male patients with female partners of reproductive potential or who are pregnant to use effective contraception during treatment and for 3 months following the last dose of Lynparza. Advise male patients not to donate sperm during therapy and for 3 months following the last dose of Lynparza *[see Use in Specific Populations (8.1) and Nonclinical Toxicology (13.1) in the full Prescribing Information]*.

Pediatric Use

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

Geriatric Use

Of the 2351 patients with advanced solid tumors who received Lynparza tablets 300 mg orally twice daily as monotherapy, 596 (25%) patients were aged ≥65 years, and this included 137 (6%) patients who were aged ≥75 years. Seven (0.3%) patients were aged ≥85 years *[see Adverse Reactions (6.1) in the full Prescribing Information]*.

Of the 535 patients with advanced solid tumors who received Lynparza tablets 300 mg orally twice daily in combination with bevacizumab, 204 (38%) patients were aged ≥65 years, and this included 31 (6%) patients who were aged ≥75 years.

No overall differences in the safety or effectiveness of Lynparza were observed between these patients and younger patients.

Renal Impairment

No dosage modification is recommended in patients with mild renal impairment (CLcr 51 to 80 mL/min estimated by Cockcroft-Gault). Reduce Lynparza dosage to 200 mg twice daily in patients with moderate renal impairment (CLcr 31 to 50 mL/min) *[see Dosage and Administration (2.5) in the full Prescribing Information]*. There are no data in patients with severe renal impairment or end-stage disease (CLcr ≤30 mL/min) *[see Clinical Pharmacology (12.3) in the full Prescribing Information]*.

Hepatic Impairment

No adjustment to the starting dose is required in patients with mild or moderate hepatic impairment (Child-Pugh classification A and B). There are no data in patients with severe hepatic impairment (Child-Pugh classification C) *[see Clinical Pharmacology (12.3) in the full Prescribing Information]*.

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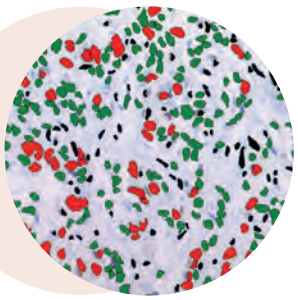

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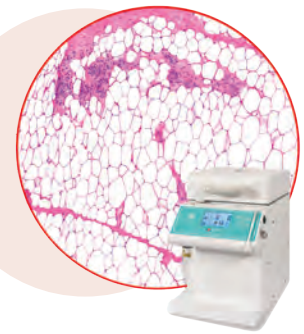

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A Voice for the Dead

Sitting Down With… Dame Sue Black,
President of the Royal Anthropological Institute and
Pro-Vice-Chancellor for Engagement, Lancaster University, UK

Why did you choose to specialize in forensic anthropology?

In many ways, I've never really chosen to be a forensic anthropologist. Each time I've come to a crossroads in my life, I've taken the route I felt most comfortable with. In my third year of university, I had to choose between the two subjects I was good at: anatomy and botany. I couldn't face naming and drawing plants for the rest of my life, so I became an anatomist and did my research project on human skeletons. When I was allowed to go on a case with my supervisor, I thought, "Can I deal with dead animals? Yes. Can I deal with dead humans? Yes. Can I deal with humans whose death was recent and it's not just dry skeletons? Yes."

It's a great honor to look inside somebody who has given you permission by donating their body to science; all they are asking you to do is learn.

What is your relationship with forensic pathologists like?

It's very different today compared with the past. The old-time forensic pathologists had anthropological training, so they didn't need someone else to do that part of the job. But, as forensic pathology and anthropology have advanced, they have diverged slightly – although they still run in parallel. A modern-day pathologist is more likely to recognize that anthropologists have expertise they don't, and so it has become a strong, valuable relationship where complementary skills are shared between the disciplines.

Tell us about H-unique…

H-unique is a project that allows us to study the anatomical variation of the human hand – particularly when seen in images of child indecency. We know that, for example, the pattern of veins on the back of your hands will not match even those of your identical twin – so when we consider all of the different anatomical features, there is a very good chance that the human hand is unique to the individual.

We've created large databases where people upload photographs of their hands and we compare the vein patterns, skin creases, patterns of freckles and pigmentation, liver spots, and size and orientation of scars, and then train a computer to recognize them and search for them. They all have different etiology, so when you combine all of those features, the possibility of a particular hand or forearm being somebody else's becomes infinitesimally small.

Once we have those algorithms, the police can search the millions of indecent images of children and investigate whether a perpetrator shows up more than once in any of them. And that allows us to connect cases we've never been able to before and work across different countries; child sexual abuse is an international crime – so our techniques cannot be limited by our borders.

What was the inspiration for your book, "Written in Bone?"

Most people know very little about their own bodies and don't always feel comfortable with the language used in doctors' offices or hospitals. My area of expertise is criminal dismemberment, so I was able to talk about anatomy in simple language and in segments that people could relate to with their own bodies. I illustrate each body part with cases where that region was important to show that there is no area of the body that is any less important than the others – and so, in forensics, you need to know as much as you possibly can about the human body in its entirety

What do you think about the blurred line between real life and forensic TV shows – and how does it affect the field?

Humans are innately curious beings who love a good mystery – we are really captivated by it. Most of the time, it's not about the flashy science – it's about the story of the victim, the perpetrators, the interactions with the police and the court. Very few people pursued forensics as a career back in my school days but, in the late 1990s, there was a surge of these shows that hooked people and made them consider a career in the field.

What's the number one prerequisite for being successful in the forensic space?

You need to be curious – to always be asking questions. If you don't know the answer, then you need to have the tenacity to go and research it. If it isn't in the literature, go and do it yourself. The innate curiosity of humans drives us all to ask questions and to find answers. Then we must decide if the answers are absolute – which is rare – or whether they're biased or a reflection of probability

What single aspect of forensic anthropology would you change, if you could?

I would make everyone study human anatomy and conduct a whole-body dissection. We have good practitioners, but many have only worked on dry bone. Understanding the human body in its entirety makes you a more rounded practitioner.

What advice would you give to those who aspire to a career in a forensic discipline?

Don't do an undergraduate degree with the word "forensic" in the title. Universities put "forensic" in the title because it attracts students – but, if you're serious about going into a forensic discipline, nail the discipline first. Be the pathologist, biologist, chemist, physicist, mathematician… Once you're sure that's the discipline for you, then look at how you can use it to help the courts.

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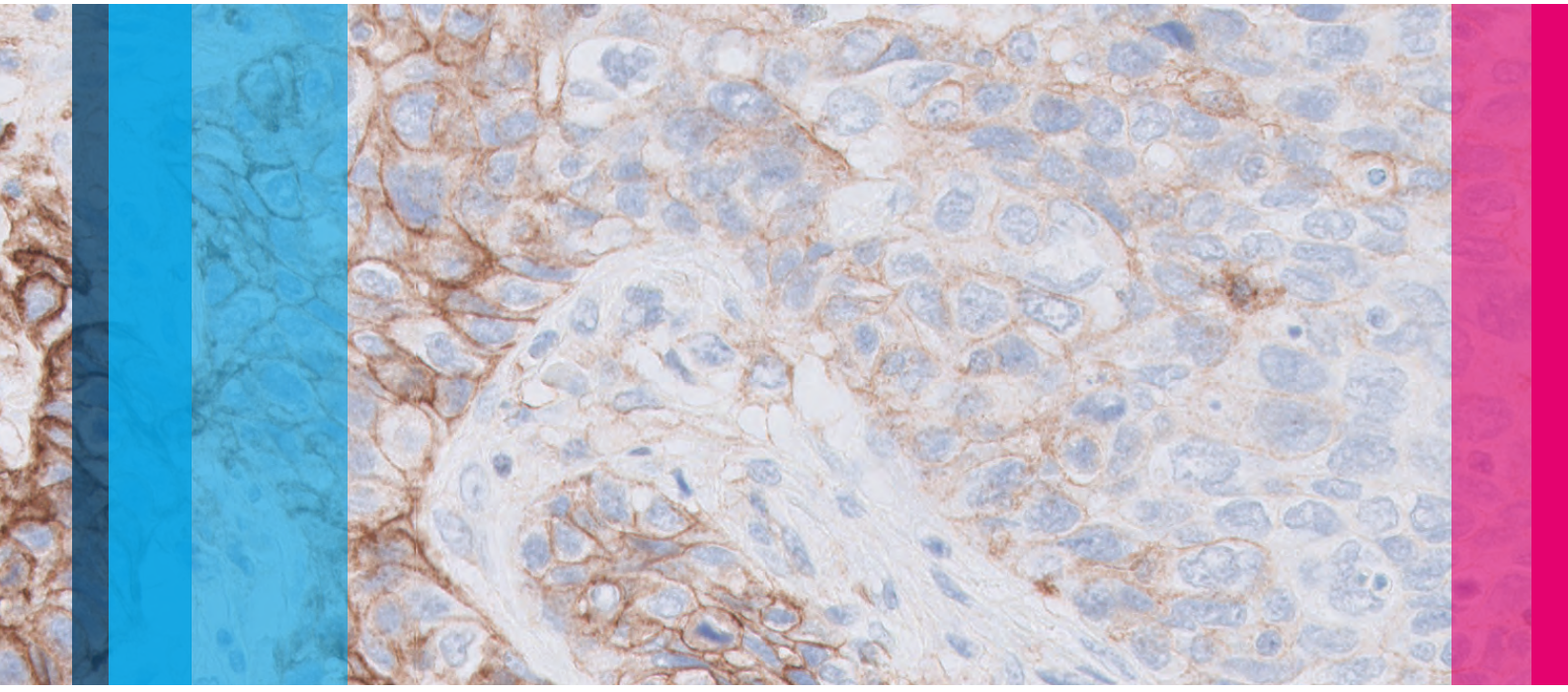

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TNBC interactive case studies: the current PD-L1 landscape and the near horizon of biomarkers for treatment selection

In November 2020 PD-L1 IHC 22C3 pharmDx received FDA approval for expanded use in Triple Negative Breast Cancer (TNBC). PD-L1 testing with PD-L1 IHC 22C3 pharmDx can help identify TNBC patients for treatment with the checkpoint inhibitor KEYTRUDA. In this live session Dr. Corrado D'Arrigo and Dr. Teresa Thomas will analyze four TNBC cases, showing how and at what stage PD-L1 IHC 22C3 pharmDx is integrated with other biomarkers testing in the pathology routine. The results will then be discussed with an oncologist in a tumor board fashion. The session will be interactive: every registered participant will have access to the cases in advance and will be able to anonymously provide input on the case analysis.

Speakers: Corrado D'Arrigo, MD, Poundbury Cancer Institute for Personalized Medicine, UK and Teresa Thomas, MD, Poundbury Cancer Institute For Personalized Medicine, UK

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