MAY 2021 # 75

the Pathologist®

Official society partner of The Pathologist

The New Scientists

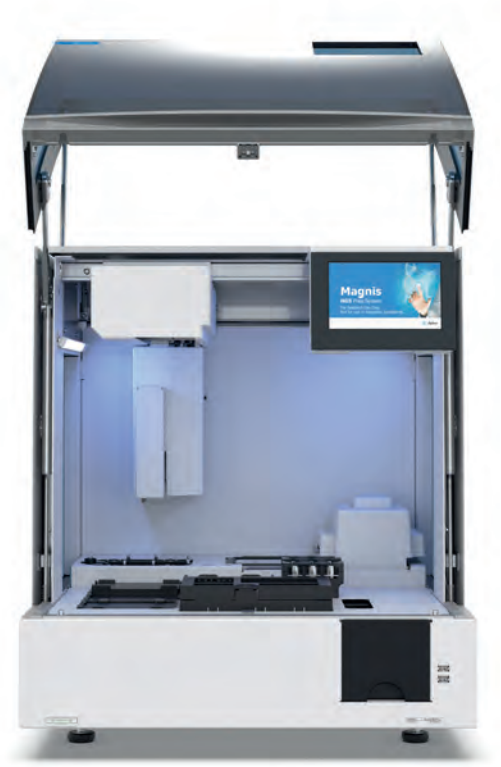
Cultivating a love of the lab in students – from the ground up

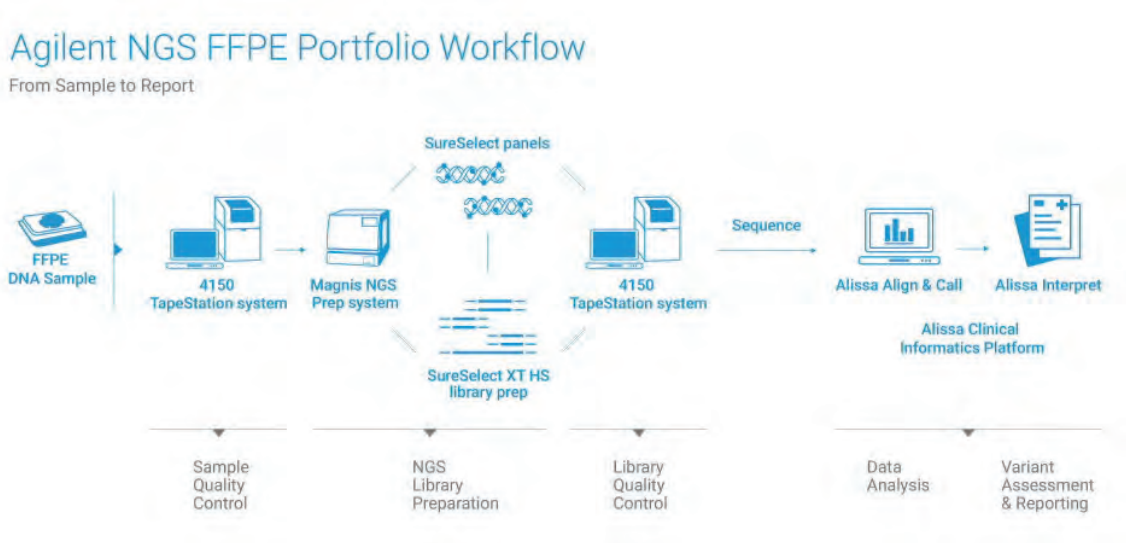
Agilent

Trusted Answers

Powerful Does Not Mean Complicated

NGS library prep automation transforms workflow





For in vitro diagnostic use.
D64534_2021FEB24
PR7000-7732

Physician, Heal Thyself

An approach to wellness for the pandemic – and for life

Before the pandemic, I thought wellness could be conceptualized as a hierarchy – one in which adequate sleep, regular exercise, nutritious meals, and self-care provided a foundation for wellbeing. I theorized, through some sort of pseudo-Maslow's hierarchy of needs, one should first strengthen the physical body as a means of achieving self-fulfillment.

But how does one maintain physical health when stuck indoors during a pandemic?

In Japan, there is a philosophical concept called *ikigai* or "the reason for being." It uses four overlapping Venn diagrams to define the metaphysical "sweet spot" between your passion, your mission, your vocation, and your profession. On the surface, ikigai seemed to be a closer approximation of personal wellness. It attributes self-worth to purposeful work.

But how can you achieve "a reason for being" when you are unemployed or unable to work?

Perhaps, instead, healing the mind is the path to wellness. Being mindful of one's thoughts and emotions can center our awareness of all things. Studies show that mindfulness can improve focus, reduce blood pressure, and help reduce chronic pain. At its core, mindfulness is a way for us to build a relationship with our body and mind.

But is a strong relationship with yourself enough?

My daughter is five months old at the time of writing. Her arrival has marked a significant disruption in my sleep hygiene. I no longer surf before work. Exercise is sporadic. I occasionally eat meals standing in the kitchen, scarfing food quickly so I can help change a diaper. Aubrey has successfully eliminated all quiet moments dedicated to self-reflection. She is a clear affront to my personal wellness – yet she is my ikigai.

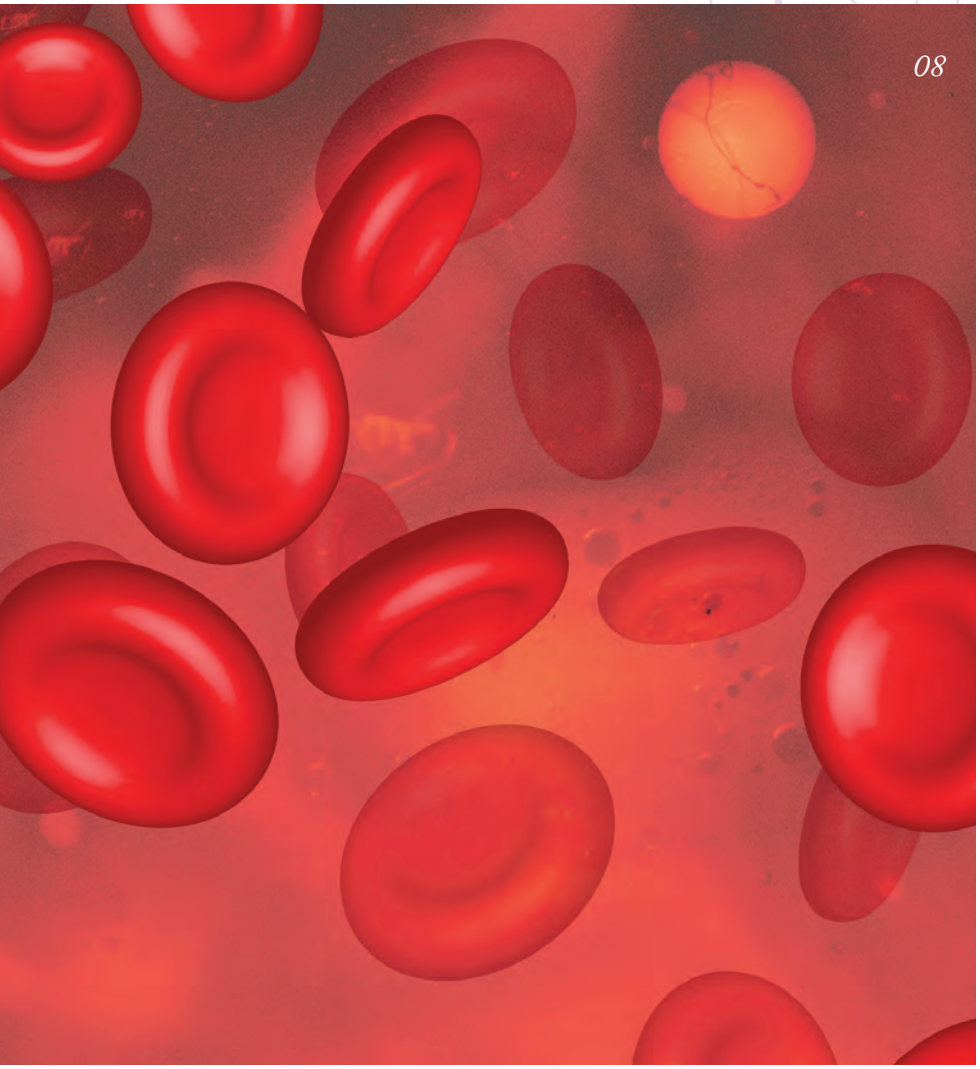
Take a moment to reflect upon your relationships. Which ones do you value most?

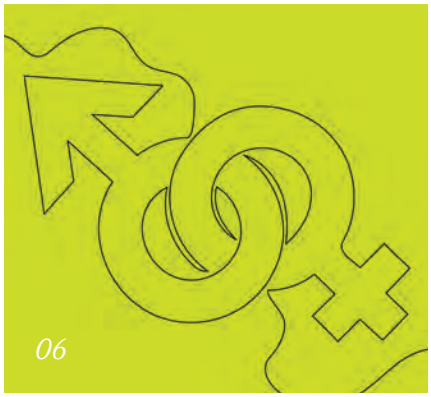
Personally, I find the most fulfilling relationships are those where we seek to better the life of another. I do not believe that this is necessarily a profound realization, but it is frequently overlooked. Emotional connections drastically improve our physical and mental wellbeing. Take inventory of the relationships that may have been strained through the pandemic. Reach out to those you value. Achieving wellness can start with something as simple as a phone call.

Brian Cox

Brian Cox is a fourth-year resident in the Department of Pathology and Laboratory Medicine, Cedars-Sinai, Los Angeles, California, USA.

Contents





On The Cover

Artist's representation of hands-on learning in the lab.

Feature

NextGen

In Practice

Profession

Reports

Sitting Down With

the Pathologist

ISSUE 75 - MAY 2021

Feel free to contact any one of us: first.lastname@texerepublishing.com

Content Team
Editor - Michael Schubert
Olivia Gaskill (Associate Editor)

Commercial Team
Publisher - Lee Noyes
Sally Loftus (Associate Publisher)
Danny Crowe (Business Development Executive North America)
Paul Longley (Business Development Executive)

Design Team
Head of Design - Marc Bird
Hannah Ennis (Senior Designer)
Charlotte Brittain (Designer)

Digital Team
Digital Team Lead - David Roberts
Peter Bartley (Digital Producer Web/Email)
Abygail Bradley (Digital Producer Web/App)

Audience Team
Audience Growth Strategy Manager – Brice Agamemnon

CRM & Compliance
CRM & Compliance Manager - Tracey Nicholls
Hayley Atiz (CRM Assistant)

Commercial Support Team
Internal Systems Manager - Jody Fryett
Dan Marr (Campaign Reporting Analyst)

Commercial Services
Commercial Service and Social Media Manager- Matt Everett
Kevin O'Donnell (Marketing Executive)
Alice Daniels-Wright (Video Project Manager)
Jess Lines (Project Support Coordinator)
Lindsey Vickers (Sales Support Project Manager)
Julie Wheeler (Sales Support Coordinator)

Marketing Team
Marketing Manager - Katy Pearson
Jo Baylay (Marketing Executive)

Accounts Team
Kerri Benson (Accounts Assistant)
Emily Scragg (Accounts Apprentice)

Human Resources
Human Resource Manager - Tara Higby

Management Team
Chief Executive Officer - Andy Davies
Chief Operating Officer - Tracey Peers
Senior Vice President (North America) - Fedra Pavlou
Financial Director - Phil Dale
Commercial Director - Richard Hodson
Content Director - Rich Whitworth

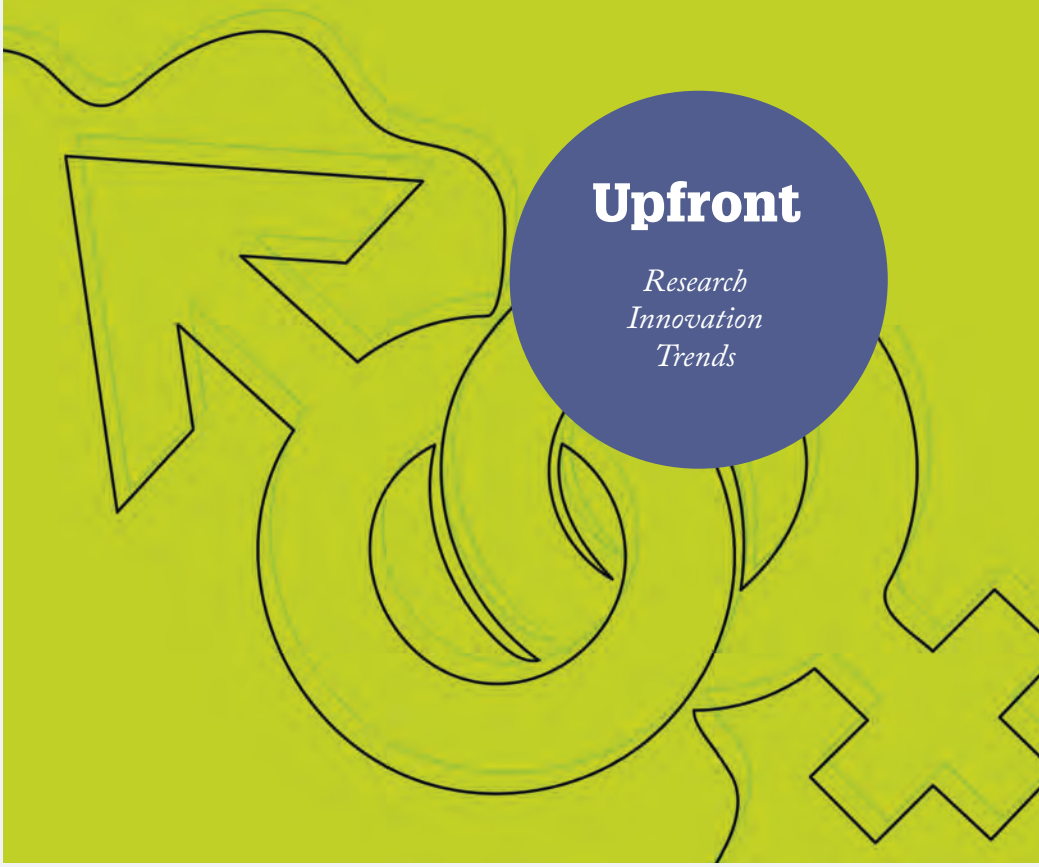
Change of address info@thepathologist.com
Hayley Atiz, The Pathologist, Texere Publishing Limited, Booths Park 1, Chelford Road, Knutsford, Cheshire, WA16 8GS, UK

General enquiries
www.texerepublishing.com | info@thepathologist.com
+44 (0) 1565 745 200 | sales@texerepublishing.com

Distribution: The Pathologist (ISSN 2055-8228), is published monthly by Texere Publishing Limited, Booths Park 1, Chelford Road, Knutsford, Cheshire, WA16 8GS, UK. Single copy sales $15 (plus postage, cost available on request info@thepathologist.com). Non-qualified annual subscription cost is available on request.

texere publishing

Available on the App Store



Gender Reveal

Sex-dependent genetic risks found for three major mood and psychiatric disorders

Previous research suggests there may be sex-dependent risks for several major psychiatric disorders (1). However, according to Jill M. Goldstein, founder and executive director of the Innovation Center on Sex Differences in Medicine at Massachusetts General Hospital, "medicine, essentially, has been built on models of men's health and male animals. We need to develop our precision medicine models incorporating the effect of sex (2)."

Recognizing the need for a genotype-by-sex (GxS) interaction study, an international collaboration of researchers conducted a large-scale genome-wide study to assess the sex-dependent and sex-specific risks of schizophrenia, major depressive disorder (MDD), and bipolar disorder (3). Though there was some genetic overlap between the sexes, they found significant sex-dependent effects for genes associated with neuronal development and immune and vascular pathway functioning across the disorders.

Heritability estimates differed between males and females for schizophrenia and MDD, but not for bipolar disorder, suggesting there are sex differences in incidence for schizophrenia and MDD. For all disorders, a single nucleotide polymorphism (SNP)-by-sex interaction was found at a locus encompassing *NKAIN2* – a gene associated with cognitive ability and risk of schizophrenia. They also found a significant GxS interaction for the *STLM* gene and a SNP adjacent to *AMIGO1*.

The authors did note that the study lacked access to detailed clinical data, preventing them from delving deeper into GxS associations with age of onset, symptom type and severity, and cognitive deficits. However, their research still demonstrates a vital call for reform in genetics research.

"Our study underscores the importance of designing large-scale genetic studies that have the statistical power to test for interactions with sex," said Goldstein (2). "Dissecting the impact of sex, genes, and pathophysiology will identify potential targets for sex-dependent or sex-specific therapeutic interventions – creating more effective therapies for both men and women."

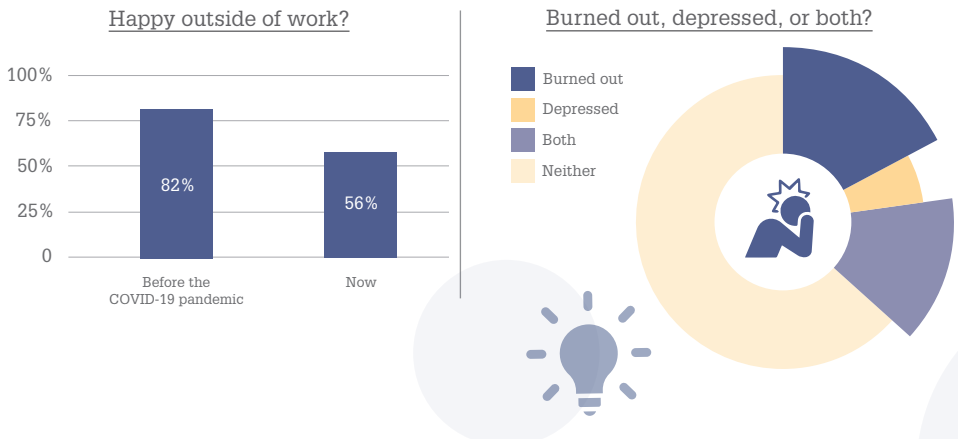
References

1. *HE Jongsma et al., Lancet Public Health, 4, e229 (2019). PMID: 31054641.*
2. *N Brown (2021). Available at: https://bit.ly/3tV8fQD.*
3. *GAM Blokland et al., Biol Psych, [Preprint] (2021).*

INFOGRAPHIC

Are Pathologists Happy?

Findings from the Medscape Pathologist Lifestyle, Happiness, and Burnout Report 2021



QUICK HITS

The latest breakthroughs in pathology and laboratory medicine research

Brain Tumor Biomarker

Grade II meningiomas express significantly higher levels of fibulin-2, a calcium-binding extracellular matrix glycoprotein, than their grade I counterparts (1). The protein could be used as a novel biomarker to differentiate the two grades – a task that has previously suffered from high interobserver discordance.

Assessing Alterations

Researchers have found genomic alterations that may affect treatment success in androgen receptor (AR)-V7-positive metastatic castration-resistant prostate cancer (2). *ATM*, *NCOR2*, and *HSD17B4* gains were associated with AR inhibitor sensitivity, whereas *BRCA2*, *APC*, *KDM5D*, *CYP11B1*, and *SPARC* gains and *CHD1*, *PHLPP1*, *ERG*, *ZFHX3*, and *NCOR2* losses were linked to AR inhibitor resistance.

Speedy Serology

A low-cost, solution-based assay has been developed to detect SARS-CoV-2 antibodies within 30 minutes in serum, plasma, blood, and saliva (3). The engineers hope their serological test will increase access to antibody testing in resource-limited areas, with future research aiming to develop the method for infectious diseases beyond SARS-CoV-2.

Not What We Thought

Polycystic ovary syndrome (PCOS) has been regarded as a female reproductive disorder; however, new evidence suggests that men with genetic risk factors for the syndrome exhibit an increased risk of diabetes, obesity, and cardiovascular disease (4). This suggests that PCOS may not be primarily caused by the ovaries.

Life After Death

By analyzing gene expression in fresh post-surgical brain tissue, researchers have studied transcription patterns during the postmortem interval (5). Neuronal gene expression decreased during this interval, but expression of astroglial and microglial genes increased for at least 24 hours after tissue resection.

References

1. *AA Sofela et al., Int J Mol Sci, 22, 560 (2021). PMID: 33429944.*
2. *S Gupta et al., Mol Cancer Res (2021). PMID: 33771885.*
3. *SK Elledge et al., Nat Biotechnol (2021). PMID: 33767397.*
4. *Endocrine Society (2021). Available at: https://bit.ly/3tyI6Hm.*
5. *F Dachet et al., Sci Rep, 11, 6078 (2021). PMID: 33758256.*

Do You Know?

The history of a hepatitis virus

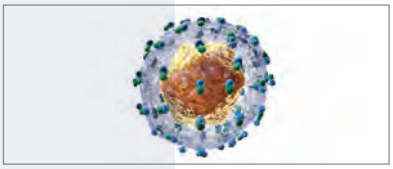
Harvey J. Alter, Michael Houghton, and Charles M. Rice received the 2020 Nobel Prize in Physiology or Medicine for their discovery of a novel hepatitis virus.

What was the initial name for this virus?

a) Hepatitis C virus
b) Bloodborne non-B hepatitis virus
c) Antigen-negative viral hepatitis
d) Non-A, non-B hepatitis virus

Find out the answer below!

Find out the answer below!



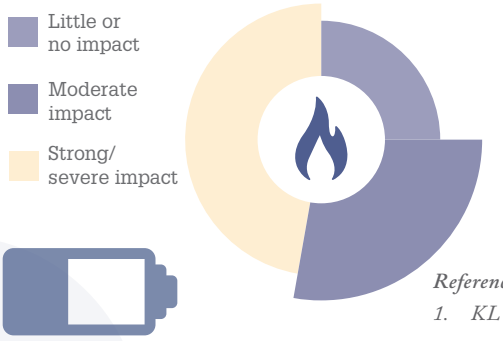
Credit: Bruce Blaus

Answer: d) Non-A, non-B hepatitis virus

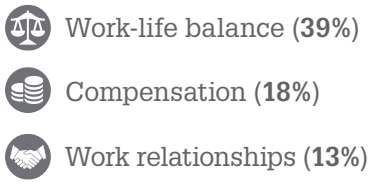
The three Nobel Prize-winning physicians were credited with discovering the hepatitis C virus, which was initially known as the presumptive cause of "non-A, non-B hepatitis" (1).

See references online at: tp.txp.to/hep-c-history

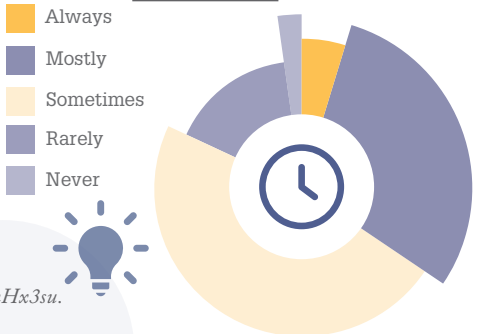
Burnout severity: Impact on life



Top three workplace concerns

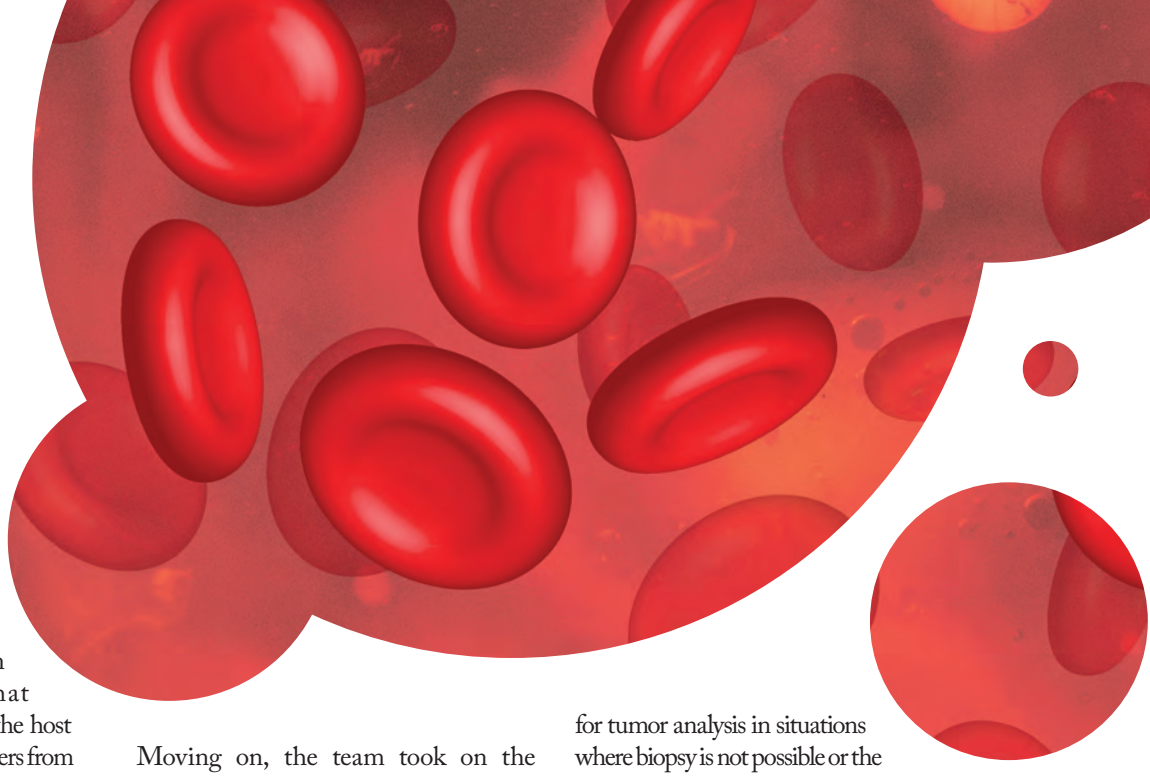


Spending enough time on health and wellness?



Reference

1. *KL Martin, ML Koval (2021). Available at: https://wb.md/3mHx3su.*



Tracing Origins

Genetic-epigenetic tissue mapping can help determine the origins of plasma DNA

Not all DNA is created equal – and that's never truer than when investigating plasma DNA that carries different genetic variants to the host constitutional genome. Now, researchers from the Chinese University of Hong Kong have developed a method called genetic-epigenetic tissue mapping (GETMap) to determine the origin of such DNA (1). GETMap is based on a comparison between the methylation profiles of plasma DNA and DNA from the potential tissue or organ of origin. In a comprehensive study, the approach was tested in pregnant women, lung transplant patients, and liver cancer patients.

First validating the approach in pregnant women, they investigated whether GETMap could determine the tissue contributions of genetic variations in plasma DNA. They found that plasma DNA carrying fetus-specific alleles originated in the placenta, whereas maternal-specific alleles were derived from white blood cells.

Moving on, the team took on the challenge of catching allograft rejection in post-transplant patients. High levels of DNA from the transplanted organ can indicate rejection – but high levels of donor DNA are also common in the recipient's blood immediately after surgery. To overcome this, GETMap combined genetic and epigenetic markers to determine the source of the post-transplant increase and found that, over time, lung-derived plasma DNA increased and blood cell-derived DNA decreased. They also found that patients who rejected their new lungs had higher levels of donor lung DNA than successful patients.

Using methylation profiles, the team also identified tumor mutations from plasma DNA and correctly identified the liver as the origin of the DNA molecules, creating the potential for tumor analysis in situations where biopsy is not possible or the tissue of origin is unknown.

In their final analysis, they tested a woman who developed lymphoma during pregnancy and successfully distinguished between placenta-derived fetal genes and tumor genes that originated from disease-associated white blood cells.

"We have demonstrated the powerful synergy between genetic and epigenetic approaches for identifying the origin of circulating DNA in the blood, and shown its potential applications in cancer screening, prenatal testing, and organ transplant monitoring," said co-senior author Dennis Lo (2).

See references online at: tp.txp.to/plas-dna

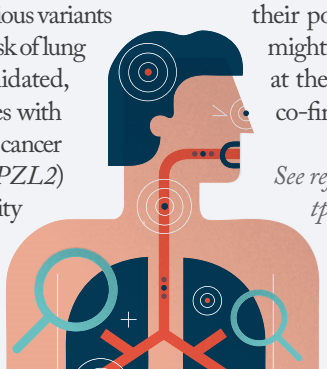
Weighing Up the Risk

Investigating rare genetic variants' contribution to lung cancer susceptibility

Researchers have previously investigated risk genes for lung cancer – but we still don't fully understand how these genes contribute to an individual's likelihood of the disease. Now, a team at Baylor College of Medicine have used whole exome sequencing and targeted sequencing on high-risk lung cancer cases with the highest genetic predisposition to the disease – for example, early-onset or family history of lung cancer (1).

They identified 25 rare deleterious variants associated with an increased risk of lung cancer. Five variants were validated, two of which mapped to genes with a known association with lung cancer susceptibility (*ATM* and *MPZL2*) and three to novel susceptibility genes (*POMC*, *STAU2*, and *MLNR*).

Endogenous DNA damage assays further supported the genes' role in lung cancer susceptibility. "We found that dysregulation or mutations in these candidate genes showed increased DNA damage, suggesting that their potential cancer-causing role might be due to genome instability at the DNA level," said Jun Xia, co-first author of the study (2).



See references online at: tp.txp.to/risk-lung-c

IMAGE OF THE MONTH

Musings on a Missing Mass Spectrometer Vacuum

Nothing exists in a vacuum, but without it, Nothing reaches the detector and when it's not there, Nothing fills the space like a new vacuum pump.

Credit: Jinny Jeffery, Derriford Hospital, Plymouth, United Kingdom.

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

QUOTE of the month

"There were several months where all elective procedures were canceled. All the screening tests, the colonoscopies, the mammography, things like that. They were not happening. And there's a lot of concern that cancer incidence is going to go up in the next couple of years because of that delay. The other part is people who were already diagnosed – maybe it wasn't an emergency surgery, but they had to wait. So now you've got cancer cases at a higher stage than you would have had, worse prognoses, things like that. Not a lot of data just yet, but it is a concern among the pathology community."

Dennis Strenk is a Pathologists' Assistant at Wisconsin Diagnostic Laboratories, Milwaukee, Wisconsin, USA.
To learn more, check out our "The Pandemic: One Year On" roundtable at: tp.txp.to/pand-yearon

Differential Decisions

A new AI model uses electronic health records to make differential diagnoses

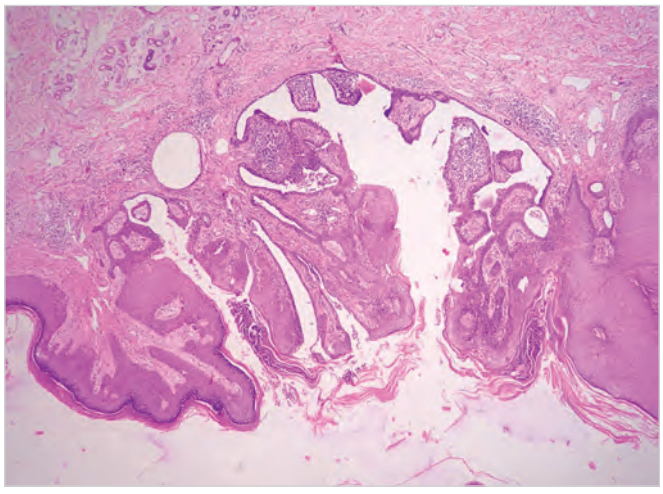
A new algorithm has been developed to help physicians make differential diagnoses (1). Current methods use Bayesian inference to determine the most likely diagnosis; however, Gerald Loeb, the engineer of the new tool, says, "What has been missing so far – and is provided by the algorithm – is a way to decide which clinical data to obtain at each point in the work-up."

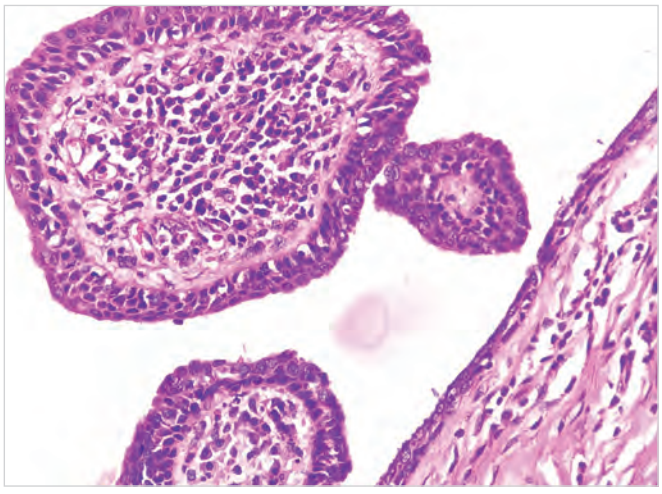
He continues, "It prioritizes diagnostic options based on their likelihood to advance the process toward a definitive diagnosis vs. their cost in dollars, delay, and possible adverse events." How? "It looks at the cumulative electronic health records (EHRs) of all patients in the database, including all tests that were run on those patients and their final diagnoses."

Though the model assesses EHRs, pathologists have a vital role to play in the wider adoption of the model. Loeb believes it will "require substantial input from pathologists and laboratory medicine specialists to standardize the reporting of test results – particularly for newer modalities, such as genomic and antibody testing."

See references online at: tp.txp.to/diff-ai

CASE OF THE MONTH





A 53-year-old lady presented with swelling at the right temporal region of the head. Excisional biopsy was performed.

What is the diagnosis?

a) Hidradenoma papilliferum
b) Tubular apocrine adenoma
c) Papillary eccrine adenoma
d) Syringocystadenoma papilliferum

Submitted by San Yu Maung, Pathologist, Mandalay General Hospital, Mandalay, Myanmar.

Answer to last issue's Case of the Month…
b) p63

The images show metaplastic squamous cell carcinoma (SCC), an aggressive variant of metaplastic breast carcinoma (MBC) that demonstrates squamous differentiation. Histologically, metaplastic SCC are frequently cystic and are lined by atypical squamous cells; however, they can also demonstrate solid architecture (1–3). Like other MBC, these tumors are typically positive for p63 and high-molecular-weight cytokeratin. p63 is a highly sensitive and specific marker for MBC (86.7 and 99.4 percent, respectively) (4). In daily practice, a combination of several stains (such as cytokeratin cocktail, p63, or high-molecular-weight cytokeratin) is usually needed for an accurate diagnosis of MBC.

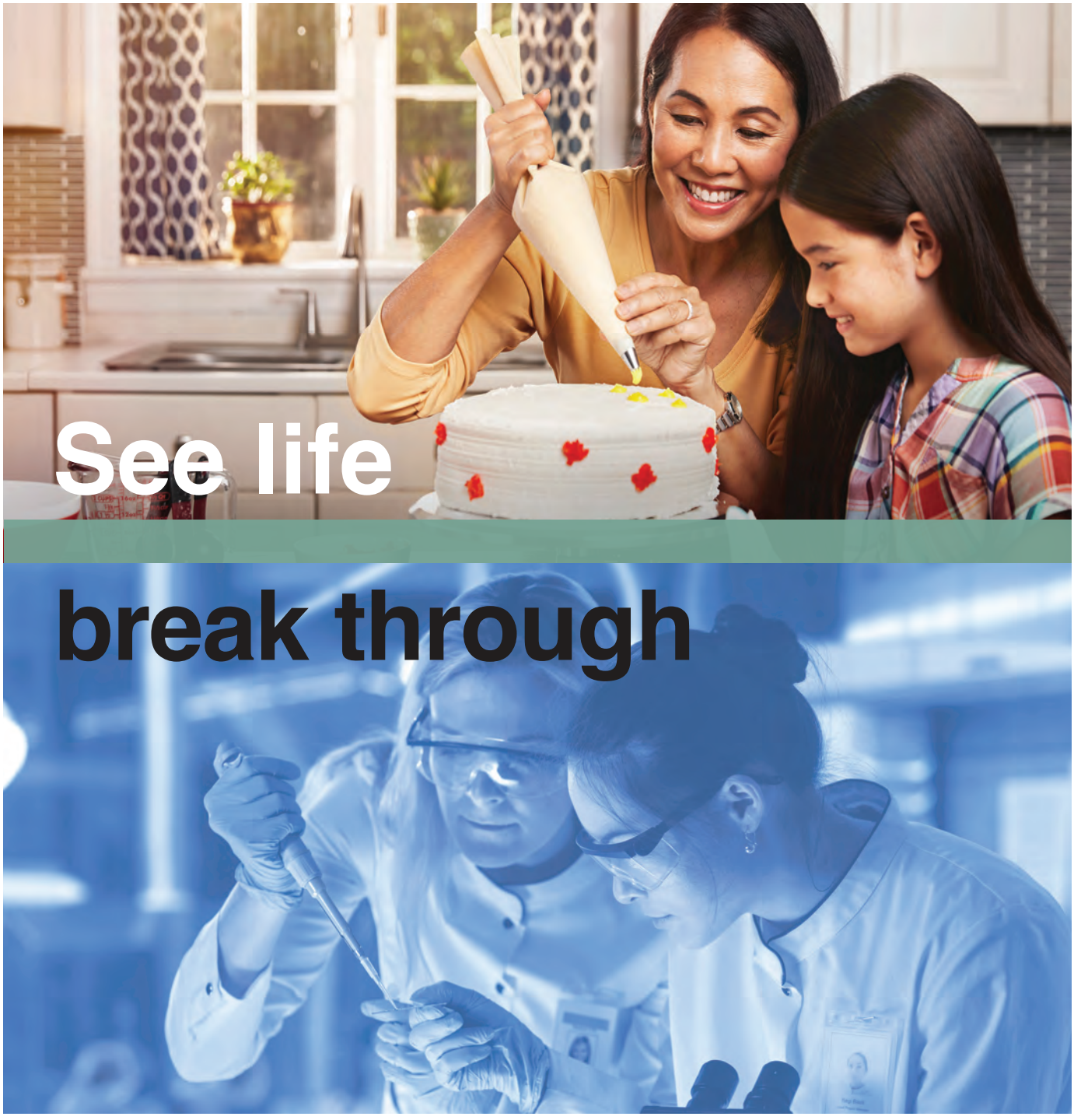
Submitted by Emily R. McMullen, House Officer IV at the University of Michigan, Ann Arbor, Michigan, USA.

References

1. *JS Reis-Filho et al., WHO Classification of Tumours of the Breast, 4th edition. International Agency for Research on Cancer: 2012.*
2. *N Cha et al., Am J Case Rep, 19, 203 (2018). PMID: 29472521.*
3. *ER McMullen et al., Arch Pathol Lab Med, 143, 1492 (2019). PMID: 31765246.*
4. *MM Koker, CG Kleer, Am J Surg Pathol, 28, 1506 (2004). PMID: 15489655.*

To register your guess, please go to http://tp.txp.to/0521/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.



Advancing oncology at the speed of life™

AMGEN®
Oncology

Follow us @AmgenOncology

Visit us at www.AmgenOncology.com

SPECIAL SERIES
Education & Training

In My View

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

On Investigating Death

Resident perception of autopsy education in Canada

By Michael Multan, Anatomical Pathology Resident at the University of British Columbia, Vancouver, British Columbia, Canada

Most people in North America die of natural causes – cardiovascular disease, cancer, or complications of diabetes to name just a few. The timing of these deaths is usually unsurprising and often doesn't warrant further investigation. But in instances of accident, homicide, and suicide – or when a natural cause cannot be easily determined – the circumstances surrounding the death warrant expert opinion. The investigation of an unexpected death in hospital or following a surgical procedure can provide clinicians and surgeons with important quality control feedback. This information is important to families, the justice system, public health, and for future healthcare planning.

Although the Canadian population is approximately 10 percent of the US population, many of the challenges surrounding death investigation are similar in both countries. As a current pathology trainee with an interest in forensic pathology, I often wonder what these challenges mean for the future.

Death investigation in North America is the responsibility of each state and follows either the coroner system, the medical examiner system, or a hybrid of the two. Simply put, not all cause-of-death determinations require an autopsy and, although pathologists are the ones to perform the autopsy when required, whether or not they certify the final manner of death varies by region.

Autopsies fall into two general categories: forensic (medicolegal) and hospital (medical). Forensic autopsies fall under the jurisdiction of the local governmental death investigation system (coroner or medical examiner), whereas hospital autopsies are performed with consent of the deceased's family in an attempt to answer specific questions regarding disease extent, effectiveness of therapy, or for hospital quality assurance.

Over the last few decades, autopsies have become less common in North America. Approximately 6 percent of all deaths in Canada lead to autopsy – a number that was closer to 13 percent in the early 1990s. The advent of advanced imaging techniques and the medical system's increased ability to capture underlying disease early means that more deaths occur as a result of known complications of well-documented medical conditions. Because our understanding of normal disease timelines has improved, the decline in overall autopsy numbers is unlikely a major issue.

Prioritizing the diagnosis and treatment of living patients is a great thing – but the overall decrease in autopsy numbers, along with limited funding for death investigation in some regions, may create a catch-22 scenario for future workforce planning. Residents training to become pathologists are doing fewer autopsies than their predecessors and may therefore eventually be practicing with a diminished level of comfort in autopsy pathology. Could this have implications for death investigation capacity in the future?

In Canada, pathology residency spans five years and often includes further subspecialty fellowship training. Over the last decade, science has made great strides in cancer biology and we have seen greater focus on personalized medicine; residents have more to learn about the routine cancer subtypes that encompass the majority of a typical pathologist's workload.

Canadian pathology training programs often look to the US as a benchmark and guide to structure training. After all, it is not uncommon for Canadian graduates to complete fellowships or seek job opportunities in the US. In 2019, the Association of Pathology Chairs looked at the issue of autopsy education in the US in the context of declining numbers and competing educational demands (1). They concluded that autopsy training should remain an essential part of US pathology education, but that two residents could share the responsibility of an autopsy

and have it count toward the 50-autopsy requirement (which was closer to 100 a few decades ago) for both of them. In the wake of the COVID-19 pandemic, the American Board of Pathology further decreased this requirement to 30 to allow residents to graduate on time. After all, for most grads, autopsies will form a very minor component of their careers.

"As a current pathology trainee with an interest in forensic pathology, I often wonder what these challenges mean for the future."

As a trainee interested in autopsy and forensic pathology, I wanted to know how my colleagues felt about the role of autopsy in their education. Do they think it informs their general dissection and anatomy skills? Or is it useless if their end goal is to end up working in gastrointestinal or thoracic pathology?

In March 2020, just as the pandemic hit, I designed a national survey of Canadian pathology residents to learn more about what my resident colleagues thought (2). My goal was to quantify the number of autopsies Canadian residents aim to complete during training, understand their perception of access to and quality of autopsy skills education, and evaluate their interest in autopsy and forensic pathology as a future career. Across all Canadian institutions offering anatomical or general pathology programs, 26 percent of residents participated in the survey.

The results are in many ways reassuring – Canadian pathology residents do see value in the autopsy, with 83 percent of respondents rating autopsy education as either very important or important. However, only 47 percent of participants agreed that all residents would easily be able to complete 50 autopsies during residency – and only 18 percent were interested in performing autopsies as a major part of their career. A combined 52 percent were only interested in performing autopsies to secure a desired position or felt having to do autopsies would be a job deterrent.

The quality of autopsy teaching and the number of autopsies performed were identified as the most significant factors affecting interest in performing autopsies as part of a future career. A combined 68 percent of respondents felt that the job market in forensic pathology in Canada was either good (better than most subspecialties) or very good (more jobs than graduating fellows). Of fifth-year residents in their final few months of residency, 71 percent reported having completed 50 or more autopsies.

Given the ambitious national focus of this survey study, the results may be limited by self-selection bias and a relatively low response rate. Nonetheless, they lead me to think that general autopsy skills likely have a role in the future of pathology education. With younger physicians across all specialties having less exposure to autopsy, is there a benefit to bringing an abbreviated version of an "autopsy experience" into the general medical curriculum? I think so – and I urge my clinical colleagues to better familiarize themselves with the role, benefits, and limitations of the autopsy in modern medicine. As with any medical test, it's important that we preserve scarce resources and choose wisely – but let's not lose this important tool forever.

References

1. *RD Hoffman et al., "Position paper from the Association of Pathology Chairs: assessing autopsy competency in pathology residency training," Acad Pathol, 6, 2374289518824057 (2019). PMID: 30783620.*
2. *M Multan et al., "Autopsy education in Canadian pathology programs: a survey of Canadian trainees," Am J Forensic Med Pathol, [Online ahead of print] (2021).*

168 Hours – Maximized

How to make the most of your day in the lab

By Sanam Husain, Senior Staff Pathologist at Henry Ford Health System, Detroit, Michigan, USA

Time management is a crucial factor not just in physicians' performance, but also their wellbeing. So why is it so uncommon to teach this skill in residency training – or at any career stage? Although there is no lack of information on increasing productivity and efficiency in various industries, advice for physicians is hard to find – and specific tips for pathologists are practically nonexistent. Pathologists are generally considered to have higher job satisfaction and be at lower risk of burnout, but increasing workloads,

shorter turnaround time requirements, inadequate staffing, and increased teaching and research expectations are changing that paradigm. As demands on our time grow, we must assess our workdays and look for areas we can modify to increase productivity, improve performance, decrease stress, and provide work-life balance for a fulfilling career.

The average work week consists of 168 hours – not an insignificant amount of time. It may be easier said than done, but adjusting our perspectives – and our habits – can greatly enhance productivity. How do we achieve this?

Prioritize your tasks.

Applying the "triage" concept will help you identify the biopsies and large resections that should be reviewed first. Identifying cases that are urgent at the beginning of sign-out is key to making a noticeable impact in patient care. When clinicians rounding on patients have biopsy results available, they can select the best possible treatment plan for the patient.

Compartmentalize your time.

Designating time slots for sign-out, resident teaching, case consultations, and administrative tasks is crucial. "Time boxing" helps streamline fragmented days – and fewer sign-out interruptions means greater diagnostic accuracy and fewer typographical errors. The Pomodoro technique, which involves working continuously on a task for 25 minutes and then breaking for five minutes, can be applied to any task and can be modified to suit the situation (for instance, with longer working times or extended breaks). Using such techniques can decrease the cerebral and visual fatigue pathologists may experience in a typical workday.

Stop multitasking.

Studies have demonstrated up to a 40 percent decrease in efficiency when attention is split between tasks. Laser-sharp focus on a case will increase diagnostic accuracy, decrease errors, and improve turnaround times.

Eliminating all distractions and focusing on histologic patterns is a vital skill. Entering a state of hyperfocus, or "flow," can facilitate quick and accurate diagnoses. Reduce interruptions by closing your office door or posting a sign – try "Sign-Out In Progress" or "Do Not Disturb."

Set time limits.

To improve turnaround times, keep track of how much time is spent on individual cases. Parkinson's law states that work expands to fill the time available, so a complex resection case may take hours if you are not mindful of time. On the other hand, if you decide to complete a case in 90 minutes, you will give it your undivided attention and – unless further workup is required – you will succeed. Just like surgeons have designated times in the operating room and internists have time limits on each patient encounter, pathologists can delineate time periods in which they expect to complete each case. For example, a tray of uncomplicated gastrointestinal biopsies will be completed in X amount of time depending on the experience and expertise of the pathologist and on the nature of the cases.

Plan ahead.

Reviewing service assignments, teaching responsibilities, and meetings before the work week starts can give a good overview of what to expect from the week. You may want to write tasks in a planner or use software to outline your priorities. For lighter weeks with less clinical work, you can plan to catch up on administrative tasks, work on research projects, develop teaching materials, assemble presentations for upcoming meetings, or read recent literature. Designing and implementing a plan can give you a sense of control and decrease feelings of overwhelm.

Eliminate wasted time.

Audit your usual workday to identify time-wasting activities – for instance, frequent email checks, a simple activity that can consume far more time than expected.

End the day right.

Productivity tips typically include starting the day right – but how it ends has a big impact on overall wellbeing. Wrapping up the day with the knowledge that all important cases are taken care of, and perhaps quickly auditing your pending cases, can yield a sense of gratification that combats physical and mental fatigue. Identifying the first case to be reviewed the next morning is a helpful practice that will give you a sense of control over the following day.

Take breaks.

Taking restful breaks during the workday can greatly increase productivity. A nutritious lunch, walking, quick stretches in the office, and connecting with colleagues (and having meaningful conversations) can all decrease fatigue and help you avoid the classic afternoon slump.

Rest.

One of the best ways to increase productivity is to rest and recuperate. Relaxation through music, reading, socializing, or exercise can tremendously boost productivity. There should be no guilt in taking time off to restore mental, physical, and emotional energy. Carving out time in the evenings and weekends for activities that bring joy and relaxation can do wonders for tired eyes and minds.

Last, but not least, remember that you are not on this journey alone. To improve time management and wellbeing, these efforts must be both personal and management-driven – and they should be implemented at every stage of a pathologist's career, from training to retirement.

Focus on the Future

We're in the spotlight now – so let's use that attention to encourage the next generation of lab professionals

By E. Blair Holladay

The past year has put the laboratory at the center of health care – and put a spotlight on pathologists and medical laboratory professionals like never before. With such attention on our profession, this is our chance to underscore both the essential role we play in patient health and the value of the laboratory as a knowledge center for healthcare. It is an opportunity to emphasize to both patients and health care colleagues that the laboratory cannot and should not be relegated to the back row of health or patient care. At this point, we cannot go back to the way things were, with the vision of the laboratory as a "black box" that does nothing but spit out test results. We have always known what the rest of the world now realizes: that there is so much more to the laboratory than tests in and results out.

Despite the attention now turned our way, our profession is grappling with a major issue: developing a robust workforce. And although innovation and automation surround us, it's clear that the role of the pathologist or medical laboratory scientist – though changing – is still critical to patient care. That's why it's imperative that we fortify our efforts to build a strong, sustainable pipeline of pathology and medical laboratory professionals who will continue to champion the laboratory as a provider of high-quality care for patients as well as a significant and strategic partner in healthcare.

The American Society for Clinical Pathology (ASCP) has developed several programs that speak to these efforts. Our Career Ambassador and Pathology Ambassador programs are dedicated to connecting with students and sparking an interest in the profession. Career Ambassadors targets high school and college students, sharing information and insight on careers in the laboratory; Pathology Ambassadors engage with medical students to encourage them to consider our discipline. Through its NEXTPO program, ASCP has also provided scholarships to college-bound high school students to help them pursue the field of medical laboratory science.

When we concentrate our efforts on building the workforce that is coming up behind us, we are both giving back and giving forward to this incredible profession. Medical laboratory science touches almost every part of a patient's journey, and it is our duty as pathologists and medical laboratory scientists to amplify the voice of the profession. It is our duty to share our knowledge, joy, and satisfaction we get from our own careers with others – and to show them how their own career in the field could provide the same level of fulfillment.

There has been so much attention focused on the laboratory lately that we would be remiss not to capitalize on it by using it to inspire the next generation of pathologists and medical laboratory scientists who will lead our profession. We are at the apex of a premier opportunity to push ourselves deeper into the spotlight – so let's let the incredible and indispensable work we do shine!

Fostering Collaboration and Sharing Know-How

The key to enabling precision medicine in emerging markets

An interview with Umberto Malapelle

Why should we foster precision medicine?

Precision medicine represents the most relevant "break in the wall" of the 20th century – paving the way to improving diagnosis and treatment in a plethora of different pathology settings. Only by fostering the spread of precision medicine and predictive molecular pathology – our key weapons in the fight against cancer and other diseases – can we make a "quantum leap" in our treatment strategies for patients. To scale up precision medicine approaches around the world, we need to address three important points.

1. Boost investment in specific training programs for physicians.
2. Support and accelerate the adoption of next-generation technologies.
3. Foster the molecular tumor board as the new standard of care, rather than an exception to the rule.

How do you envision the molecular pathologist's role in shaping the present and the future of precision medicine?

Predictive molecular pathology is the linchpin of an effective precision medicine approach in routine clinical diagnostics. In this "new world," molecular pathology will play a central role in diagnosis and treatment decision-making. True tailored treatment can only be achieved by starting from a specific morpho-molecular characterization of the patient's lesions aimed at identifying actionable ("druggable") alterations. In this fascinating landscape, I like to think of the molecular pathologist as the "midfielder" of the medical care team.

Can we expect increased collaboration on molecular pathology between Europe and emerging markets?

That would greatly benefit the medical community and, eventually, our patients! I recently had the opportunity to share my personal experiences in predictive molecular pathology with a number of outstanding colleagues from different emerging markets. Nonetheless, the lack of adequate molecular diagnostic infrastructure combined with reduced access to specific training programs – for example regarding next-generation sequencing (NGS) in routine clinical settings – truly struck me, especially considering that NGS platforms are at the heart of predictive molecular pathology today. But I see great opportunities for increasing the mutual exchange of knowledge. We have a lot to learn from each other!

If NGS is at the heart of predictive pathology, why do we still struggle to see wider adoption in the field?

That's a question I have asked myself many times.

In my opinion, we need to take into account the fact that is difficult to leave one's "comfort zone." Conventional technologies, such as Sanger sequencing and real-time PCR, represent simple, robust tools for identifying different types of gene alterations. These are established technologies that have been mainstays in molecular laboratories worldwide for many years. Nonetheless, considering labs' needs in the new era of molecular medicine, the main limitations of such technologies lies in their reduced multiplexing power and low limits of detection. A move from this "comfort zone" to NGS requires infrastructure upgrades (such as data storage), validation experiments, and specific training (with particular attention to data interpretation). These latter represent the main challenges that my team faced while implementing NGS in our clinical practice a few years ago. But it was worth the hard work – overcoming those challenges has led to gains we could not have imagined!

"In the new world of precision medicine, molecular pathology will play a central role in diagnosis and treatment decision-making."

What are the "must-have" features in an NGS platform to simplify the sequencing process?

This is a straightforward answer: speed, simplicity, and automation! Ideally, all of these features would be available in a fully enclosed, fully integrated platform. It pleases me very much to know that, nowadays, such a solution is finally available.

"Speed, simplicity, and automation are the 'must-have' features in an NGS platform to make it more accessible and speeds up the technology adoption."

Does the existence of such a solution mean that predictive pathology implementation in emerging markets can now begin to move faster?

Yes; in fact, this is exactly the right way to speed up adoption! By implementing a streamlined, easy-to-use NGS approach, we can flatten the learning curve regarding the "wet" part of the NGS workflow and the time saved can be used to train personnel in data management and interpretation, improving the quality of clinical reports. In my opinion, this is the best path forward!

How are you assisting with the adoption of NGS technology in other pathology labs?

We have "opened the doors" of our lab by sharing our experience and know-how. We work with our colleagues in other laboratories to identify local problems and find the local solutions. For many years now, our department has offered a master's degree focused on this topic and, thanks to that degree, we have had the opportunity to support a number of laboratories in implementing NGS.

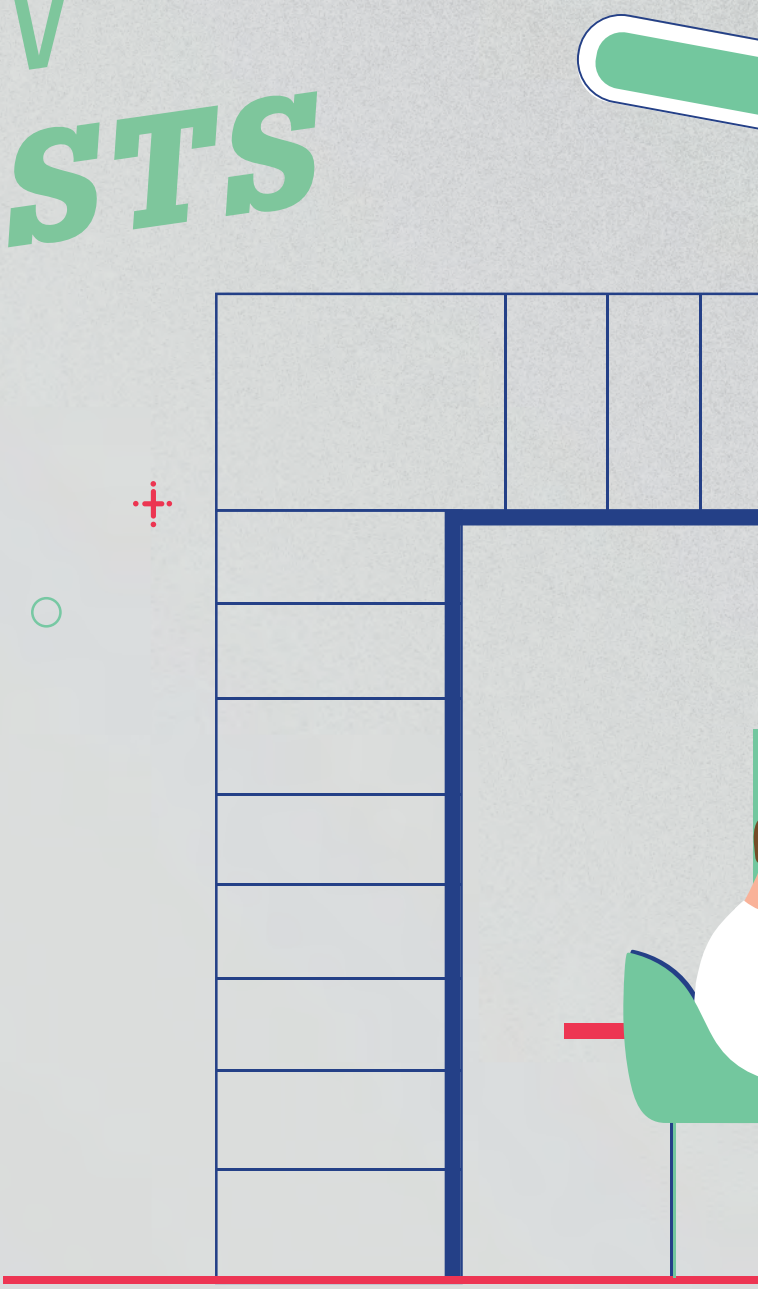
We treasure this experience – and I think we can apply the same model to fostering collaboration, exchanging clinical knowledge, and sharing technical experiences. In addition, we are working with the International Society of Liquid Biopsy to organize an educational program focused on the minimum lab requirements for boosting NGS utilization for liquid biopsy testing. So, in other words I am fully open for collaborations!

SPECIAL SERIES
Education & Training

THE NEW SCIENTISTS

Introducing the Einstein Montefiore Summer High School Research Program: building the future of science and medicine

A fly-on-the-wall interview with
Amy S. Fox and Victoria Freedman



MEET THE FOUNDERS

Amy Fox (pictured left) is Professor of Pathology and of Pediatrics at Albert Einstein College of Medicine and Chief of Point of Care Testing and Outreach Laboratories and Director of Clinical Research and Clinical Trials at Montefiore Einstein Department of Pathology.

Victoria Freedman (pictured right) is Assistant Professor of Microbiology and Immunology and Associate Dean for Graduate Programs in Biomedical Sciences at Albert Einstein College of Medicine.

SERENDIPITY IN THE WORST SEATS

Victoria Freedman: I'm perennially late – always running from one thing to the next – and so is Amy. Now, it's important to note that the "best" seats in a lecture are always at the back of the auditorium so that you can get out quickly if your beeper goes off. Or, strategically, if you're a busy person and the lecture doesn't look like it holds value, you want to be able to get out...

Amy Fox: But when Vici and I were both late to the same lecture, the only seats left were in the very front row. Our shared bond over terrible seating got us talking. I mentioned that I did clinical research and Vici brought up her undergraduate research program (for university students) and said, "Maybe we could work together." It was as simple as that!

Vici: When Amy and I met, I had established a robust summer undergraduate research program that brought students into labs to introduce them to research and prepare them for careers in the biomedical sciences. The only piece we were missing? Clinical research. And that's what Amy brought to the equation.

Amy: It's something I was already doing informally, but without the classes, field trips, and other benefits Vici and her team had organized. Bringing the two together was a perfect marriage! The only problem was that, as we explored the possibilities, we realized that we were reaching students way too late. Ideally, we'd get them in kindergarten – but that's impossible, so

high school is the next best thing!

Vici: We realized that the students in our program were already committed to the career paths they had chosen – and that, with or without our program, they had every opportunity available to them. These students were going to do well no matter what. We wanted to open a program to students who had few opportunities – students who didn't know much about science or medicine, may not speak English well, and had no chance of success without support. That's when we started talking about a high school program focused on students from the Bronx – our local area, where the income level is extremely low and the educational resources very poor.

Amy: We're both from the school of "it's better to ask forgiveness than permission," so we wrote and submitted a grant to the Siemens Corporation – and they gave us US$25,000. It was like Christmas! Next problem? We had money – but no students.

"WE WANTED TO OPEN A PROGRAM TO STUDENTS WHO HAD FEW OPPORTUNITIES – STUDENTS WHO [...] HAD NO CHANCE OF SUCCESS WITHOUT SUPPORT."

So I sat down and I began to call high school principals. Can you imagine taking this call? "My name's Amy Fox. I'm a physician at Montefiore, we've just received a grant from the Siemens Corporation, and we're starting a high school research program at the Albert Einstein College of Medicine. Can I get on your calendar?" Who would say no? And no one did – from the prestigious Bronx High School of Science to the local schools that barely had a science program, everyone called us back. And then we came to our next problem – who was going to invite these 16-year-olds into their labs for the summer?

Vici: We asked faculty to identify graduate students and postdocs in their labs who were interested in working with high school students. It was not only an intellectual commitment, but a time commitment as well – scientists, who typically work odd hours, had to commit to being in the lab during the same "daylight hours" as their students. One by one, we identified the problems and – by sheer force of will – overcame them. Everything from participant permission slips to which chemicals minors are allowed to use. In the end, we had a lot of opportunities for zebrafish studies – educational, but innocuous!

Amy: We didn't just want students who had top

grades in top schools; we wanted students with a passion for intellectual inquiry into the areas of scientific discovery. And that's what we told them from day one: that the six weeks of the program were about nurturing their love of science.

Vici: We wanted the students to know that science is all around us, so we didn't limit their experience of science to our labs at a major research institute. We took a trip to the Bronx Zoo, where we spent the morning in the veterinary pathology lab and had a series of lectures by veterinary pathologists about all kinds of zoonotic diseases. We also took them to a genome exhibit at the American Museum of Natural History and behind the scenes at the New York Botanical Gardens, where they study the active ingredients in folk medicines to identify future drugs. The students even got to see Charles Darwin's original writings there!

Amy: I went on that trip three times. We also took the students to a Broadway show with the undergraduate summer students, which helped the two groups form a relationship. The natural conversation that evolved over time between the high school students and the undergraduates gave them a view of the future; they could see where they might be in four years' time.

Our students are a heterogeneous group; we get people from the inner-city Bronx who have never even considered college or a professional career and we also get people from the elite high schools of New York. Once they get here, though, they're all one group – and each side derives benefit from a relationship with the other. The program has helped us form unique relationships with inner-city Bronx high schools. We have students who originally believed their education would end at high school – but who go on to attend Ivy League universities. So many young people have said to us, "I didn't know I could be a nurse." "I didn't know I could be a doctor." "I didn't know I could be a scientist." The Einstein Montefiore Summer High School Research Program isn't just about six weeks of research; it's about opening up the whole world to every participant.

We've been doing this for seven full years now and not only have we seen students from our high school program return to do undergraduate research at Montefiore, but we've even seen two of our former students get married while attending medical school together!

TWO SIDES TO EVERY COIN

Vici: Although the experience has been amazing, we have to be realistic – it's not a bed of roses!

Amy: This is not a program for everyone; we've had one or two students who have had to drop out of the program. These are students who have family responsibilities or night jobs they have to work to support themselves. It would be miraculous if we could give these students a stipend so that they could complete the program. We're not there yet, but one day we might be.

Vici: We've learned some important lessons along the way – for instance, that it's hard to fund a program year on year. Each year, we scrambled to find funding – and each year we managed to find just enough for that summer. We need a sustained source of funds, which we have yet to find.

We also had communication issues. Because we're involved with medical students, graduate students, and postdocs, it took us a while to learn how to speak the language of teenagers. We also had to shift our expectations. When we started, we had the notion that all of our students would be from underserved areas – but it turned out that, although we could have done that, it was even more powerful to bring those students together with peers from more privileged backgrounds.

Amy: They all learned from each other. One student had no computer – so the others banded together and lent him one. Another traveled two hours each way on public transportation to get to campus – so the others found ways to drive him or at least to meet him on the journey. The camaraderie between these young people was inspiring.

Vici: It also helped that the students with more resources were completely focused, not only what college they were going to, but also on what they might do afterward – careers, graduate school, medical school… The other students hadn't even had those ideas yet, so when they saw others their age with such lofty goals, they began to "think big," too. It changed everyone's perspective.

Amy: To ensure we reached the under-resourced communities we wanted to serve, we cast a wide net early on. We phoned all of the high schools in our area – we don't offer boarding, so students must live locally – and, thanks to our early networking success, the program now has tremendous word of mouth. It takes tenacity to get to this point, though.

Vici: It's also important to understand our environment. It's not difficult to find underprivileged schools; in fact every school in our local area qualifies. It's actually more difficult to find students from privileged schools because that is a different net – and we have to balance the two sides carefully.

Amy: Establishing this kind of program is not without its challenges – but if I could send one message to anyone in a position to do it, I would say, "Just do it." It may not be easy – especially if you have to find support and funding – but it's worth it. And we're happy to share our blueprint. There are many science programs for high schoolers, but ours stands out in two key ways: it offers six weeks of daily interaction with both peers and professionals – and it's free to access.

I've now passed the co-directorship of the program on to my colleague Michele Ewart, but I'm remaining on board in an advisory role.

Vici: We want to see this work spread around the world. It's an investment in our future. We're capturing

> "WE WANT TO SEE THIS WORK SPREAD AROUND THE WORLD. IT'S AN INVESTMENT IN OUR FUTURE. WE'RE CAPTURING STUDENTS' ATTENTION YOUNG."

students' attention young – and now, in the midst of a pandemic, it's the perfect time to not only spot the scientists of the future, but get them excited about science.

SUPPORT IS EVERYTHING

Vici: Amy and I had a great idea – but what really made it work was the synergistic effect we had on each other. What one of us didn't do, the other did. We didn't plan that; it was serendipity!

Because of Amy's position in the Department of Pathology (and her status as a well-known pathologist, virologist, and

point-of-care testing expert), everyone knew her. I was also relatively well-established on the academic side of things. As a result, we had a lot of relationships to draw on. Would another clinical department have worked equally well? I don't know – but I do know the breadth of pathology made it a good place to start.

Amy: I couldn't have done this without the support of my department. In fact, I co-opted everyone who worked with me and said, "How can you help?" The students became part of the department, so everyone became invested. Instead of asking me why I had to miss a meeting for a field trip, it was, "Can I come on the trip, too?" Instead of trying to avoid meet-and-greets with the students, it was, "Can I do a demonstration? Can I show slides? Can I give a tour of my lab? Can I introduce them to what it means to be a pathologist?"

I was surprised at how eager my colleagues were to share their work with high-schoolers. They weren't just coming for a free lunch – they didn't want to leave!

Vici: We make it clear to both participants and supporters that our goal is to foster a love of science. The program isn't a fast-track to a Nobel prize – or any prize. It's not a fast-track to scholarships or admissions. We're very proud of everything our alumni have achieved, but those achievements are because we gave them a chance to experience the realities of a career in science early – and that brand-new experience kindled their passion for science.

If you ask children in elementary school to picture a scientist, they'll think of an old white man with crazy hair. But if we ask students who have finished our program, they picture themselves.

Amy: It opens up a world to them that they never realized could be theirs.

STARTING YOUR OWN PROGRAM

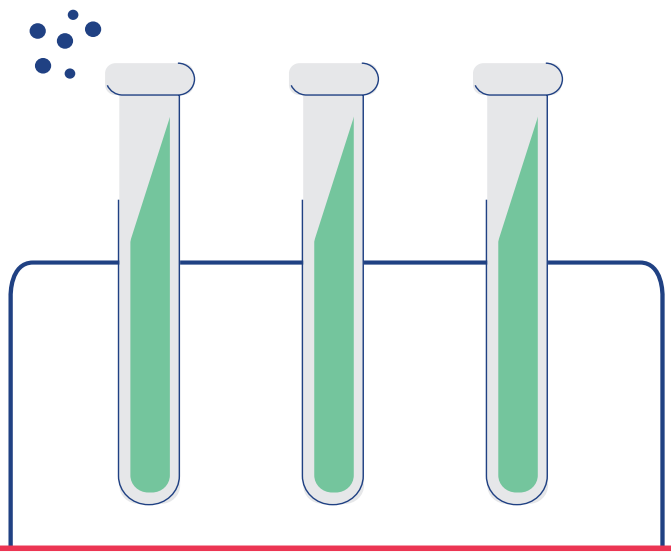
Amy: Even now, in the age of the five-second email, I'd encourage people to begin just like we did – with a phone (or video) call. Nothing replaces a personal relationship. Why? Everything revolves around trust: between us and the institution; between us and the high schools; between us and the parents. Can you imagine asking the parents of an inner-city teenager to let their child travel two hours a day to join our program instead of earning a summer wage and helping support the family? That has to be personal. You can't put it in an email; you have to pick up the phone and say, "Trust me with your 16-year-old because, if we're successful, this may change their life."

Vici: You need to engage parents. Before the summer high school research program started, I hosted an event called Bronx

"IF YOU ASK CHILDREN TO PICTURE A SCIENTIST, THEY'LL THINK OF AN OLD WHITE MAN WITH CRAZY HAIR. STUDENTS WHO HAVE FINISHED OUR PROGRAM PICTURE THEMSELVES."

Science Day for middle-schoolers and their families. A team of graduate students and I took over an empty lab, borrowed equipment, and set up experiments. And I discovered that kids love this stuff, but they're also used to it. It was the parents who had never seen an experiment before – and, when we showed them, they couldn't get enough! That really taught me the value of reaching out to not just children, but parents as well.

Amy: We also serve a wide range of cultures. We've had female students whose culture didn't permit them to be alone in the lab with a man – so we worked with their families



to find ways for her to complete the program under those conditions. We've had students who were heavily involved in competitive sports and we've had to work with parents to evaluate whether or not the program could accommodate that involvement – and, if not, which option was in the student's best interests. After all, our participants are still children. They need to explore their interests and pursue their passions.

So my advice is to stay personal. Consider the whole child and the whole family, and build a relationship with them that sets the student up for success.

LESSONS LEARNED

Vici: The most important thing I've learned is never to underestimate the talent, interest, or energy of a young person who is exposed to science for the first time.

Amy: With the right set of ingredients, our students' eagerness and desire to learn permeates all spaces. Faculty become not just willing partners, but devoted mentors. And that initially surprised me; these are extraordinarily busy people and there's no incentive to participate – but the students' enthusiasm is an irresistible force. When we say that children are the future, it's not just conversation.

Amy S. Fox is Professor of Pathology and of Pediatrics at Albert Einstein College of Medicine; Chief of Point of Care Testing and Outreach Laboratories and Director of Clinical Research and Clinical Trials at Montefiore Einstein Department of Pathology, Montefiore Health System, Bronx, New York, USA.

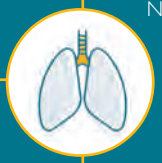
Victoria Freedman is Assistant Professor of Microbiology and Immunology and Associate Dean for Graduate Programs in Biomedical Sciences at Albert Einstein College of Medicine, Bronx, New York, USA.

KRAS G12C: The Mutation You Thought You Knew
Six reasons the *KRAS* G12C mutation matters

1. *KRAS* G12C IS TUMORIGENIC AND SUPPORTS CANCER GROWTH AND SURVIVAL

KRAS regulates multiple signaling pathways involved in cell proliferation, differentiation, and survival, including the PI3K, MAPK, and RAL pathways.[1,2] *KRAS* G12C, a point mutation at codon 12, substitutes a cysteine for the original glycine, favoring the activated state of *KRAS* and driving oncogenic signaling and tumorigenesis.[3]

2. *KRAS* G12C IS THE SECOND-MOST COMMON DRIVER MUTATION IN NON-SQUAMOUS NON-SMALL CELL LUNG CANCER (NSCLC)



KRAS is the most frequently mutated oncogene across human cancers. Among patients with non-squamous NSCLC, 13 percent – more than one in eight – will exhibit the *KRAS* G12C point mutation.[4] This is comparable to the prevalence of *EGFR* mutations (15 percent),[5] and this prevalence is more than the other six actionable biomarkers (*ALK, BRAF V600E, MET exon 14* skipping, *RET, ROS1,* and *NTRK*) combined.

3. TARGETING KRAS^{G12C} HAS BEEN A 40-YEAR QUEST

Historically, KRAS targeting has proved challenging due to a lack of surface pockets on the KRAS protein for binding, a high affinity for GTP (preventing competitive inhibition), and non-selective binding of inhibitors to wild-type KRAS. Now, structural analysis has revealed a narrow binding pocket (P2) along with an adjacent histidine near the G12C mutation on the inactive form that may provide an allosteric site to stabilize drug-protein interaction. Covalent inhibitors may be able to bind to the inactive form of KRAS^{G12C}, with the goal of locking KRAS^{G12C} in its inactive form, thereby disrupting oncogenic signaling.[6,7]

4. CLINICAL GUIDELINES RECOGNIZE THE VALUE OF KNOWING *KRAS* STATUS IN NSCLC

CAP/IASLC/AMP and ASCO guidelines recommend testing for both actionable and emerging biomarkers for all patients with advanced NSCLC. Targeted testing may be considered for some actionable biomarkers, whereas a comprehensive panel is recommended for some actionable and emerging biomarkers.[8,9,10] CAP/IASLC/AMP and ASCO guidelines currently recommend *KRAS* testing as part of a comprehensive testing panel.

5. THE TRUNCAL NATURE OF *KRAS* MATTERS

KRAS mutations are truncal in nature, meaning that they occur early and are generally stable throughout the course of the disease – as opposed to other mutations, such as *EGFR T790M,* that may develop over time.[8,11] This means *KRAS* status can be known at diagnosis of NSCLC. The presence of *KRAS* mutations may also eliminate the need for further molecular testing, because *KRAS* mutations are typically mutually exclusive of other driver mutations, such as *EGFR, ALK,* and *ROS1.*[12,13]

6. YOU CAN TEST FOR *KRAS* G12C USING YOUR EXISTING APPROACHES

The *KRAS* G12C point mutation can be detected in tissue and liquid biopsy specimens via common molecular testing methods such as next-generation sequencing (NGS) and polymerase chain reaction (PCR).[14,15] It already appears on most NGS panels – and it's why, if you aren't already testing for *KRAS* G12C, you should consider starting. Already testing for *KRAS* G12C? Consider specifically calling it out at the variant level in your reports – and standardizing notation by placing "G12C" in the synopsis.

To learn more about Amgen's work in *KRAS* G12C and the importance of biomarker testing visit *FindKRASG12C.com*.

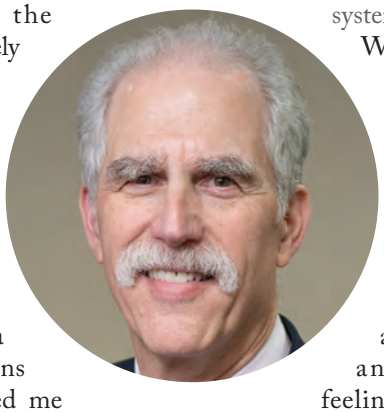
References available online at: tp.txp.to/amg-kras

An Untapped Opportunity for the Laboratory

Reducing diagnostic error with the Society to Improve Diagnosis in Medicine

By Paul L. Epner

Every year, 12 million adult Americans in outpatient settings experience a diagnostic error (1), defined by the National Academy of Medicine as the "the failure to establish an accurate and timely explanation of the patient's health problem(s) or communicate that explanation to the patient (2)." Approximately 100,000 patients lose their lives prematurely in hospitals alone (3). It is a complex problem and the causes are many, but the opportunity for laboratory physicians and scientists to play a greater role in solutions to this problem spurred me to leave my longstanding career in laboratory diagnostics to focus on the notion that laboratory medicine can make a greater difference to patient outcomes than it does now. In fact, it is a critical element of healthcare and can make or break a patient's hopes for the future – particularly in the context of diagnostic error.

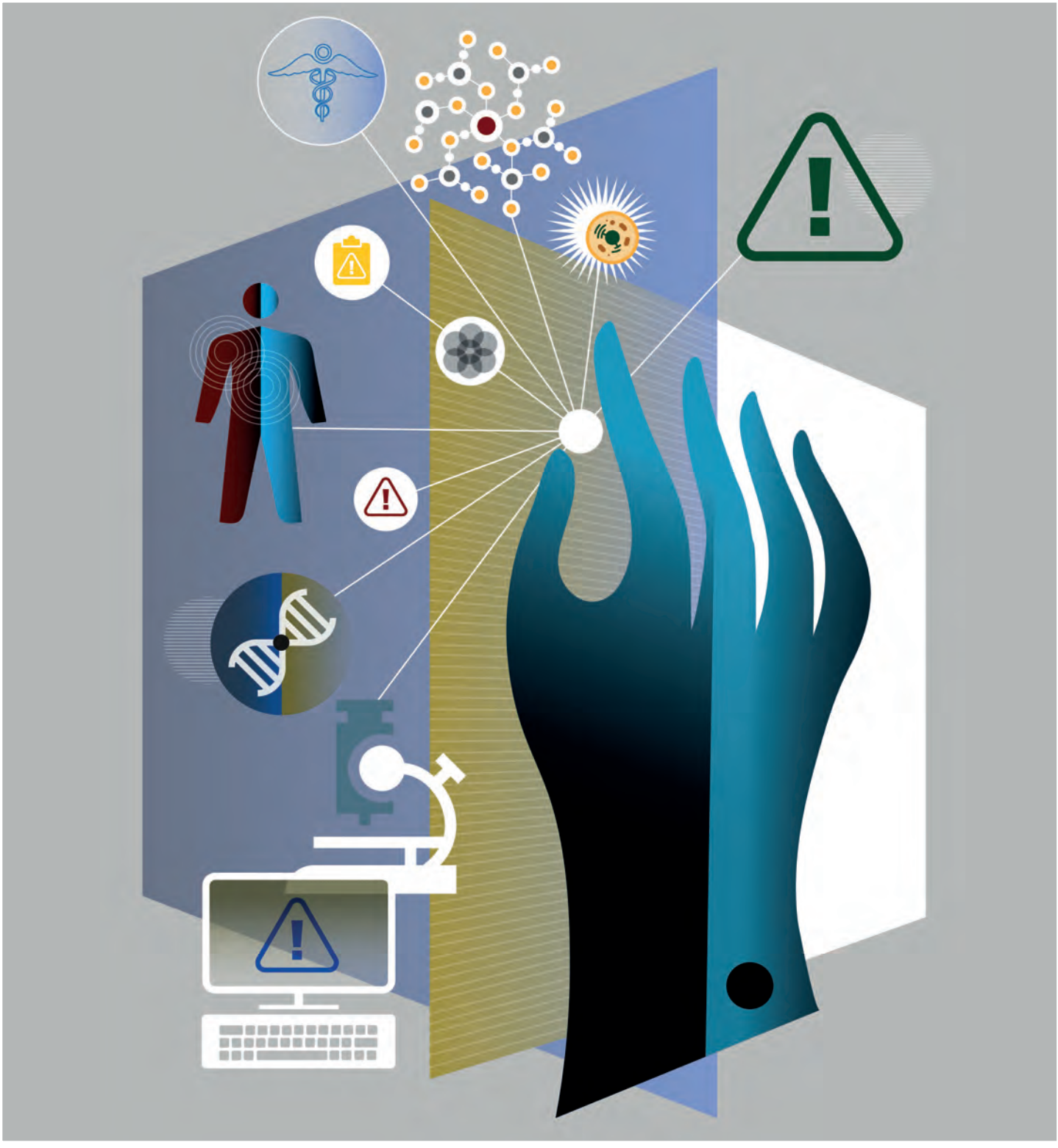


Patient and health system impact

When patients seek medical care, they trust their clinicians to make the right diagnosis. When failures happen, this trust is tested, the relationship between doctor and patient weakens, and patients are left feeling worried that they may not get well or find out what is wrong with them. We all know a family member or friend who has gone on diagnostic journeys that went on too long or produced wrong answers, sometimes with catastrophic outcomes.

"Diagnostic error is the number one cause of preventable harm in our health system."

Diagnostic error is the number one cause of preventable harm in our health system – some say larger than every other safety issue (e.g. medication errors, wrong-side surgery, hospital-acquired infections) combined. But the significance of diagnostic error impacts not just the patient, but also the health system – there are estimates that it costs the US economy



in excess of US$100 billion per year (4). The domino effect of such an error is intuitive: if the diagnosis is wrong, how likely is it that the treatment plan is right?

Common causes

The causes of missed or delayed diagnosis are many. With over 10,000 diseases, 4,000 tests (not including all genetic variants available for testing), and only 50-100 common symptoms, coming up with an accurate diagnosis is a complex process. And with all diagnoses, there is uncertainty. The disease process and its presentation evolve over the course of the illness, but presentations can also vary substantially between patients – only adding to the difficulty. With this level of uncertainty and variability, it can be hard to generalize about what constitutes a timely diagnosis. Egregious delays tend to be obvious in retrospect, but differentiating between inappropriate delay and conservative approaches to diagnosis can be daunting. In many ways, it's amazing that clinicians do as well as they do with estimates of diagnostic accuracy and timeliness at approximately 90%. Still, some clinicians and some systems do better than others, so we know improvement is possible.

The role of testing in diagnostic quality

If you examine malpractice claims leading to death or permanent disability, diagnostic errors form the largest category. Of these claims, approximately 75 percent fit into one of three categories: vascular events, infections, and cancers. While the average claim had more than three contributing factors, clinician judgment was involved in 85 percent of all serious diagnostic errors – often due to the failure to order the correct test or interpret the result properly (5).

Ordering the correct test has been made somewhat more difficult by the attention given to the overuse of tests and procedures in medicine. While unintentional, this focus has potentially led to a bias towards under-ordering rather than appropriateness. Yet, research has shown that under-ordering of appropriate tests is more prevalent than over-ordering (6). A focus on appropriateness could have a large positive impact on reducing diagnostic error.

Another common cause of diagnostic error related to judgment is failure to create a proper differential diagnosis – that is, the establishment of the list of disorders that could fit the signs and symptoms (5). If the true disorder is not on the differential, then it is likely that the tests needed to confirm or rule it out won't be ordered. Independent of the differential, we also know that clinicians are often uncertain about what tests to order or how to interpret the results (7).

In addition to clinical judgment issues, the research highlights communication and system issues. In fact, 33 percent of claims involve communication issues – some of which involve communicating test results to patients. System issues include failure or delay in processing tests, receiving results, or executing follow-up of test results (5)

What needs to be done

We owe it to patients to improve diagnosis and this will take addressing multiple structural and process gaps, because there is no one cause for this tragic problem. We need a standardized approach to identifying diagnostic errors when they occur, a quality system that collects diagnostic error data, processes to learn from the data, and the tools to do something about it.

Despite its prevalence, diagnostic error is rarely a top priority for healthcare quality. Most incident reporting systems do not have a category for these errors; instead, they are distributed across multiple other categories, concealing their cumulative burden. We also haven't established consistent methods to study them effectively. For example, if an adverse event involves clinician judgment, it is typically sent to peer review; if system failures are identified, it goes to root-cause analysis. But we know that most diagnostic errors involve both cognitive and system failures, thus this bifurcated approach fails to holistically analyze causes which could lead to more impactful findings.

"We owe it to patients to improve diagnosis and this will take addressing multiple structural and process gaps, because there is no one cause for this tragic problem."

The clinical laboratory has a major opportunity to contribute to resolving this problem. While the laboratory itself is one of the highest quality and most reliable settings in the health system, the pre- and post-analytical phases that include test ordering and result interpretation are major opportunities for improvement – and laboratory physicians and scientists are uniquely positioned to provide leadership in this area. Recognizing this need, many laboratory

professional organizations have joined with the Society to Improve Diagnosis in Medicine (SIDM) and participate in its Coalition to Improve Diagnosis

SIDM and the Coalition to Improve Diagnosis

At SIDM's strategic planning meeting in 2013, we discussed the lack of awareness of the problem and the dearth of research to understand and improve it. We petitioned the National Academy of Medicine (NAM, formerly the Institute of Medicine) to study the problem, which they agreed to do. Expecting the results in 2015, and concerned that the report might not drive action without purposeful next steps, SIDM convened the Coalition to Improve Diagnosis.

The Coalition formed in August 2015 with 14 members, one month prior to the publication of the NAM report – and we have been growing ever since, numbering now more than sixty. Our membership is diverse and includes medical professional associations, accrediting organizations, health systems, and patient safety, disease-specific patient advocacy, and health management organizations. It also includes liaisons from multiple government agencies.

The objectives of the Coalition are threefold: subscribe to a common set of principles; work together on collective actions; and have member organizations commit to taking their own action directed toward improving diagnosis. The collective actions thus far have focused on: building awareness and engagement; advocating for increased research funding from Congress; and identifying and disseminating effective interventions.

The success story – so far

The group's collective actions have already helped raise awareness of the challenges facing diagnostic medicine. In 2018, the coalition launched the ACT for Better Diagnosis campaign as a targeted effort to increase awareness of the need to improve Accuracy, Communication, and Timeliness. The group developed a consensus document calling for more congressional funding and, in 2019, Congress created a new line item with earmarked funding for diagnostic quality, along with the creation of an interagency taskforce to address a coordinated response. In 2020, an increase in the funding occurred.

Media coverage of diagnostic error has grown dramatically since our efforts began, which has helped significantly, and our members are making great progress in their individual actions. Several organizations have established major initiatives around this problem – some small, some large – which represent a tremendous effort that was non-existent before the coalition was formed.

Measuring future success

Going forward, a clear reduction in diagnostic errors will be the best evidence of the Coalition's success. Even now, activities in the field are snowballing – from the National Quality Forum's new study section (their second on diagnostic errors) to an increase in grant opportunities from government agencies and private foundations.

Significant progress takes time. Engaging a community of stakeholders to successfully run a multipronged initiative on the problem reflected by a marked decrease in errors will be a multi-year effort. Given that we still are absent rigorous measures to count diagnostic errors locally or nationally, seeing a numerical reduction in error in the next two to three years is unlikely. However, we can assemble an ever-growing body of anecdotal evidence about what works and slowly move towards consensus measures and improvement strategies. It is a long process, but we will only get there by taking action now.

At this moment, the Coalition is solely a US effort because so much of practice is driven by country-specific policies and payment systems. However, diagnostic error is a global problem and SIDM works with stakeholders in every country that is interested, convening educational meetings. We even recently established an affiliate chapter in Australia. Global problems need global efforts to find global solutions.

Based on SIDM's research, we know that diagnostic errors are the most common, most catastrophic, and most costly of all medical errors. To make a significant difference, each of us needs to play a part to reduce these errors. In particular, laboratory physicians and scientists have a growing number of tools to increase objective evidence that supports diagnosis, but they are tools that need the professionals who wield them to ensure they are used properly. Together, we will reduce the devastating consequences for our patients and for the healthcare system.

Paul Epner is Chief Executive Officer and Co-Founder of the Society to Improve Diagnosis in Medicine, and Chair of the Coalition to Improve Diagnosis.

References

1. *H Singh et al., BMJ Qual Saf, 23, 727 (2014). PMID: 24742777.*
2. *National Academies of Sciences, Engineering, and Medicine, Improving Diagnosis in Health Care. The National Academies Press: 2015. PMID: 26803862.*
3. *CG Gunderson et al., BMJ Qual Saf, 29, 1008 (2020). PMID: 32269070.*
4. *DE Newman-Toker, "The Team Sport of Diagnosis: A Culture Shift Can Reduce Missed Diagnoses" (2016). Available at: http://bit.ly/3dU9ESs.*
5. *DE Newman-Toker et al., Diagnosis, 6, 227 (2019). PMID: 31535832.*
6. *M Zhi et al., PLoS ONE, 8, e78962 (2013). PMID: 24260139.*
7. *J Hickner et al., J Am Board Family Med, 27, 268 (2014). PMID: 24610189.*

Prognostic Patterns in Gigapixel Images

Risk-stratifying patients through deep learning

By Heather D. Couture

From detecting and classifying cells and tissue to predicting biomarkers and patient outcomes, computational pathology applications are becoming increasingly complex. Simpler tasks rely upon pathologists' annotations of specific features in the tissue – but biomarkers and outcomes are more complex. Algorithms must decipher whole-slide images without any prior knowledge of which characteristics or tissue regions are important. And the task becomes even more difficult when machines are asked to forecast patients' prognoses over time.

Risk stratification can already be done using cancer staging, molecular features, or clinical variables. Improving prognostic insights – predicting the likely outcome for a patient following the standard treatment – is a greater challenge and an active area of research. Take, for example, ductal carcinoma in situ (DCIS), a pre-invasive form of breast cancer. Many such cancers do not become invasive – but which ones will? There is a great deal of interobserver variability amongst pathologists assessing such lesions (1,2). But researchers at Georgia State University have developed an algorithm

that can predict the risk of local recurrence of DCIS within 10 years using digitized whole-slide images (3). Risk stratification could also involve forecasting tasks; for example, predicting whether a distant metastasis will occur or how long a patient is likely to live. Regardless of the target, the challenges in creating such algorithms are similar.

H&E whole slide images are large and tissue appearance is diverse. Unlike methods to find mitoses or segment tissue types, pathologists cannot annotate which regions of the tissue are associated with patient outcome – at least not with any degree of certainty.

Capturing prognostic patterns

Traditional approaches to predicting patient outcomes from histopathology mimic the work of a pathologist. They take features that pathologists already use to stratify patients and create algorithms to automate the extraction of these characteristics. For instance, both human pathologists and automated algorithms will demonstrate an association between cellular diversity and lower survival rates in non-small cell lung cancer (4). One major advantage of this approach is interpretability; because pathologists already understand what these features look like, the results from automated methods make sense.

If pathologists already had a superior ability to predict patient outcomes from histopathology, this approach would be great. However, the visual complexity of these gigapixel whole-slide images presents a challenge because of their huge size, intricate appearance, and internal heterogeneity. So if pathologists cannot reliably stratify tumors by risk, an algorithm that takes the same approach is unlikely to do much better.

Enter deep learning. Over the last decade, deep learning has revolutionized speech recognition, language translation, facial recognition, and many other tasks. The keys to its success are large amounts of data and the end-to-end method for learning models. Image features don't need to be predefined; the model learns them itself. It can learn complex and abstract properties even beyond the capabilities of human visual processing – all based on a training set of labeled images.

Such models learn to extract patterns that are predictive of some target – for instance, whether a tumor is low- or high-grade. For outcome prediction, the target could be the time to a particular event – such as cancer recurrence or death.

Of course, many factors determine how long a patient lives. The morphology of their tumor is only one piece of the puzzle. Predicting the time to event (recurrence or death) directly is challenging for two additional reasons: only a small fraction of patients will experience the event during the study and not all patients who experience the given event will be recorded. Instead of predicting exactly how long a patient is likely to live, most survival models take a contrastive approach: is patient A likely to live longer than patient B? If the model incorrectly predicts which patient lived longer, it gets penalized. From each incorrect prediction, the model adapts to perform slightly better for subsequent examples.

From hypothesis to risk prediction

Deep learning models consist of multiple layers, with higher-level concepts built upon lower-level ones. Each layer of the network has a set of weights that are used to compute a representation for the next layer. The weights are like a hypothesis regarding what properties to look for in the image. Models often have over 100 layers and, across all layers, upwards of 10 million weights to tune.

After passing an image into the network, each layer computes a new representation based on the output from the previous layer. At the end of the network, it predicts the target – in this case, a patient risk score. The goal in training the network is to minimize erroneous predictions.

Training a model involves adjusting each weight a little bit at a time to lower the total error. This way, the model improves its hypothesis about which image properties are important. With each new patient image and the associated survival time, the model gets a little better. After seeing many images – and artificial variations of each to provide extra examples – the model learns to predict patient risk.

But there is one more challenge in handling gigapixel histopathology images

– their size. Whole-slide images can be more than 100,000 pixels across. End-to-end training is not possible with images this large because they won't fit on the graphics processing unit that trains deep learning models. Most solutions to this problem break the images into small patches. In some studies, a (human) pathologist identifies tumor regions for training, whereas in others, the deep learning model is trained on all tissue patches (5). Another approach is to first cluster the patches by visual appearance, then use a subset of patches from each cluster (6). Regardless of the chosen approach, risk predictions from the patches must then be aggregated to form a final risk score for the patient. Often, this is done by a model that learns to select the most informative patches.

The power of histopathology

Histopathology brings with it some unique challenges – and advantages. Outcome prediction models specific to histopathology data have been built to overcome those challenges. Federated learning models, for instance, can handle datasets located in different centers to preserve privacy (7). And models can learn to predict survival across multiple types of cancer simultaneously (8,9).

Histopathology is, of course, not the only modality with a demonstrated ability to predict patient outcomes. Whole-slide images can be combined with genomic and clinical features to improve outcome predictions, all within the same deep learning model (9,10,11). Some pan-cancer studies have shown that clinical data and gene expression are most beneficial in predicting prognosis and that histopathology features provided no additional predictive power (9,12). However, deep learning-based methods for whole-slide images are still a new innovation – and they have yet to reach their full potential.

Histopathology provides a unique perspective that a single genomic profile cannot: a spatial view of the tumor. Researchers are just beginning to understand the role that intratumoral heterogeneity plays in tumor progression (13,14,15). These spatial variations can be captured from images far more efficiently than with genomic profiling.

Although interpretability is still a challenge for deep learning models, they also benefit from the spatial variations of whole-slide images by indicating which regions of the tissue are most associated with a poor outcome. In some cases, the highlighted regions are not even in the tumor itself, but in the adjacent stroma (16) – information that can provide new insights for pathologists.

H&E histology is a routine part of the pathology pipeline. It is cheaper and faster than molecular analyses. As the transition to digital pathology accelerates, these whole-slide images provide many new opportunities to capitalize on artificial intelligence. Prognostic models with deep learning are promising, even if they are just beginning to show their potential. Perhaps all we need is a larger dataset to allow us to find the most prognostic patterns in these gigapixel images.

See references online at: tp.txp.to/giga-imgs

European Society of Pathology

33rd European Congress of Pathology

Pathology: Compass for optimal patient therapy

29 – 31 August 2021

www.esp-congress.org

One Slide, All the Answers

An innovative RNA in situ hybridization (ISH) technology both localizes and quantifies RNA biomarkers, providing comprehensive diagnostic information on a single slide

Traditional ISH techniques rely on directly labeled nucleic acid probes and, consequently, may suffer from suboptimal sensitivity and specificity (limited ability to detect low-expression transcripts and relatively high levels of nonspecific staining). Advanced Cell Diagnostics (ACD, a Bio-Techne brand) RNA ISH – RNAscope™ – overcomes sensitivity issues by amplifying mRNA transcripts ~100-fold relative to traditional ISH technology. At the same time, it largely eliminates background noise by means of a paired probe approach. To learn more about this highly specific and sensitive system and its expanding diagnostic applications, we spoke to Dr. Rob Monroe, pathologist and Chief Medical Officer of Bio-Techne.

Superior detection, adaptable readout

RNAscope employs the proprietary Double-Z system, comprising Z-shaped paired probes in which the lower regions are complementary to target RNA and the upper regions consist of a 14-base tail sequence. Both probes must hybridize to contiguous target sequences for amplification to occur, greatly improving specificity. And, because a signal can be detected from only three Double-Z probe hybridizations, Bio-Techne's approach enables unambiguous identification of even very low-expression targets or fragmented mRNA transcripts common in formalin-fixed paraffin embedded (FFPE) tissue specimens. Notably, detection at a single-RNA molecular level is possible with the RNAscope signal amplification system. "The biomarker targets can be visualized with either chromogenic or fluorescent RNAscope detection kits according to user requirements," says Monroe.

Easy adoption

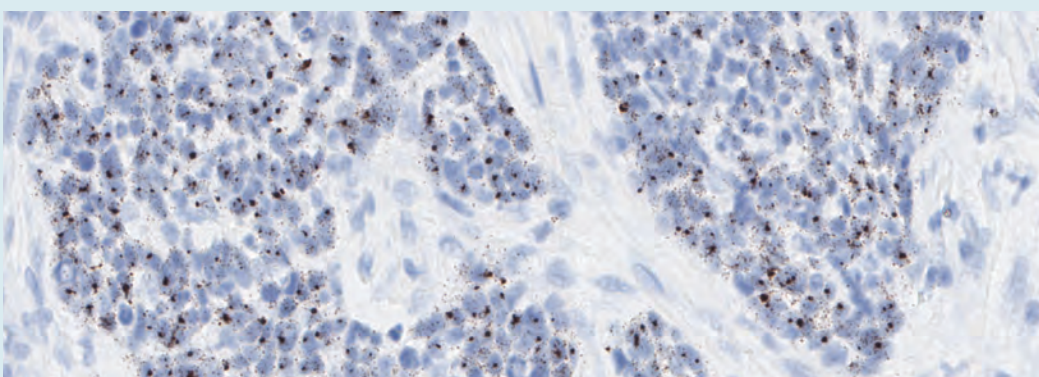
Monroe emphasizes the technology's user-friendliness, noting that no specific training or technical expertise is needed. "Lab technicians or researchers need only two ACD reagents: a target-specific probe and a detection kit," he says. Regarding the former, many users find what they need in ACD's catalogue of >30,000 probes spanning many different organisms and species. Failing that, says Monroe, submission of a GenBank target sequence will be used by ACD to design a sensitive and specific probe with an extremely low probability of cross-reacting with other targets.

The RNAscope procedure is straightforward and is ideally performed on an automated platform or with a hybridization oven to control slide temperature and humidity during amplification reactions. Unlike immunohistochemistry (IHC), RNAscope assay protocols are similar regardless of the target probe. Assay optimization steps are minimal relative to IHC antibody optimization, which requires testing various antibody clones, titers, and antigen retrieval methods. The technique's simplicity, reliability, and uniformity make it accessible to almost all clinical and research laboratories.

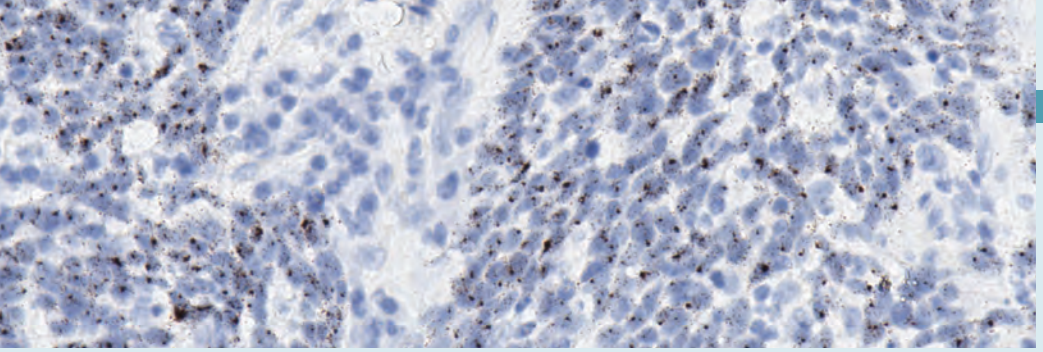
Meeting real-world needs

Monroe highlights RNAscope's compatibility with a broad range of sample types, including fresh frozen tissues and alcohol-fixed cytology specimens. "Most importantly, RNAscope is compatible with FFPE tissues – in fact, the system has been optimized for this type of sample." The assays are available for either manual or automated operation; compatible automation options include standard ISH staining platforms such as Leica BOND III, the Leica Bond Rx, and the Ventana Discovery instruments. This adaptability enables RNAscope to easily fit into existing IHC workflows and systems. Consequently, says Monroe, anatomic pathology labs can run RNAscope in parallel with normal IHC and provide outputs from both methodologies.

This flexibility makes RNAscope a pragmatic option; Monroe states that it is applicable to clinical diagnostics and translational pathology in a broad range of fields, including oncology, immuno-oncology, cell and gene therapy, neuroscience, and infectious disease. "It is of particular benefit for routine diagnostic pathology when IHC options are limited, for example where antibodies are unavailable or have poor specificity or low sensitivity," he says. In such cases RNAscope ISH often provides a better solution. "For example, IHC assessment of immunoglobulin expression in B cell lymphomas can be very challenging due to the low levels of kappa and lambda light chains, which are difficult to visualize over background; by contrast, the RNAscope readout comprises very discrete, punctate dots, simplifying the identification of cells



bio-techne



that express the gene of interest, such as immunoglobulin kappa or lambda in this case."

New insights in infectious disease

Ideal diagnostic reagents discriminate between related infectious agents – for example, between viruses in a given family (such as different SARS viruses). Does RNAscope ISH meet this ideal? Monroe is clear. "RNAscope can detect subtle differences based on nucleic acid changes and is therefore superior to IHC for infectious disease diagnostic applications." Furthermore, he adds, RNA ISH probes can be designed and produced quickly based on a target sequence. "Finding antibodies of similar discriminatory capacity is far more time-consuming and expensive."

In fact, says Monroe, RNAscope's utility in infectious disease diagnostics is already being realized, particularly for the detection of human papillomaviruses (HPV) in various clinical settings. "We now have RNAscope probes specific to almost all of the closely related HPV types," he states. "This permits elucidation of HPV's critical role in diseases such as head and neck cancer (HNC) and cervical dysplasia by providing the pathologist with a tool to both detect HPV and distinguish between types, including high- and low-risk, in biopsy samples." RNAscope is fast becoming the gold standard for the diagnosis of HPV-associated oropharyngeal squamous cell carcinoma (OPSCC), a unique subset of HNC associated with fewer recurrences, improved survival, and, in many cases, less aggressive treatment strategies. Relative to p16 IHC, a "surrogate" marker widely used for HPV assessment, the RNAscope test for high-risk HPV in OPSCC has similar high sensitivity but, importantly, superior specificity. Because it is not entirely specific for HPV, p16 IHC can be positive in ~10 percent of HPV-negative tumors. Such false positives are risky as they can affect treatment decisions and prognostic information provided to patients. RNAscope for high-risk HPV avoids these false-positives due to its direct detection of HPV.

Monroe also notes the technology's relevance to the COVID-19 pandemic. "Researchers put a lot of effort into developing diagnostic reagents for detection of the SARS-CoV-2 virus in nasopharyngeal samples, but paid less attention to the development of reagents for detection of the virus in situ to enable assessment of cellular targets and morphologic context, particularly in FFPE tissues." Did RNAscope ISH fill that gap? "Very effectively," says Monroe. "In many anatomic pathology labs, it has become the standard of care for assessing the presence of SARS-CoV-2 in autopsy tissues taken from patients, many of whom passed away before they could have a standard diagnostic test." Furthermore, RNAscope has been instrumental in highlighting the presence of SARS-CoV-2 in many cell types and organs affected by the virus, with over 100 publications on the virus to date using the technology. Going forward, ACD expects the RNAscope SARS-CoV-2 assay to be used broadly by anatomic pathology labs for the evaluation of various tissues suspected of involvement by the virus.

Beyond viral detection, RNAscope ISH probes are being used by pathologists for many oncology applications. One of the most useful RNAscope probes is albumin, a marker valuable in the evaluation of liver and biliary tumors. In particular, the RNAscope albumin assay helps pathologists in the diagnosis of intrahepatic cholangiocarcinoma versus extrahepatic cholangiocarcinoma and other liver tumors. Another emerging RNAscope application is detection of gene overexpression resulting from gene fusions or amplifications. The RNAscope assay for *MYB* is highly useful in the diagnosis of adenoid cystic carcinoma, with superior performance to FISH, the current gold standard. Similarly, the RNAscope *MDM2* assay is being used to distinguish benign lipomatous tumors from liposarcomas with similar performance to FISH.

Scope for the future

Novel technologies become routine over time, and RNAscope is expected to be no different. "In the near term, we are focused on making RNAscope technology and applications more widely available to help pathologists in their everyday diagnostic work. To realize this goal, automation of the technology on instruments like the BOND-III that are available in anatomic pathology labs around the world will be critical." ACD is also advancing the potential for RNAscope in the related field of companion diagnostics (CDx). Monroe notes, "We are working with a number of biopharma partners to develop RNAscope assays for predicting patient response to targeted therapies currently in clinical trials. We are optimistic that an RNAscope CDx assay will be approved in association with one of these therapeutics in the next several years."

In summary, RNAscope is an enabling technology that addresses diagnostic applications inaccessible to other approaches. It gives pathologists options for biomarker detection that traditional IHC cannot provide and is poised to become the standard of care for many targets and clinical applications. Monroe predicts that those who fail to adopt this approach in-house will, sooner or later, be compelled to send their samples to reference laboratories that offer RNAscope capabilities. ACD's vision, however, is that the simple, standardized nature of RNAscope protocols along with greater availability of automation will allow all laboratories to embrace this exciting technology. "Over time, we are confident that RNAscope will be a technique like IHC used by all anatomic pathology labs with dozens of compelling applications."

SPECIAL SERIES
Education & Training

Profession

Your career
Your business
Your life

A Divisive Passion

How pathology can overcome the "Great Divides" of Indian medicine

By Satish Ramanathan

When I began my pursuit of medicine in 2003, there was a clear hierarchy in my options. Most students wanted to become physicians or surgeons – the so-called "clinical" fields. Least popular was the trifecta of clinical laboratory medicine: biochemistry, pathology, and microbiology. These were considered to be "leftovers" or "paraclinical" fields, chosen only by those whose performance did not earn them a coveted spot in "clinical medicine."

From childhood, I had loved solving jigsaw puzzles. The search for the missing pieces and the slow discovery of the full picture excited my curiosity – but as I grew up and made career plans, it seemed to me that I had to abandon that childhood pleasure. Medicine was a serious profession. Surely there was no place in it for the joy of a jigsaw puzzle – or was there?

Satish Ramanathan.

The first Great Divide

Where did this gulf between "clinical" and "paraclinical" medicine in India arise? Although my peers and I perpetuated it, we didn't create it. Rather, we fell into stereotypes gleaned from the archaic system of medical education in our country.

India's current approach to medical education was borrowed from the British system of modern allopathic medicine nearly a century ago. Pathology, biochemistry, and microbiology are taught in the first two years of medical school – and never revisited after graduation. Unfortunately, this leads many students to believe those disciplines are purely academic and have little scope for practice or clinical relevance.

I myself was among the medical students caught in that belief. Fortunately, my preparations for the postgraduate entrance exam offered a wonderful opportunity to look back at the basics of all areas of medicine – including the laboratory. Rather than skim these areas for the sake of a passing grade, I dove deep into biochemistry, microbiology, and pathology; I found that they were not "paraclinical" at all. Every aspect of those disciplines feeds into clinical decisions about more than two-thirds of all patients! This realization allowed me to ignore tradition and fall in love with the lab.

But why did I have to rediscover these fields myself? Why didn't they feature throughout my education? In my opinion, every undergraduate medical program should revisit pathology and laboratory medicine each time a new condition is discussed. After all, few of these conditions can be diagnosed without the aid of the laboratory!

The second Great Divide

Ultimately, I chose to pursue clinical biochemistry. My three years of postgraduate training were overseen by supportive teachers who coached and guided me through the curriculum. But as a student of medicine, I was surprised – and dismayed – to discover that laboratory medicine education is academically oriented, rather than skills-based. When I entered the real world of clinical laboratory medicine, I discovered that I had not been taught the skills I needed. Of course, my teachers are not to blame for this; most medical colleges don't offer exposure to clinical laboratory culture. We are not "just" clinical biochemists; we are leaders, human resource managers, financial consultants, IT coordinators, teachers, innovators, communicators, and creators!

All of this is what leads us to the second Great Divide. Every doctor who successfully graduates from a biochemistry, pathology, or microbiology program must now ask the question: who am I?

In my professional life, this question pulled me into a whirlpool of confusing thoughts. Is clinical biochemistry an academic or a clinical profession? Why is there compartmentalization between the three areas of clinical laboratory medicine? Is the concept of integrated laboratory medicine a reality – and, if so, where?

The jigsaw of integrated lab medicine

Traditionally, the clinical biochemist's role was focused on the research, development, and production of methods – including instruments and reagents that are now closed boxes (1). This evolution has led some physicians to believe that, if machines and technologists can do the work and generate results, clinical biochemists are superfluous. Although clinical biochemists actually play a much more significant role, we need to make even greater changes to our profession if we are to survive. In my opinion, we must become consultants to the physicians. We

must show our worth through value-added services. I envision a relationship in which the clinician presents a diagnostic problem to the clinical biochemists ("What type of hepatitis does the patient have?" "Does the patient have hyperthyroidism?"), rather than just ordering a set of laboratory tests.

A clinical biochemist should have:

- the ability to adapt to ever-changing technology
- the ability to deal with objective, quantitative information
- the skill to define and solve problems at the interface between the medical and administrative domains

Physicians ideally seek help from a single source who can transcend the boundaries that traditionally divide the clinical laboratory. If clinical biochemists want to be that source, we must also learn more about clinical medicine (to understand how physicians think) and expand our knowledge of the other branches of laboratory medicine so that we can provide broad input. Diseases, after all, are not categorized by laboratory subdiscipline.

From Sanger to Sherlock

Buddha famously said, "When a student is ready, a master will appear." My intense search for a master led me through seven long years of discrimination, depression, and difficulty – but, in 2014, I finally found the mentor I had sought. Both of us were eccentric, out-of-the-box thinkers, and both of us shared a passion for laboratory integration. His favorite saying was, "Each laboratory specimen is a patient." That drop of blood or scrap of tissue represents an entire life – and one whose treatment and outcomes depend on a laboratory diagnosis.

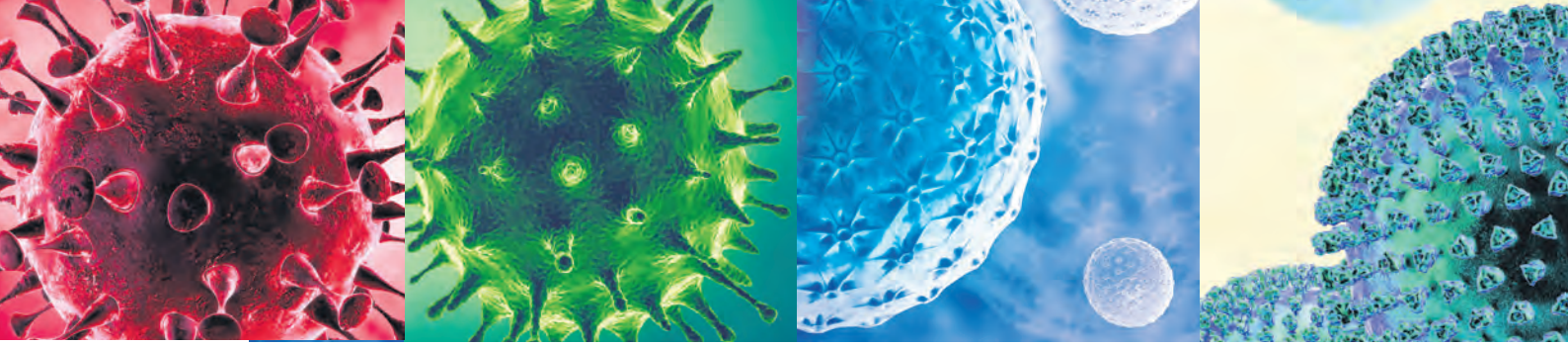
Arriving at a laboratory diagnosis is like solving a jigsaw with pieces of evidence from each division of the clinical laboratory. The puzzle cannot be solved without all of the pieces – which can only be obtained through the integration of lab medicine. It seems there is a place in medicine for the jigsaw puzzle after all!

Frederick Sanger belonged to an extraordinary league of scientists (two Nobel Prizes!), but today's laboratory medicine – and the clinical jigsaw puzzles found within – require people who share more in common with Sherlock Holmes than with Sanger.

Satish Ramanathan is Head of Clinical Biochemistry and Serology at MIOT International, Chennai, India.

Reference

1. *"The future of clinical chemistry and its role in healthcare: a report of the Athena Society", Clin Chem, 42, 96 (1996). PMID: 8565242.*



Choose the right test to detect the most prevalent respiratory infections, including COVID-19

TARGETED TESTING **SYNDROMIC TESTING**

	Amplidiag® COVID-19 (CE-IVD)	Amplidiag® RESP-4 (CE-IVD)
Targets	SARS-CoV-2 (orf1ab) SARS-CoV-2 (N)	SARS-CoV-2 (N gene) SARS-CoV-2 (E-gene) Influenza A (M gene) Influenza B (NS gene) RSV A and B (M gene)
Time to results	Amplification 60 min <3 hours with Amplidiag® Easy	~3 hours with Amplidiag® Easy (Extraction 1h50min+PCR 1h15min (46 samples))

	Novodiag® COVID-19 (CE-IVD)	Novodiag® RESP-4 (CE-IVD ongoing)
Targets	SARS-CoV-2 (orf1ab) SARS-CoV-2 (N)	SARS-CoV-2 (N gene) SARS-CoV-2 (E-gene) Influenza A (M gene) Influenza B (NS gene) RSV A and B (M gene)
Time to results	80 min	About 1 hour

Advantages :

- A complete solution for rapid and reliable molecular diagnostics of coronavirus infection (COVID-19 exclusively) and most prevalent respiratory infections (COVID-19, Flu A, Flu B, RSV)
- A test for all sample volumes (batch and on-demand testing)
- Sample quality control to prevent false negative results

Please contact us for more information or visit www.mobidiag.com

MOBIDIAG

Mobidiag Ltd. (UK)
+44 333 305 7506
sales@mobidiag.com

SPECIAL SERIES
Education & Training

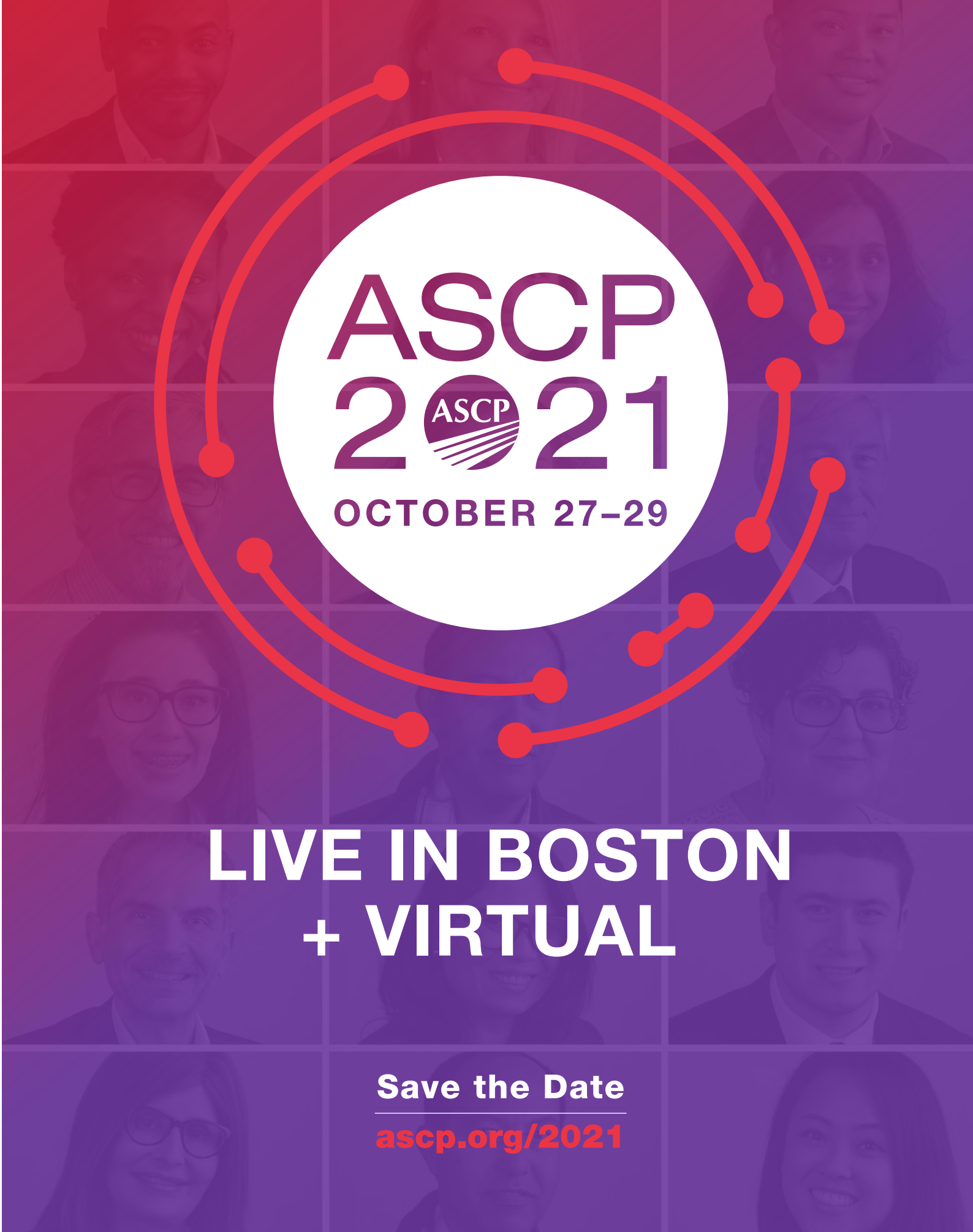
A Burst of Glass and Light

Implementing new models of pathology education and clinical support in a pandemic

By Kirill A. Lyapichev, Sanam Loghavi, L. Jeffrey Medeiros, and Joseph D. Khoury

Just a few weeks before the first documented case of COVID-19 was reported, a group of us were discussing a futuristic vision of pathology education – one that incorporated online resources and social media connectivity to enhance and enrich the scope of training for graduate students, residents, fellows, and practicing physicians. Our discussion, excited and animated, revolved around the need for alignment between digital pathology educational resources and the slow, but deliberate, expansion of expand routine clinical practice beyond the tethers of the physical optical microscope.

"The notion of shutting down our educational activities indefinitely due to COVID-19 weighed on our team."


ASCP
2021
ASCP
OCTOBER 27–29
LIVE IN BOSTON
+ VIRTUAL
Save the Date
ascp.org/2021


L. Jeffrey Medeiros

We knew that a trend toward digitization of pathology data was clearly emerging in the educational and clinical arenas. But, in the same breath, we acknowledged that too many aspects remained ensconced in the realm of glass and optics. Although glass and light have allowed physicians like us to peer into the microscopic world of human diseases for the past century or more, data portability and artificial intelligence cannot begin to be explored without broad digitization of the analog data currently imprisoned in glass slides. We envisioned a new educational model that would prepare trainees for a time when microscopic images are digitized and made available for onscreen visualization as they emerge from production lines behind the cloak of histology labs. At that moment, deliberating in a small office within arm's reach of one another, we could not have imagined how a novel virus would bring our vision into existence in short order.

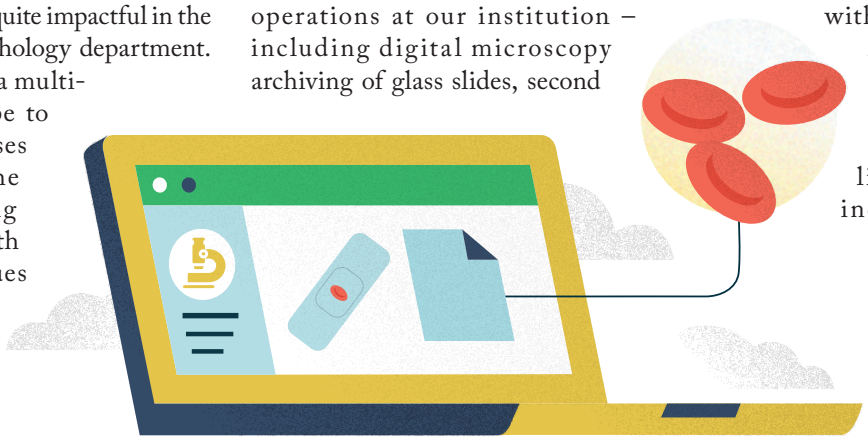
A forward leap

As COVID-19 spread through the United States and lockdown orders permeated the land, the routine clinical training activities that were our institution's crown jewel all but came to a standstill. This was quite impactful in the hallways of the pathology department. Crowding around a multi-headed microscope to review patient cases was a thing of the past. Aggregating in a dark room, with 20 or 30 colleagues hovering around a speaker clicking through a slide presentation – gone. Taking center stage to present pathology findings in multidisciplinary tumor boards – also gone. Newly implemented social distancing measures made the mundane elements at the core of pathology education impossible. An eerie silence fell on the hallways and meeting rooms. All, that is, except the stopwatch inevitably ticking down toward the end of our fellows' academic year. That countdown meant abbreviated training and lost opportunities that, for most, would never come again.


Joseph Khoury

The notion of shutting down our educational activities indefinitely due to COVID-19 weighed on our team. We knew that such an option was unsustainable – and our need for an alternative set us on the path to the most innovative educational initiative in our department's 79-year history. It was time for telepathology to take center stage in our training.

Digital platforms were already making inroads into pathology clinical operations at our institution – including digital microscopy archiving of glass slides, second opinion consultations, and remote access for intraoperative consultations or adequacy assessment for fine needle aspiration procedures. In addition, an earnest effort to develop an integrated digital pathology service had been progressing slowly and carefully at our institution for five years – but was quickly accelerated to support novel telemedicine-based care delivery. Without a blueprint, our team took early steps to build what might now be one of the leading pathology educational platforms in the world for on hematolymphoid cancers.



An opportunity for growth

Before COVID-19, our trainees benefited from a variety of educational activities that included didactic lectures, over-the-microscope seminars reviewing difficult cases, participation in various clinical diagnostic modalities from microscopy to flow cytometry, subspecialty tumor boards, quality improvement meetings, and more. Now, faced with pandemic restrictions, how could we replicate our trainees' 15 hours a week of hands-on education?

Scrambling to mitigate the disruption caused by COVID-19, we started with the easiest option to implement – a didactic lecture delivered via WebEx. It was a resonant (but choppy) start, with a limited guest list that included departmental faculty, fellows, and faculty members from neighboring hospitals. Wearing masks and keeping our distance, we

joked a few days later about the noises we heard in the background, the learning curve involved in managing a new cockpit of controls, and the oddness of lecturing while staring at a screen rather than interacting with a live audience. But it was a start – and those wobbly first steps opened our eyes to the potential of digital learning. Could we turn the calamity of COVID-19 into an opportunity to elevate our educational and clinical training activities?

We decided that such an opportunity needed the following core elements: i) open access to educational content, ii) leverage of social media platforms, iii) leverage of whole-slide imaging technologies, and iv) real-time clinical care and quality improvement discussions with restricted access to in-house personnel.

Within days, we had fully transitioned to online meeting software for our daily educational sessions. To continue our conference series – which involves unknown cases that attendees diagnose based on microscopic examination and on-the-spot drills – we developed a workflow to digitize cases on whole-slide scanners and post them online for study ahead of the virtual meeting (allowing our attendees much-needed flexibility). Finally, we used Twitter to announce our educational sessions ahead of time and share links to view the virtual slides. The process was new, exciting, and refreshing against a backdrop of unprecedented worldwide disruption. It also launched our journey into online pathology education – incarnating the very essence of our discussion only a few weeks earlier.


Kirill Lyapichev

Within a week of their debut, our virtual conferences had attracted more than 240 attendees from 79 institutions spanning 32 states within the US and 17 countries covering nearly every continent.

Within a month, we had more than 2,360 people attending our virtual educational offerings, and by three months, we were well over 10,000 – a far cry from the eight hematopathology fellows (plus a few visitors) who had attended the in-person lectures!

What was holding us back? Did we really need a pandemic to push us into the future of pathology education? And, now that many people are returning to in-person work and education, can we maintain our momentum? Only time will tell – but we think telepathology training may be the way of the future.


Sanam Loghavi

Kirill A. Lyapichev is a Fellow in the Department of Hematopathology at The University of Texas MD Anderson Cancer Center.

Sanam Loghavi is Assistant Professor of Hematopathology at The University of Texas MD Anderson Cancer Center.

L. Jeffrey Medeiros is Chair and Professor of Hematopathology Department at The University of Texas MD Anderson Cancer Center.

Joseph D. Khoury is Professor of Hematopathology and Executive Director of the MD Anderson Cancer Network, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA.

Implement – and Walk Away

Automating RNA ISH to build a robust, accurate picture of molecular pathways

Leica Biosystems has partnered with ACD to create a fully automated, walk-away solution. How? By automating RNA detection and enabling chromogenic ISH (CISH) on the BOND-III fully automated IHC/ISH stainer. BOND RNAscope® Brown Detection is intended for staining sections of FFPE tissue on the BOND-III stainer.

The ease of adoption of RNA ISH technology on the BOND-III stainer has enabled laboratories to quickly establish this technology, minimizing inter-user variation and optimizing sample pretreatment.

"We introduced BOND-III in our Pathology Department in 2016 for IHC and FISH analysis," says Denise Morotti, Molecular Geneticist at ASST Papa Giovanni XXIII in Bergamo, Italy. "From the beginning, we had good results, despite our technical staff's rotating weekly to different laboratory sectors. Thanks to the instrument's easy setup and intuitive programming, we quickly obtained reproducible staining in a standardized and fully traceable way."

She continues, "Last spring our hospital was the first in Europe to face the COVID-19 pandemic. We started using BOND-III to look for virus in autopsy samples with a default pretreatment protocol. Within few days, we were able to set up different protocols for a number of tissue specimens – lung, kidney, heart, and placenta. In a couple of weeks, we had collected enough data to better describe and understand what was going on."

Padua University in Padua, Italy, introduced the fully automated RNAscope Brown Detection kit on BOND-III in the summer of 2020. "By introducing the automated method, we have improved workflow productivity and produced clear staining in a standardized and repeatable way," says Matteo Fassan, Professor of Pathology.

The BOND RNAscope Brown Detection kit's ease of adoption has allowed laboratories to effortlessly introduce this new technology into their workflows. Using BOND RNAscope Detection in combination with the BOND-III fully automated IHC/ISH stainer reduces the possibility of human error and the inherent variability that results from repeated reagent dilution, pipetting, and application.

"By introducing the automated method, we have improved workflow productivity and produced clear staining in a standardized and repeatable way."

Performance claims for compatible probes have not been established. Probes used in conjunction with BOND RNAscope® Brown Detection should be validated by the user in accordance with local laws and regulations.

the Pathologist®

THE PANDEMIC: *One Year On Roundtable*

COVID-19: WHERE DID WE START, WHERE ARE WE NOW, AND WHERE ARE WE GOING?

Watch our expert panel of pathologists, laboratory professionals, and infectious disease experts discuss lessons learned from COVID-19 so far; the current state of testing, treatment, and vaccines; and what we can expect in the future from both SARS-CoV-2 and other potentially threatening pathogens.

WATCH OUR FREE ROUNDTABLE TODAY:
www.bit.ly/3mrs6Eg

SUPPORTING *Sponsors*

Asuragen®

SpeeDx

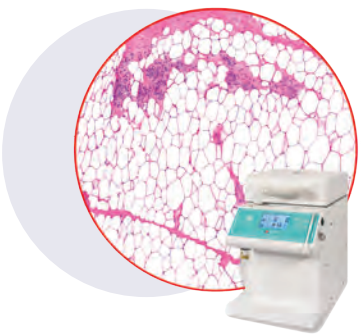
Spotlight on... Technology

PathScan® Combi: Slide Scanner Dedicated to FISH on Tissue

The most common FISH scanner in France to manage up to 5,000 slides yearly. With the additional bright field scanning feature, you can easily define the area of interest on an H&E or IHC slide and match with a FISH one. The onboard image analysis module manages every kind of probe and allows the automation of FISH activity from slides to reports.
www.excilone.com

DTM Medical shows Signature Cassette Printer at Medlab Middle East

Signature Cassette Printer significantly increases the efficiency of labs and reduces the risk of misidentification of specimens by printing text, graphics, and 2D barcodes directly onto tissue cassettes. It is used in pathology and histology labs. A manual feed and an automatic feed model are available and will be shown at Medlab June 21–24, 2021.
pt.dtm-medical.eu



Advanced System for Rapid, High-Quality Frozen Sections

PrestoCHILL reduces freezing time to 60 seconds and eliminates freezing artifacts through ultrafast freezing (at -40°C), preventing ice crystal formations.

Thanks to Milestone's patented "face-down" embedding technique, you will achieve fast and standardized frozen blocks, with perfectly "flat plane" surfaces to reduce trimming time and cut more easily
tp.txp.to/Milestone

Professional grossing tables perfectly suited to your lab

GrossPath – the special worktable that ensures a pollution-free environment for histological slide preparations. Buy it, set it up, and power it on: thanks to its generously proportioned active-carbon air recirculation system, it is ready for immediate use! Hazardous vapors are vacuumed downward; formalin concentrations are significantly below maximum allowable concentrations throughout the extraction zone.
tp.txp.to/Kugel/GrossPath

Weathering the Storm

Sitting Down With… Mike Osborn,
President of the Royal College of Pathologists and Consultant Histopathologist for North West London Pathology at Imperial College Healthcare NHS Trust, London, UK

How did you get started in pathology?

At Guy's and St. Thomas' Hospital, we had an amazing one-block pathology course of three or four months. It was a highlight of the whole five years, not just for me, but for everybody. All of the lectures were good, it was very interactive, and there was a lot of small-group teaching – and that introduction to pathology got me interested.

When I left medical school, there were no training opportunities in pathology – so I did a surgery rotation instead. By the time I finished that, there were no jobs available in surgery – so I went back to pathology!

What was it like to become President of the Royal College of Pathologists during a pandemic?

It's a bit like being handed a ship in the middle of a storm. I was lucky to have an excellent crew in both the College staff and the Vice-Presidents who were appointed at the same time as I was. It's a difficult time with unique challenges, but the College is capable of handling it – and I'm not on my own in the storm.

At the beginning of the pandemic, all routine work around the country stopped and we focused exclusively on COVID-19 because it was new and we had no systems in place to deal with it. Our priority was to develop and roll out testing – that's how we were able to prevent the National Health Service from being overwhelmed. As cases decreased over the summer, we resumed our routine work – and now, even after facing a resurgence, we've maintained near-normal levels of routine pathology work. That's not to say that there isn't a significant backlog of cases; there is, and addressing that alongside our usual workload is currently our top priority.

As a senior figure in pathology in general, what are your goals for the discipline?

I think the big issue for pathology is that we're often forgotten. The fundamental thing we need to do is highlight that pathology is important and that it needs to be supported because, without pathology, you don't have a diagnosis. And that's not all; whereas some disciplines – for instance, histopathology – play a leading role in diagnosis, others – such as clinical chemistry or hematology – may have an equal or even greater role in treatment selection and support. Every aspect of our discipline needs to be remembered and supported. We need to increase our visibility so that policymakers realize they need to build pathology and laboratory medicine into their plans.

Where do you see pathology in 10 years' time?

Everything will look different.

There will be increased automation and digitization. I suspect histopathology labs will be mainly digital – and digital images will be used in other areas as well. There's already a huge amount of automation in pathology, but I think there will be even more in the future. That will increase capacity; labs that do 3,000 cases a day now might do 7,000 in 10 years' time. Those will be the big things.

Genomics, precision medicine, and artificial intelligence (AI) are playing an increasingly large role. If you compare the laboratories of today to the laboratories of a decade from now, I don't think you'll see a massive difference – but if you read a report from 10 years in the future, I think it will be more complex. It will have more genomics content and be more strongly supported by AI technologies. Those technologies won't replace pathologists, but they will certainly assist us.

Genomics, in particular, is an area of significant importance. Two patients may have the same illness, but the best treatment options for them may differ widely – and the only way to find that out is through genomics testing. I don't think we'll reach a stage where we biopsy a tumor, put the sample in a machine, and it spits out a treatment. History shows us that our clinical colleagues like what they have, but welcome "a little bit extra." They'll still want to know the tumor size, how far it has invaded, the histology, and so on – but they'll want to know the genomics as well, so that they can offer the patient the best possible treatment options.

"I think the big issue for pathology is that we're often forgotten."

Our main obstacle right now is logistical. The science of genomics is fantastic. Oncologists, surgeons, and pathologists are very good at obtaining, testing, and interpreting findings – but, in many areas, genomics is still separate from the main laboratory, which means you might encounter problems in getting the samples to genomics and the results back. Our key focus at the moment is speeding that process up so that we can get results into patients' files as quickly and accurately as possible.

If you could give one piece of advice to pathologists and lab medicine professionals at the start of their careers, what would you say?

Take all the opportunities that present themselves to you. Your career will develop in ways you might not have anticipated, but that you will enjoy. Be enthusiastic about your specialty. And be reliable.

ACD™
a bio-techne® brand

RNASCOPE™ FOR ANATOMIC PATHOLOGY

RNAscope is a robust technology that identifies RNA expression patterns and localization at the single cell level with spatial and morphologic context.

It's highly sensitive and specific, resulting in an extremely high signal-to-noise ratio of staining in FFPE tissues, allowing diagnostic pathologists to visualize, localize, and quantify biomarker expression simultaneously.

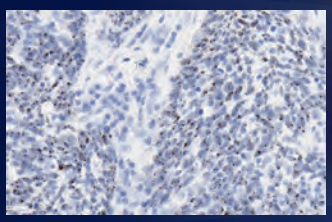
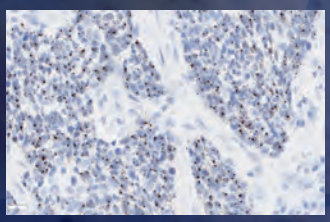
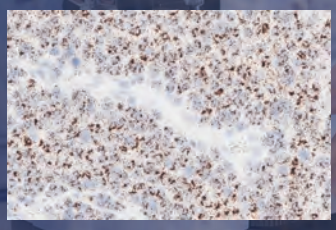
UNPARALLELED SENSITIVITY AND SPECIFICITY

- Detect any marker of interest to complement your IHC or DNA ISH, with consistently reliable results.

SURPASS TRADITIONAL IHC CHALLENGES

- Easy validation, omit issues with high background, low signal or suboptimal antibodies.

INTUITIVE PROTOCOL, IMPLEMENTED SEAMLESSLY INTO YOUR WORKFLOW

LEARN MORE | acdbio.com/diagnostics

bio-techne®
bio-techne.com

R&D SYSTEMS | NOVUS BIOLOGICALS | TOCRIS | protein simple | ACD™ | exosomedx™

Global info@bio-techne.com bio-techne.com/find-us/distributors TEL +1 612 379 2956 North America TEL 800 343 7475
Europe | Middle East | Africa TEL +44 (0)1235 529449 China info.cn@bio-techne.com TEL +86 (21) 52380373