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Training Places

Breaking down the barriers to pathology residency placements

To Screen, or Not to Screen

How would you respond to the pediatric diabetes screening debate?

Just because we can do something that will improve health outcomes – does that mean we should do it? I ask because a recent article in Science (1) raised an interesting question: should all children be screened for type 1 diabetes? After all, blood tests are available that can predict the onset of the disease years in advance. And tepilizumab, which can delay the onset of the condition, is now available in the USA. So why not simply screen all children and keep those at risk healthier for longer?

Well, mental health experts might object to a mass screening program to spare youngsters from health anxiety – itself a detrimental condition (2). Reports suggest that health anxiety amongst children has increased since the COVID-19 pandemic (3), when screening for infection became commonplace. Many of us may have observed young family members obsessively washing hands or repeatedly questioning their chances of survival during that time. Could screening children for diabetes cause them to grow up with a gnawing fear of developing a dreadful, incurable illness? Might it lead to years of hypervigilance, self-monitoring, detrimental Googling, and overuse of medical care?

Pandemic aside, health screening is somewhat alien to most children. They might be tested for a range of conditions before and immediately after they are born, and then offered no further tests until middle or old age. And though inoculations – which kids are more likely to experience – undoubtedly raise their awareness of deadly diseases, they also allay the fears of contracting them. Screening, it could be argued, might do the opposite.

Economists may also have concerns about such a scheme. Less than one percent of children are likely to test positive for diabetes biomarkers; health authorities might find it difficult to justify the huge bill for mass screening versus potential savings to the costs of treating adolescents with diabetes.
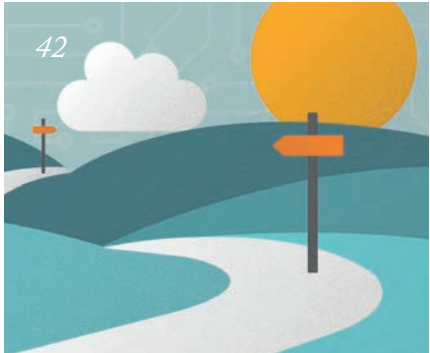
Might there be a compromise that addresses both of the above-mentioned barriers? Perhaps families should decide whether their children should be screened?

In any case, questions like those raised here are guaranteed to divide opinions – and The Pathologist team is always interested to hear yours. Join the debate by dropping us an email: *edit@thepathologist.com.*

Helen Bristow
Editor

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1. *Science, "Should doctors screen all kids for type 1 diabetes" (2024).*
2. *A Haig-Ferguson et al, Behav Cogn Psychother, 49, 2 (2021). PMID: 32829718.*
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An Established Relationship

How semi-automated biomedical evidence curation could open up genetic diagnostics

A new approach to creating a genomics database could move the field one step closer to curating the clinical exome for gene–disease relationships. The approach combines a human element – systematic literature review – with AI indexing of millions of published abstracts and full-text references with genetic information. Results of a study testing the new approach, presented at the Annual Clinical Genetics Meeting 2024, identified over 10,000 germline gene–disease relationships – more than half of which showed positive associations with a specific disease (1).

Mark Kiel, Chief Scientific Officer of Genomenon – and one of the study leads – explains the drivers for the project: "It is estimated that about one-third of all genomic analyses result in a variant of unknown significance in a gene with either known or unknown classification. If the gene is inaccurately classified, it can lead to incorrect diagnosis and treatment. Thus, the accurate and standardized classification of genes and genetic variants is imperative for advancing both clinical practice and scientific research."

To ensure the robustness of the methodology, a comparison with other databases, such as ClinGen and GenCC, was conducted to assess the results in light of currently used standards. High concordance was observed between the databases, indicating the success of the new approach.

The proof-of-concept study has created a genetic evidence database that can be continuously and rapidly updated as new gene–disease relationships are established. "This will result in the resolution of genes of unknown significance (GUS) into more defined categories, such as the limited, strong, and definitive designations," predicts Kiel. "As more GUS are resolved, the diagnostic workup and patient diagnosis rates are improved."

The study could prove particularly beneficial to patients with rare or unassigned genetic diseases. Kiel concludes, "This study will help clinical labs and clinicians in determining which genes should be tested and which should be omitted from testing for a particular disease, avoiding unnecessary testing, inaccurate diagnosis, and treatment."

As to future developments, further AI capabilities will be implemented to the system to enhance expert human curation efficiency and the user experience.

Reference
1. M Kiel et al, Gen Med, 2, Suppl. 1, Abstract O33 (2024).

Around the Plaque

Collaborative efforts in flow cytometry could produce personalized treatment options for patients with coronary artery disease

A collaboration between the Babraham Institute and PlaqueTec will focus on developing a bespoke cell phenotyping assay (1) that will be used in conjunction with multiomics and imaging data collected in the ongoing BIOPATTERN trial (1,2). The aim? To improve our understanding of coronary artery disease (CAD) biology with a view to more personalized treatment options.

Thanks to UKRI-BBSRC Campus Collaboration Funding, the two partners will explore cellular and molecular intricacies of CAD by applying the assay to
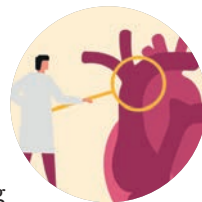
coronary artery samples collected from patients in the ongoing trial using a liquid biopsy system.

"We're able to use our state-of-art technology and combine it with our expertise in cytometry." says Rachel Walker, Head of the Flow Cytometry Facility at Babraham,. "We've relished our involvement in the project and the chance to inform better treatment options for people with CAD."

See references online
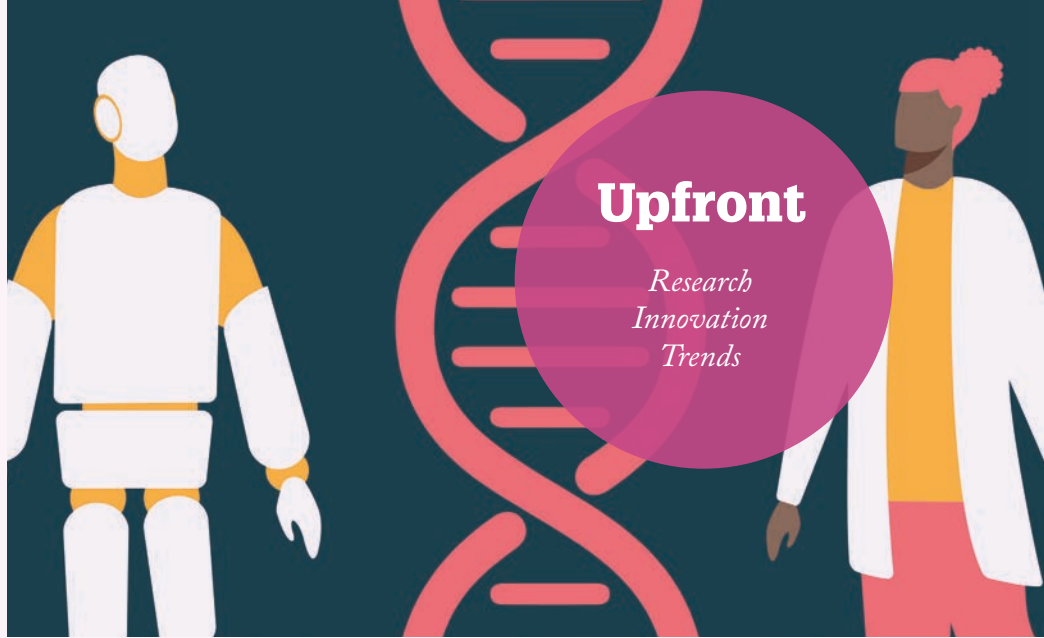
RESEARCH ROUNDUP

A handpicked selection of the laboratory medicine news stories that caught our eye – from predictive tools to missing links

Chemistry lessons

Many neurological conditions could be linked to changes in brain pH, according to a study in Japan (PMID: 38529532). In animal models of neuropsychiatric disorders, such as schizophrenia, depression, epilepsy, and Alheimer's, decreased brain pH and increased lactate levels were found to be common features of the conditions.

Listen to your gut

A gut microbiome study has offered new insights into antimicrobial resistance (PMID: 38528147). The study, steered by a research group in Germany, identified small RNA molecules that influence the sensitivity of *Bacteroides thetaiotaomicron* to tetracycline antibiotics. It demonstrates the utility of generating atlases of bacterial expression for microbiome research.

Suite success

Biomarker profiles in patients with breast cancer could predict their response to chemotherapy, according to a study published in Diagnostic Pathology (PMID: 38509525). Levels of a suite of biomarkers were measured before and after neoadjuvant chemotherapy, and compared between groups showing different response levels. Such testing could inform more personalized treatment strategies.

A(I)-grade student

A deep learning algorithm has been trained to predict brain metastases in lung cancer patients (PMID: 38433721). The AI tool reviewed whole-slide images of tumor tissue from patients with NSCLC over five years' follow up and outperformed pathologists in predicting progression to the brain, particularly in Stage I patients.

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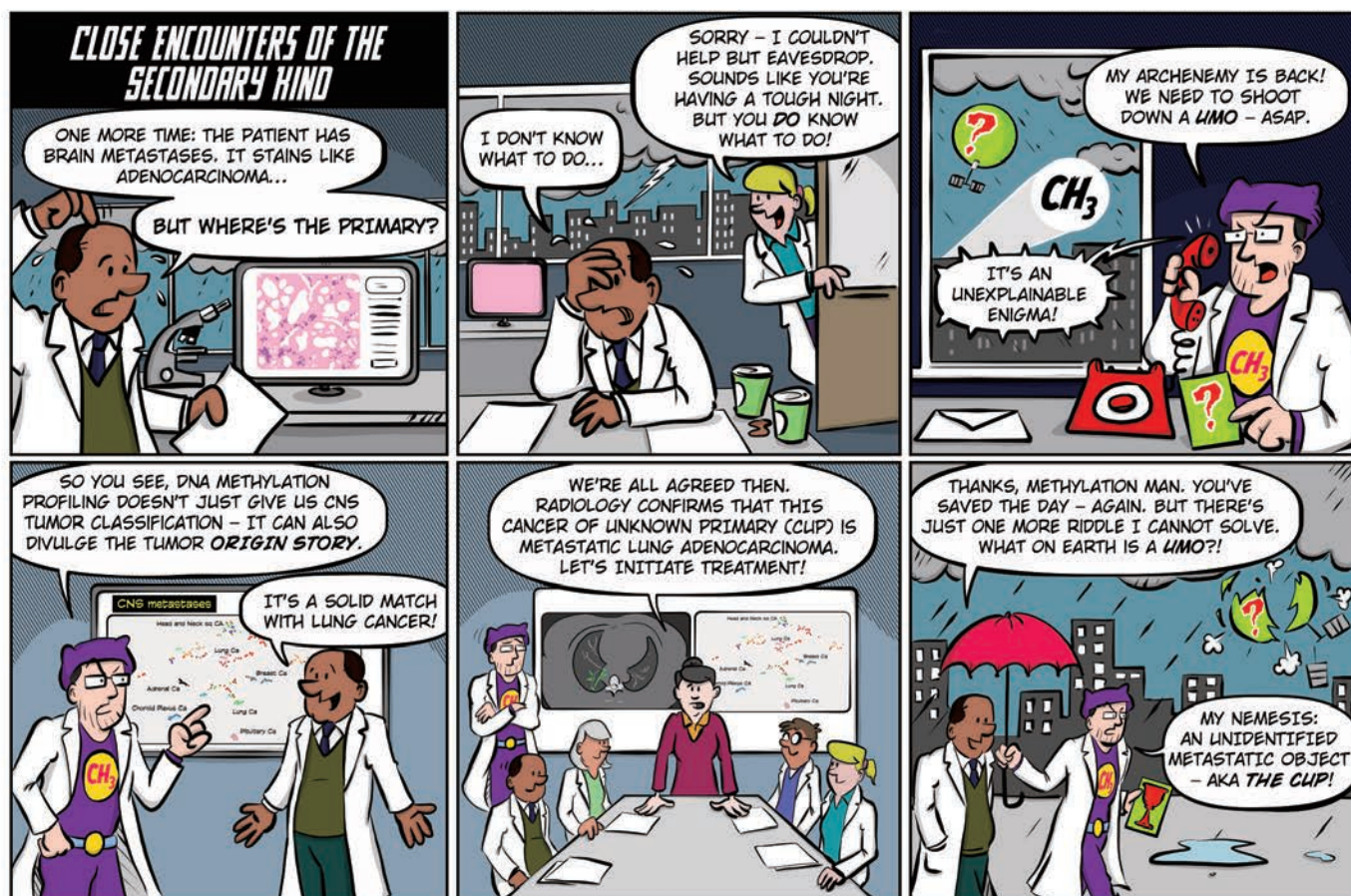
Apex of Understanding

How a new blood test could offer a breakthrough in Alzheimer's disease diagnosis

A test for detecting low levels of disease-specific proteins in blood, presented at the AD/PD 2024 conference, could be a crucial indicator of Alzheimer's disease. Study results suggest that the APEX test accurately measures relevant levels of amyloid beta (Aβ) in blood, aligning with amyloid deposition measured in the brain by positron emission tomography (PET) scans.

John McDonough, Executive Chairman and CEO of Sunbird Bio, comments, "Whilst PET brain imaging is the gold standard to detect brain amyloid deposition with spatial resolution, it can be subject to high costs and limited availability. Cerebrospinal fluid-based testing can also be used, but it is invasive and often painful for patients. Thus, a simple, affordable, and accurate blood-based molecular Alzheimer's disease test could be game changing."

In the study, researchers prospectively collected blood samples from 32 patients with confirmed PET scans (14 Aβ– and 18 Aβ+ samples). The APEX platform was used to measure extracellular vesicle (EV)-associated Aβ biomarkers, and demonstrated effective discrimination between Aβ+ and Aβ– PET status. Additionally, data demonstrated that EV-associated Aβ in blood is highly correlative with Aβ build-up in the brain – a crucial indicator of Alzheimer's disease.

The new study adds to the team's earlier findings – published in *Nature* (1) – that demonstrated that EVs from the brain carry sticky proteins and other biomarkers through the blood-brain barrier and reflect the state of protein aggregation in the brain. The latest results demonstrate the ability of the APEX technology to directly detect these specific pathogenic proteins deposited in the brain through a simple venous blood draw.

"Across the globe, the rate of undetected dementia is as high as 60 percent, and Alzheimer's disease is typically detected at mild-to-moderate stage with current diagnostics," adds McDonough. "The expanding set of APEX data support the test's potential to offer best-in-class diagnostic performance and improve outcomes for patients with multiple neurological disorders."

Notably, the APEX platform can be adapted to potentially detect a wide range of nanoscale molecular targets.

Reference
1. Carine Z J Lim et al, "Subtyping of circulating exosome-bound amyloid β reflects brain plaque deposition", Nat Commun, 10, 1144 (2019). PMID: 30850633

Within Spitting Distance

Could saliva sampling be the key to fast, affordable, and accurate breast cancer screening?

Researchers from the University of Florida and National Yang Ming Chiao Tung University in Taiwan have created a non-invasive and accessible approach for detecting breast cancer biomarkers in saliva samples (1).

Using commercially available strips akin to those used in glucose testing and a handheld printed circuit board (PCB), researchers created a handheld biosensor for portable testing. Each strip is functionalized with antibodies specific to biomarkers HER2 and CA15-3. The team demonstrated limits of detection as low as 1 fg/mL – and with as little as 3 µL of saliva.

Lead author Hsiao-Hsuan Wan states, "This breakthrough is particularly useful in resource-limited regions that can't access advanced technologies, such as MRI."

Looking ahead, Wan and colleagues have set their sights on other health conditions, using a similar approach to develop a screening test for oral cancer and expanding into infectious diseases, such as Lyme disease and foot and mouth disease.

See references online

IMAGE OF THE MONTH

A Tissue Slide after My Own Heart

"In pathology, there are so many things to see, you just have to be willing to see them."

Our image of the month comes from Laura J. Tafe, Associate Professor of Pathology and Laboratory Medicine, Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire, US. Laura shared a photo collage of H&E and negative (green) images of tissue hearts via X (formerly known as Twitter), of glandular epithelium and blood vessels sourced from GYN, thoracic, and head and neck areas during her work in anatomic pathology.

"The visual aspect of anatomic pathology is a huge part of what attracted me to the field in the first place. It truly is a wonderful part of anatomic pathology."

You can find Laura @LJTafeMD

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

QUOTE of the month

"Pathology is a hidden gem. You would be surprised how little is known about our field, even within the medical community. The same phenomenon occurs at the subspecialty level with pediatric and perinatal pathology. I aim to showcase what we do as pathologists (and pediatric pathologists) and encourage others to find fulfillment and purpose in the art of diagnosing diseases."

Oscar Lopez Nunez (see page 19)

Back to the Black Death

Forensic genomic research opens the door to further discoveries around the Black Death pandemic

A worldwide collaborative research study has started to unveil the hidden genetic effects from one of the most fatal pandemics in history (1).

Reconstruction images produced by Mark Gridley for the After the Plague project

Focusing on Cambridgeshire, UK, researchers examined 275 ancient genomes from medieval and post-medieval individuals buried before and after the Black Death. With bioinformatics capable of working with reduced quality and quantity of ancient DNA, they found fewer close relatives among friars and hospital inmates compared with general urban and rural communities – suggesting a change in social structure.

The team continue to work on similar projects across Europe as well as exploring the effect of an earlier plague pandemic in the Early Middle Ages.

Lead author Ruoyun Hui concludes, "It is perhaps fair to say that we are indeed at the beginning of tests and research on past pandemics and their effect on our genes."

See references online
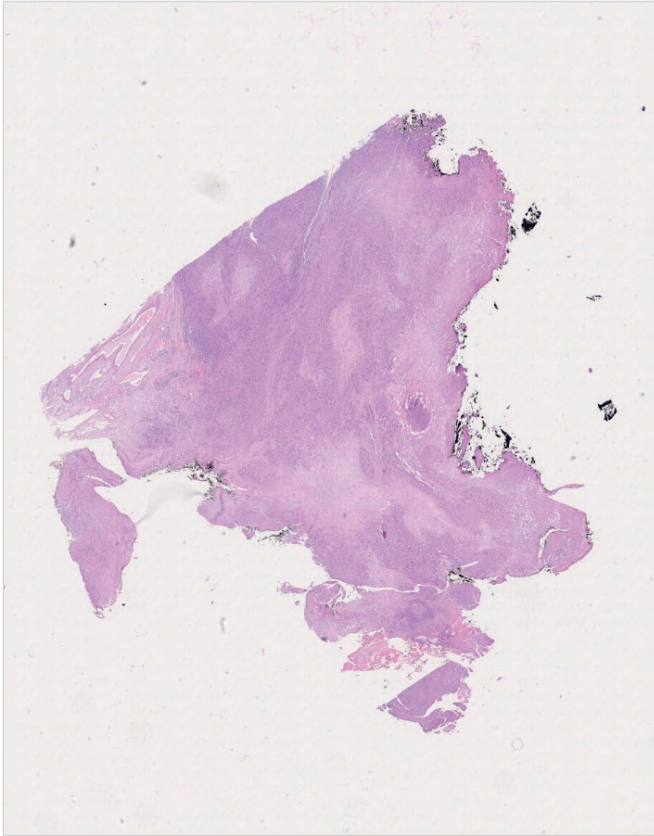
CASE OF THE MONTH

A 42-year-old male presented with intraorbital mass in the kidney. The tumor was resected and the patient relapsed in 2011, 2013, and 2018 after radiation therapy. He died one year after the last treatment with widespread metastases.

The tumor was composed of sheets of large polygonal cells with pleomorphic vesicular nuclei and prominent nucleoli. The neoplastic cells showed eosinophilic cytoplasm with rhabdoid features. There were also pleomorphic cells and a minor spindle cell component.

What is the most likely diagnosis of this renal tumor?

a) *Epithelioid sarcoma, distal type*
b) *Proximal type of epithelioid sarcoma*
c) *Rhabdomyosarcoma*
d) *Synovial sarcoma*

Submitted to the 11th Arkadi M. Rywlin symposium by Franco Fedeli, Malpighi Pathology Academy, Florence, Italy.

Image courtesy of Pathcore®

Answer to last issue's Case of the Month…

d) *HEY1-NCOA2 fusion*

This case demonstrates a mesenchymal chondrosarcoma, a bone or soft tissue lesion with a predilection for adolescents and young adults (1). Characteristically, these malignant tumors show a biphasic morphology: a small round blue cell component and a mature hyaline cartilage component. Mesenchymal chondrosarcomas are most commonly associated with HEY1-NCOA2 fusions. However, these tumors show a degree of genetic heterogeneity and have less frequently shown IRF2BP2-CDX1 fusion. The genetic abnormality t(11;12)(q24;12) - resulting in a EWSR1-FLI1 fusion - is often seen in Ewing sarcoma, another lesion with prominent small round blue cells.

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

Reference
1. *PathologyOutlines (2023). Available at: https://bit.ly/3OfBbiy.*

**To register your guess, please go to http://tp.txp.to/0424/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.

Resistance is Futile

The role of microbiology diagnostics data in antimicrobial resistance surveillance and monitoring

As antimicrobial resistance becomes increasingly common, a precise microbiological diagnosis – along with the determination of antimicrobial susceptibility and the minimum inhibitory concentration (MIC) for antibiotics – is fundamental to its combat.

Here we examine some of the ways in which microbiology diagnostics contribute to the timely detection and surveillance of drug-resistant pathogens, and the technology and initiatives that help us achieve that.

Microbiology diagnostics

The microbiological diagnosis, through the determination of the MIC, provides information on the susceptibility of pathogens to various antimicrobials. Likewise, the microbiological diagnosis can allow the detection of the main multi-resistant microorganisms that can be the cause of therapeutic failures and even patient's death. This can then activate alerts for the control and exhaustive surveillance of multi-resistance strains to mitigate their spread.

Microbiology laboratories monitor the trend and evolution not only of resistance itself but also of the year-on-year increases in MIC50 and MIC90 for some antimicrobials of special interest. Without a doubt, a correct microbiological diagnosis is the starting point to establish truly effective surveillance.

Patient data analysis tools

Correct interpretation of pathogen identification or an antimicrobial sensitivity test requires basic patient data such as: where the sample was collected, previous positive samples, and more. But the data need to be selected judiciously – too much information could hinder a clinical decision.

Integrative middleware tools, such as HighFlexX, are available to enhance the microbiological diagnostic process. They can merge a wide range of data, such as patient demographic data, sample data from the laboratory information system historical archives, and ongoing samples from different diagnostic systems. The implementation of such tools can lead to improved productivity, efficient workflows, standardized processes, and a reduction in human errors.

Importantly, this connected environment enables the knowledge gained from microbial analyses to contribute seamlessly to the broader healthcare narrative. With a simple "click," staff can obtain a visually integrated dashboard by searching for a patient name, sample number, or culture, which optimizes customer loyalty to the system.

Interconnected systems facilitate an efficient workflow in the microbiology laboratory. For example, the MicroScan products, to determine the susceptibility of antimicrobials, and mass spectrometry for bacterial identification can be integrated via HighFlexX middleware. Laboratories using this solution have reported satisfaction with its ease of use, robustness, and versatility.

Antimicrobial stewardship

Clinicians can establish effective isolation measures, and provide appropriate treatment to reduce antibiotic pressure and treat the infection. But how can society in general help with the resistance battle?

International organizations are already raising awareness about a "One Health Response" to address the issue of antimicrobial resistance. This multidisciplinary approach includes medical, veterinary, agricultural, environmental, and other relevant fields. Since the use and abuse of antimicrobials is widespread in various areas, measures need to be taken in all of them to tackle the issue of antimicrobial resistance.

To this end, it should be noted that more and more centers have established antimicrobial stewardship committees that are directly involved in projects such as "Sepsis code", "Zero resistance", or "PROA project". All of them aim to achieve responsible use of antimicrobials to reduce the number of infections due to multidrug-resistant microorganisms.

Ana Ortiz is a sales representative for MicroScan products for Beckman Coulter in Spain.

Ignasi Baliarda is Manager of Application Microbiology Support for Beckman Coulter in Spain.

2024-12683

Women in Pathology

Why we need more women in mentoring and leadership roles

By Ann M. Gronowski, Co-Division Chief of Laboratory and Genomic Medicine at Washington University School of Medicine, St. Louis, Missouri, USA

There are literally decades of data showing that diversity in the workplace improves creativity, productivity, problem solving, innovation, and teamwork. Why is it, then, that in the US women still comprise less than 25 percent of medical school deans, department chairs and full professors? The lack of female mentorship and leadership role models is almost certainly a contributing factor – and it's preventing women from maximizing their performance in the workplace. Here I present my blueprint for redressing the balance.

1. Eliminate blind spots

Recently, I was in a leadership meeting where it was determined that our annual (mandatory) faculty retreat would be held 8 am–5 pm on a Saturday. This is a perfect example of how lack of diversity can create blind spots. None of the organizers with leadership roles had small children. Thus, they did not consider how this would impact families with young children or responsibilities outside the workplace. Holding important work events outside of normal working hours unfairly biases people with childcare, eldercare, or other household responsibilities. This bias falls disproportionately on women. A study has shown that female job candidates who disclose that they are mothers and list child-related activities on their CV are hired less frequently, paid less, and given fewer days off than women with the same CV without such disclosures (1). Male candidates with the same CV were seen as more committed to their jobs and paid more than the women. Diversity in leadership roles leads to more equity and inclusion. To build successful long-lasting teams, we need to create a workplace that fosters work–life balance for all, and ensure leadership teams are not blind to the needs of their employees.

2. Show the way

Imagine trying to nurture a great baseball player without ever being able to show someone how a great baseball player performs. The same is true for leadership. We watch and we learn. Certainly, a good leader is a good leader – and everyone can learn from

> *"Female role models and leaders are needed to let women see what they can be."*

that, regardless of sex or gender. Yet, experience has shown me that men and women often lead differently, and it is important for people to observe those different leadership styles. For example, women leaders are more likely than men to share power and information, encourage participation, and enhance other people's work. In addition, since women still hold a disproportionate percentage of household duties, it can be inspiring to observe how successful women juggle their duties. Female role models and leaders are needed to let women see what they can be.

3. Expand social and political capital

The network and experiences that an individual brings to the workplace are shaped by the social circles in which they travel – both inside and outside of work. These circles are, of course, influenced by things like gender, race, and religion. We have all heard the expression "it is not what you know, but who you know." A diverse team has a larger network of colleagues, more innovative ideas, and a larger skill set to draw from. Interestingly, when it comes to building relationships and networking, men tend to focus on the short-term need, whereas women nurture long-term connections. The latter can lead to very strong social and political capital that teams can benefit from.

4. Improve negotiations

The ability to negotiate is a key skill set for any leader; however, there are whole books written about how women don't negotiate (2). For a long time, I thought that meant that women were not good at negotiation. It turns out women are actually fantastic at negotiating for others; however, they tend not to negotiate for themselves. Women's capacity for empathy, active listening, and problem solving make them well positioned to excel at negotiation.

They advocate for others and focus on building relationships and trust more frequently than men. Studies have shown that men tend to focus on getting the best deal, while women work to avoid impasses (3). The addition of female leaders to a team can provide diversity and innovation to important negotiations.

What team would not want to improve performance by eliminating blind spots and expanding its ability to attain assets? Increasing the number of female mentors and leaders seems like common sense to me!

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2. *2. L Babcock, S Dunbrooke. "Women don't ask". Princeton University Press, 2021.*
3. *3. A Ma et al. "Asking for less (but receiving more): Women avoid impasses and outperform men when negotiators have weak alternatives". J Appl Psychol, [Online ahead of print] (2023). PMID: 37824267*

Gone but Not Forgotten

The dangers of inadequate decedent care – and how today's technology can help

By Nick Nell, CEO and co-founder of MorgueBoard

Devastating errors can happen when decedents are mismanaged. As we see more harrowing stories of morgue mix-ups, when can we expect the healthcare system to recognize that decedent care is just as important as living care? As a society, we expect healthcare organizations to care for our loved ones in the same manner before and after death, but all too often this is not the case. And we're in dire need of a solution.

Most hospitals assign responsibility for decedent management to their laboratory, nursing, and/or security leaders who ensure services run smoothly and appropriately. This includes autopsies, organ and tissue donation, medical examiner releases, holding a patient until family matters are resolved, and any of the myriad of possible scenarios that can arise at the time of a patient's death. In addition, the process requires bodies to be identified appropriately, personal belongings to be kept secure, and all deceased patients' whereabouts be properly tracked and recorded.

Hospital morgues and decedent affairs are rarely the recipient of capital infrastructure dollars, IT software enhancements, or workflow upgrades. Today's healthcare leaders have often inadequately tried to resolve these important requirements by providing staff with antiquated, low budget tools, such as manual paper logs, archaic clip boards, and spreadsheets, to satisfy a process that needs as much attention as any living patient.

In some cases, organizations try to leverage a piece of their electronic health record (EHR) system. However, these accessory software options have clearly not been developed by decedent affairs experts. Most out-of-the-box EHR enhancements do not provide the detailed pathology or decedent care industry-specific details necessary to assure proper patient care. The EHR system alternatives are simply not designed to meet the demands of decedent management. Few offer all of the key communication options needed for efficient and accurate management of outside autopsy cases, funeral home details, medical examiner cases, organ bank information, and special case considerations. Simply put, most hospital leaders are not properly supporting the departments and personnel who handle decedent affairs on a day-to-day basis.

This essential health care area has been neglected by most healthcare technology advancements. However, it remains the responsibility of our hospitals and supporting services to ensure that the same heightened focus on patient safety, hand-off tracking, and respect for family continue well after the death of the patient.

All that said, a brighter future is now within reach to solve this critical gap in healthcare. The solution is targeted IT software designed to work with a compatible streamlined workflow to set a higher standard in managing care after death. These new technologies offer admitting-type case creation upon the death of a patient to initiate a workflow management system equivalent to that offered to living patients. Person-to-person hand offs can be recorded using any institution's integrated employee sign-on access identification systems.

Through this EHR integration, the morgue management system communicates all patient details, including autopsy, organ donation, patient belongings, medical examiner status, and all special circumstances, to key personnel – assuring the decedent receives proper care. Comprehensive case management allows designated personnel to input or view important information for all decedents, such as autopsy consent, infectious case information, personal belonging details, and family/guardian-related issues. All case details are visible anytime, on any device (including a phone app) to create streamlined communication. From the time of death to the release to a funeral home or medical examiner, every detail is traceable and visible to key personnel. Robust necrology data reporting is also available and customizable.

Today's technology is already capable of performing at this level to support a better care-after-death process, as well as reducing the looming hospital liability associated with the large number of manual systems currently used to manage deceased patients.

In short, death care is important and hospitals must start paying more attention.

The Diversity Drive

A more diverse workforce is crucial to the success of pathology labs

By E. Blair Holladay

The pursuit of a more diverse workforce in medical laboratories is not only a matter of social responsibility, but also imperative to foster innovation and excellence – solidifying the laboratory's place as the foundation of high-quality care. Pathologists and medical laboratory scientists play pivotal roles in shaping the culture inside the laboratory, and it is through our actions that we show how powerful the laboratory can be when we embody diverse and inclusive perspectives.

Building a more diverse laboratory workforce starts with strategic recruitment practices. By consistently reaching out to educational institutions that have a track record of cultivating diverse talent or establishing partnerships with universities and colleges serving underrepresented communities, we can create pipelines for diverse candidates.

Mentorship is also instrumental in nurturing talent from underrepresented groups. Pathologists and medical laboratory scientists can serve as mentors to guide individuals through their career development, providing insights, advice, and networking opportunities.

Promoting diversity and inclusion also requires a commitment to cultural competence within the laboratory. Implementing training programs that enhance the understanding of diverse cultural practices, languages, and patient perspectives is imperative to fostering an equitable and inclusive workplace. To prioritize high-quality patient care, pathologists and laboratory professionals must be equipped to navigate the complexities of working with individuals from varied backgrounds.

Beyond the laboratory's walls

It's not only inside the laboratory, but also outside of the laboratory where we must do our part to break down barriers to healthy equity. Over the past year, ASCP has focused on the strategic pillar of diversity, equity, and inclusion (DEI) – and made the laboratory a leader in DEI initiatives. This has included leveraging our Career Ambassadors and partnering with The Lab Drawer to bring interactive and hands-on hematology and microbiology experiments to middle and high school students, building awareness of the profession. ASCP has also partnered with the National Kidney Foundation and the wider medical community to endorse eGFR calculations for diagnosing and treating chronic kidney disease (CKD) that do not depend on race adjustment factors. Our collaboration with AABB and blood banking and transfusion experts has led to the growth of our national registry and data exchange for red blood cell alloantibodies – enhancing care for individuals with conditions such as sickle cell disease.

Creating a more diverse laboratory workforce requires intentional and sustained efforts from every member of the laboratory. As leaders in healthcare, we can shape our culture inside and outside of the laboratory, and in doing so, contribute to the health and wellbeing of our laboratory teams and patients. As medical science advances through the inclusion of varied perspectives and talents, we showcase the power of celebrating diversity.

TRAINING
PLACES

Images used in collage supplied by Royal College of Pathologists

THE MATCHMAKERS

The pathologists behind MatchToPath.com (@MatchToPath) – a free online resource for pathology residency applicants

By Meredith Herman and Helen Bristow

"Hey Google, how do you become a pathologist?" Across the globe, medical students scour the depths of the internet – from reputable resources to obscure online chat forums – to find answers to guide their future decisions. As pathology content is watered down in medical school curriculums, medical students seldom learn about the realities of pathology. Instead, they turn to websites, such as StudentDoctorNet for (questionable) advice. The combination of poor academic advice, limited exposure, and inaccurate information online is a constant source of detriment and misguidance among medical students.

In 2019, the co-founders of MatchToPath.com bonded over their frustrations of navigating to pathology as pathology residents. Each had faced obstacles to get to residency and saw numerous students go through the same hurdles (obtaining US pathology experience, awareness of opportunities and scholarships, mentorship in the field, and so on). The answer to the problem was simple: create a comprehensive resource from pathologists who understand the process.

Four years later, the vision for this website has amazed the group. Website metrics were presented at ASCP 2023, and demonstrated the breadth of reach to students across the globe. Their instagram account (@matchtopath) has grown to over 800 followers and their X page (@MatchToPath) has accrued 1.6K followers as new content and opportunities are shared, garnering attention and appreciation from students worldwide.

The resources have continued to grow as a helpful aid to students around various questions such as visas, elective opportunities, and success on interviews through a pilot mentorship program. Moreover, their active social media presence has helped reach young medical students worldwide and is seen as a valuable resource for all the pathology application needs. So what's the catch? There is none. It is free and accessible. No paywalls or memberships needed. For the team, this is mission accomplished!

Here, the founders reveal what the site means to them and those it helps.

Breaking down the barriers to pathology residency placements

The demand for pathologists has never been higher, with many labs reporting a staff shortage. There are also abundant training opportunities in laboratory medicine, but not all vacancies are being filled. Where is the disconnect?

Fortunately, there are people who are addressing this question head-on. Meet the tireless volunteers and forward-thinking organizations who are helping boost the numbers of candidates entering pathology training.

Swikrity Baskota, MatchToPath Founder and Assistant Professor at University of California, Davis in Sacramento

I am originally from Nepal. When I was applying for pathology residency in 2016, I couldn't find any resources for advice or any mentors willing to guide me. I struggled on alone and, once in my residency in Pittsburgh, I started a Facebook page to help other pathology applicants. A few years down the line, I met like-minded friends like Kamran, Terri, and Oscar – who all suggested a website and all-inclusive information for pathology residency application in one place. Hence, we founded MatchToPath in November 2021.

I personally work on most aspects of the website along with my friend, Terri. We invite guest writers to submit blogs related to different aspects of pathology residency applications. At least two of the founding members edit the blog before publication. We also organize a series of webinars throughout the year. Usually, all of our founding members are speakers or contributors at these webinars along with many invited experts. In 2023, we also organized a series of half-day bootcamps geared for #PathMatch24 candidates, where we had up to 100 attendees in a session.

Our website traffic for 2023 surpassed 4,500 visitors, with unique visitors over 3,000. But the impact is most apparent from the numerous direct messages and personal thank you notes we have received from the end-users.

I am an international medical graduate with prior training in pathology. When I decided to apply to pathology residency in the United States, it wasn't customary for many colleagues from my country to choose pathology. So I basically relied on my own research of 141 pathology programs, visiting their individual websites through FREIDA and ERAS. Also, finding observership opportunities was exceedingly difficult – I remember sending over 100 emails and ultimately hearing from three of them. It's through MatchToPath that I want to put resources at every pathology residency applicant's fingertips to make the process much easier.

Terri Jones, MatchToPath Co-founder and Assistant Professor of Gynecological, Breast, and Cytopathology at Magee Womens Hospital, University of Pittsburgh Medical Center

I became involved with MatchToPath through Swikrity. We were co-residents together (and started our first ever residency rotation together) and have been close friends since! She pitched the idea of a resource where medical students could explore what pathology has to offer and get advice on the residency application from trainees and attendings who have experienced it first-hand; I was inspired. I agreed that the platform would be an online repository for information that was typically spread by word-of mouth and might not be as accessible to applicants from US schools with smaller pathology departments or international applicants.

At MatchtoPath, I present and moderate webinars, edit blog posts, assist in the design and building of our website, and act in an advisory role. I think it is important to help others along a path you've traveled yourself. As a resident and fellow, I was active in educating med students about pathology. My interest in education and outreach continued as I transitioned into becoming an attending. MatchToPath is a wonderful resource for those interested in applying to pathology residency and it is an honor to be a part of the platform. My hope is that it can make the traditionally stressful, challenging – and, at times, frustrating – process of applying and matching a little more manageable.

Personally, I knew about pathology from an early age – my mom is a breast and gynecological pathologist. It had always fascinated me that shapes and colors under the microscope could be interpreted as cells and tissues and translated into critical patient care decisions. Now we are co-workers at Magee.

Oscar Lopez Nunez, MatchToPath Co-founder and Pediatric Pathologist, Assistant Professor of Pediatric Pathology in the Division of Pathology and Laboratory Medicine at Cincinnati Children's Hospital Medical Center

I have known Swikriti since residency; we trained in the same program and have always been close friends. One day, she approached me and shared her idea. I had been pondering a project along the same lines for quite some time, so I thought it was a perfect idea, and I became a co-founder.

My involvement in MatchToPath since its inception has been predominantly an advisory role. I was involved in planning, designing, and revamping our current website, as well as curating and peer-reviewing the posted content, particularly regarding blog entries from volunteers and other contributors. I have also helped plan and moderate our online webinars and boot camps and actively contributed to our recent scholarly activity experience as a group.

Pathology is a hidden gem. You would be surprised how little is known about our field, even within the medical community. The same phenomenon occurs at the subspecialty level with pediatric and perinatal pathology. I aim to showcase what we do as pathologists (and pediatric pathologists) and encourage others to find fulfillment and purpose in the art of diagnosing diseases. MatchToPath is a great way to do that because it's a unique opportunity to engage with a highly motivated group of prospective trainees that are craving guidance and mentorship.

We are bridging the gaps of knowledge that used to exist regarding pathology as a career option and a way of living. But more importantly, we bring kindness, inclusiveness, and selflessness to our field. We do not charge anyone for our content or advice. Most of us reached where we are thanks to the generosity of others – those who guided us and helped us throughout the process without asking for anything in return. MatchToPath is a direct response to this – it is based on the premise of "paying it forward," which is why our project has been successful and quite contagious.

I migrated to the US to pursue specialized residency training

WEBSITE TRAFFIC AND GEOGRAPHY FROM JANUARY 1 TO DECEMBER 31, 2023

4,645 total visits **(+146% year/year)**

Source of traffic:

USA - **75.8%**	Ecuador - **0.4%**
India - **3.9%**	Mexico - **0.4%**
Nepal - **2.8%**	Bahrain - **0.4%**
Canada - **2.2%**	Ethiopia - **0.3%**
Pakistan - **1.9%**	Peru - **0.3%**
Russia - **1.4%**	Columbia - **0.3%**
Saudi Arabia - **1.1%**	Turkey - **0.3%**
Egypt - **0.7%**	United Arab Emirates - **0.3%**
United Kingdom - **0.6%**	Spain - **0.3%**
Puerto Rico - **0.5%**	Thailand - **0.3%**
Japan - **0.5%**	Bulgaria - **0.2%**
Germany - **0.4%**	

in internal medicine. Interestingly, I never considered pathology as a career simply because my exposure to the field was minimal and somewhat superficial. However, preparing for the United States Medical Licensing Examination exams changed my perspective completely. Being forced to re-study basic sciences was an eye-opener. After several years of focusing only on clinical practice in my home country, things suddenly made more sense. I realized pathology was the perfect midpoint connecting the basic and clinical sciences.

Fortunately (and almost by luck) I found some helpers who provided their kindness and generosity as mentors, advisors, and sponsors. Because of them, I managed to observe and rotate in two different pathology departments for several months to understand what it means to be a pathology resident in the US. At the end of this period, I was convinced this was my right choice and applied exclusively to pathology residency programs.

DOING
OUR PART

Chatting with the contributors who make MatchToPath.com possible

Who better to inform a platform advising medical students on finding pathology residencies than a bunch of pathology residents? This intrepid team of volunteers have all battled through the barriers, obstacles, and downright frustrations of finding postgraduate placements in pathology departments. Reflecting on what would have helped them, they are now making sure that help is available to the next generation of future pathologists. Each of them volunteers their knowledge, skills, and time to the MatchToPath.com platform. We asked them what they do, why they do it, and why they believe it's an invaluable resource.

What was your route into pathology – and what support was available to you?

Meredith Herman: I was first introduced to microscope work as a laboratory science undergraduate. Fortunately, I met my mentor, who was a pathologist, and he taught me about the field and gave me a unique perspective. I knew I loved diagnostic work, so I went into medical school with pathology in mind. Sadly, my school was poorly equipped to help students navigate to pathology experiences and residency applications. I sought opportunities (and made my own) throughout school and ultimately established a pathology interest group. We went from nothing to something large that was entirely student led. This helped motivate me to continue to contribute to causes, like MatchToPath. You may be the only pathologist that someone knows – make a difference where you can!

Yasamin Mirzabeigi: Fortunately, I had ample exposure to pathology during my time in medical school, which swiftly revealed to me that pathology is my genuine passion and future

"Be proactive, optimistic, grateful, altruistic, and persistent. Be your own strongest support, and you'll find that people and resources will also rally behind you."

career. Engaging in multiple observerships here opened my eyes to the unique landscape of pathology in the US. I must emphasize that the pathology community stands out as one of the most encouraging and supportive. Throughout my elective rotations, attendance at various conferences, and even through social media platforms like X, I've received immense support from many individuals in the field.

Tiarra Price: To be honest, I didn't know much about pathology before medical school, but I enjoyed the pathology didactics during the first two years and decided to do a pathology rotation (which was hard to find). I ended up loving the rotation and felt that it was the specialty for me. Without a lot of exposure to pathology and not many other students going in the same direction, guidance was difficult to obtain at times. However, I'm grateful to have connected with a lot of amazing pathologists who have helped me along the way, and online resources like Path-SIG and MatchToPath really helped to fill in any gaps.

Chuan Chen: I am an international medical graduate with post-graduate experience conducting research. My journey into pathology was greatly facilitated by the unwavering support of my research mentor, Stephen Nimer, along with my pathology advisors, Andrew Rosenberg, Jennifer Chapman, and Minghao Zhong. Additionally, my friends within the CMG23Path group and my family played crucial roles in my endeavors. I have a message for people like me: be proactive, optimistic, grateful, altruistic, and persistent. Be your own strongest support, and you'll find that people and resources will also rally behind you.

Jenna Aungst: As an undergraduate student interested in forensic medicine, I met a forensic pathologist, Rachel Geller, while completing a skeletal pathology and remains recovery course at the University of Tennessee's Anthropology Research Facility (aka "The Body Farm"). She provided me with guidance over the years, leading to a position working with her at the DeKalb County Medical Examiner's Office in Atlanta, Georgia. At DeKalb, I had the pleasure of collaborating with a team of forensic pathologists, including Chief Medical Examiner, Gerald Gowitt, and then Deputy Chief, Geoffrey Smith, to establish an interdisciplinary

MEET THE
TEAM

Above: Tiarra Price is an AP/CP resident at The University of Pittsburgh Medical Center, Pennsylvania.

Below: Chuan Chen is an AP/CP resident at the Mayo Clinic, Minnesota
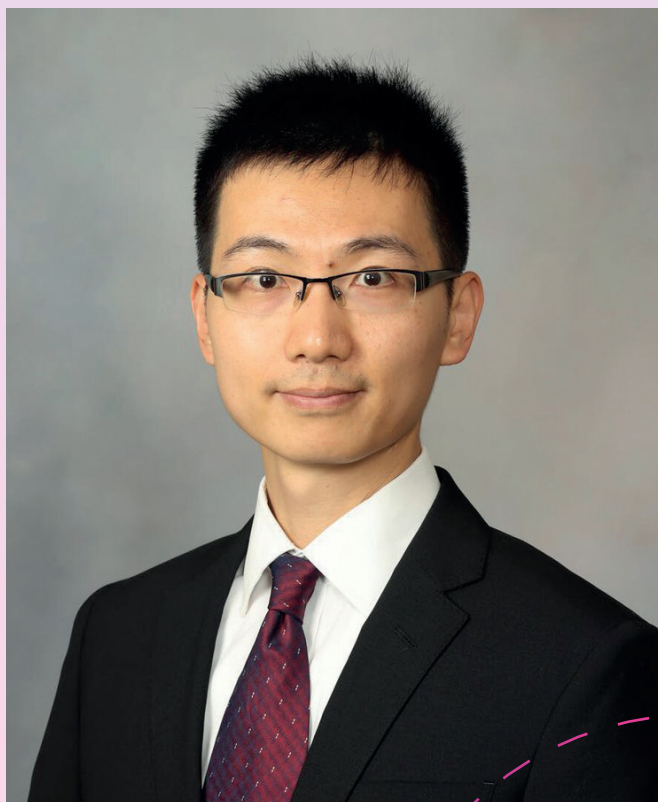
Meredith Herman is an anatomical pathology (AP)/clinical pathology (CP) resident at the University of Michigan in Ann Arbor, Michigan.

Yasamin Mirzabeigi is an AP/CP resident at the University of Miami, Florida

Jenna Aungst is a second-year medical student at Lincoln Memorial University-DeBusk College of Osteopathic Medicine in Knoxville and a Master of Public Health candidate at Georgia State University.

BUT DON'T TAKE IT FROM US. HERE'S A TESTIMONIAL!

Maral Mohammadi

"I went to the University of Debrecen in Hungary and found MatchToPath through #PathTwitter on X.

"MatchToPath was instrumental towards my journey into pathology as an international medical graduate. What distinguishes it is its mentorship program, connecting applicants with pathologists who offered guidance from the ERAS application to interview preparation. The Residency Bootcamp Series webinars were extremely helpful, and the platform's integration with X fostered a sense of community. It was more than just a platform, it became a supportive community.

"Thanks to MachtoPath's webinars, I had the incredible opportunity to connect with an amazing mentor. Her kindness and willingness to go through each draft with me, brainstorm ideas, and provide guidance were truly invaluable. Even during her first year of residency training, she dedicated time to mentor me, and I'm forever grateful for her support. Meeting her in person at CAP this year was an amazing opportunity that further solidified the sense of community within the pathology field."

Read more testimonials on the *matchtopath.com* website!

Follow the team on social media (X: @MatchToPath; Instagram: @matchtopath)

The MatchtoPath team would love to hear from you! If you have questions or comments, they can be reached at *matchtopath@gmail.com*

education program. Their passion for patient advocacy and community outreach inspired me to pursue a career in forensic pathology. After matriculating, my medical school has encouraged me to establish our school's first pathology interest group and multiple elective rotation sites, maintain involvement with national organizations, attend conferences, and engage in research related to workforce development in pathology. However, identifying opportunities for rotations and active learning – like access to a microscope – continues

to be a challenge as the students in my program approach the match. MatchToPath has helped fill this gap by providing specialized guidance to supplement institutional efforts.

How did you become involved in MatchToPath.com?

MH: I serve as a contributor to MatchToPath, creator of the #PathMatch23 mentorship program, and content creator for our Instagram and X pages. I became involved with MatchToPath when I was on an away rotation at the University of Pittsburgh, where I met co-founder Terri. We worked together on cytology and began discussing interests in medical education. We discussed my involvement as Vice President of the Virtual Pathology Student interest group (@Path_SIG) and my ideas to further help students along their journey to pathology. From there, I was connected to founder Swikrity. Both Terri and Swikrity welcomed me into the group and were very receptive to my ideas.

YM: I became involved with MatchToPath after attending the CAP2022 meeting, where I had the opportunity to meet Swikrity and Meredith in person. It was during this meeting that I was invited to join MatchToPath and began my contributions by serving as a panelist in a webinar focused on guiding individuals on finding elective rotations in pathology.

TP: During my fourth year of medical school, I was fortunate enough to serve as a social media co-chair for Path-SIG, where I worked alongside fellow MatchToPath member, Meredith. I really enjoyed my time with the group, who do similar work to help students interested in pathology. I was disappointed when the year ended, but thankfully I got an email from Meredith inviting me to join MatchToPath. It's been a great opportunity thus far!

CC: During my residency application year, I found two invaluable online platforms that greatly assisted me: MatchToPath and Path_SIG. Recognizing the absence of a pathology interest group specifically tailored for international medical graduates at the time, I took the initiative to establish the CMG23Path group. This endeavor allowed me to work with Kamran Mirza, Casey Schukow, and Meredith Herman. Following my match this year, I felt a stronger desire to contribute and support aspiring pathologists. Seeking opportunities to give back, I reached out to Path_SIG and was subsequently introduced to MatchToPath, where I now serve as a contributor.

JA: After transitioning into a leadership role in Path–SIG, I connected with Meredith. We shared a passion for educational outreach in pathology – she was incredibly encouraging, supportive of my ideas, and invaluable in helping me learn how to grow the group's initiatives. Meredith introduced me to Swikrity and MatchToPath, and now I help advocate for pathology from a medical student perspective.

OK IN THE UK?

We asked the Royal College of Pathologists (RCPath) for their observations on pathology training in the UK.

Why are pathologist numbers in decline?

For many pathology specialties, training posts are routinely filled, other than in pediatric pathology and neuropathology, which are outliers in this regard. Overall, however, the pressing issue is that there aren't enough pathology training posts, which leads to workforce gaps at consultant level. There has recently been an initiative to increase the training numbers in histopathology in England, but some NHS Trusts have not been able to take them up for a number of reasons; funding, space, having enough trainers, and so on.

What are the barriers faced by potential pathology trainees, according to RCPath's members?

Anecdotally, the barriers seem to be a lack of exposure to pathology at undergraduate and junior doctor stages of career. We are also aware of misconceptions that pathology is only for exceptionally academic graduates and/or those who want to work alone at a microscope. It is possible that there is a lack of awareness about the advantages of many pathology specialties, such as good work-life balance compared to other medical specialties.

Other issues for pathology trainees are common to trainees across other specialities – national recruitment, flexibility in training, and so on. This is being looked at by NHS England and others.

What training or recruitment initiatives are RCPath involved in or aware of that are making a difference?

RCPath runs a number of initiatives to encourage and inspire medical undergraduates to choose pathology as a career. These include:

- Medical undergraduate membership of RCPath
- Annual Pathology Summer School
- Free access to The Pathology Portal – an online educational resource with a wide range of interactive educational material
- Career webinars
- Foundation Fellowships
- Essay prizes

Credit: Royal College of Pathologists

What is your involvement in MatchToPath.com?

MH: I have dedicated time towards brainstorming initiatives like #PathMatch23 as an opportunity for students to be paired with pathologists to prepare for residency applications. From my work with @Path_SIG, we were able to collaborate on webinars to broaden our audience towards senior medical students/pathology applicants. I also take pride in growing the Instagram page through education posts and reels. I've enjoyed coming up with ideas for blogs and recruiting pathologists to write pieces about a multitude of topics. It has brought me joy to help develop this resource.

YM: My involvement in MatchToPath revolves around our team's core goal of aiding applicants in achieving their aspirations of becoming pathologists in the US. Besides gaining valuable insights from my outstanding colleagues, my primary role includes broadening applicants' comprehension of the pathology residency match journey. This involves writing blogs, engaging in webinars, and providing mentorship to prospective applicants.

TP: Thus far, I've had the opportunity to help out with our bootcamp webinar and our mentorship program. I'm looking forward to further contributing to MatchToPath's mission and broadening our outreach.

JA: As a new contributor to MatchToPath, I'm excited for the opportunity to increase awareness and accessibility in pathology. At the moment this includes expanding our database of elective rotation opportunities and mentors, as well as developing blog and social media posts addressing considerations in the forensic subspecialty.

Why is it important to you to be involved?

MH: Oftentimes, medical students are misinformed about the specialty, and so they go to the internet for answers. We want this resource to be widely accessible and free to both US and international medical students. Our goal is to create holistic, transparent information for students – all shared by pathologists who have been in their shoes. If we can help someone better understand the visa process or better prepare for residency interviews, we've helped someone get a step closer to their goals.

YM: As an international medical graduate, I navigated a distinct pathway compared with my US colleagues. As a newly arrived immigrant, I faced the challenge of understanding what criteria were crucial for pathology programs and how to make my residency application stand out. To add to this, some limitations affected the available opportunities for foreign graduates during the pandemic. MatchToPath emerged as a vital resource, providing me with precise, current information from experts – for free. It played a pivotal role in my journey, aiding me in successfully overcoming hurdles and securing my place. Having benefited so much, I am now driven by a strong desire to give back. Having been an applicant not long ago, I am acutely aware of the specific challenges faced by international medical graduates. This experience inspires me to assist future applicants, particularly international medical graduates, and continue the cycle of support.

TP: It's really important to me to be involved as a way to give back, since MatchToPath helped me so much during my pathology journey. It can be difficult to find mentorship and the residency application process can be confusing and overwhelming. MatchToPath provided a sense of community and support, in addition to sharing sound and useful advice.

CC: I aim to contribute to the team's shared objective of providing reliable and easily accessible resources and mentorship to pathology residency applicants.

JA: Pathology is the best-kept secret in medicine. A significant number of medical schools use an integrated, systems-based core curriculum to introduce pathology to students and do not require rotations during the clinical years. Consequently, there is a growing need for increasing awareness of pathology as a specialty option and supporting interested students and trainees to build an effective, diverse workforce. Getting involved with MatchToPath provides

> "Getting involved with MatchToPath provides motivated individuals with an opportunity to collaborate with like-minded professionals and inspire the next generation of pathologists."

motivated individuals with an opportunity to collaborate with like-minded professionals to engage and inspire the next generation of pathologists.

How would you describe the impact of this initiative?

MH: Recent data show that our website is used across the globe. Being visible and accessible makes a difference for those who do not know where to look. Pathology exposure is limited in medical schools across the globe. We aim to change that.

YM: The impact of this initiative is substantial and far-reaching. MatchToPath is a reliable resource, and it provides an invaluable platform for future applicants. This initiative serves as a beacon of support, bridging the gap for aspiring pathologists, especially those – like international medical graduates – navigating unique challenges. Our impact is profound as it empowers and supports aspiring pathologists on their journey and makes the process more transparent.

CC: The initiative led by Swikrity Baskota and the team is truly admirable. Many members of the CMG23Path group, myself included, have greatly benefited from the guidance provided by MatchToPath.

JA: MatchToPath is unique because it serves as a one-stop shop for all things related to pathology residency. This initiative supports medical students and residents at every stage of the match process by streamlining resources in one, easy-to-find location.

ALRIGHT IN AUSTRALASIA?

Daniel Owens, Vice President of the Royal College of Pathologists of Australasia (RCPA), updated us on the training priorities in the region.

What is the current state of the Australasian pathology workforce?

In Australasia, there is not a decline in the number of pathologists. Rather, there has been a major increase in demand for pathologists driven by increasing complexity and workload. As a consequence, there are many vacancies in the profession. There is a current shortage of microbiologists, chemical pathologists, genetic pathologists, immunopathologists, and anatomical pathologists, in particular.

Contributing to the workforce crisis is an aging workforce, a lack of awareness amongst medical students of the career option, and a lengthy training pathway. With many pathologists nearing retirement age, many of them are currently leaving the profession and there aren't enough new pathologists entering the field to replace them. It is important to note that it takes about 13 years of studying and training to become a pathologist. Additionally, pathology tends to be overlooked as a career option, resulting in fewer medical students opting for it as a specialty.

What are the barriers faced by potential pathology trainees, according to RCPA members?

Our members have identified several barriers faced by potential pathology trainees, including limited exposure to pathology for medical students during their training, making it challenging for them to fully understand the field and consider it as a career option.

Limited availability of pathology training programs and positions is also a concern, preventing aspiring pathologists from pursuing this specialty. A recent review by the RCPA recommended increasing the number of trainee pathologists, particularly in the areas of anatomical, chemical, genetics, hematology, and immunopathology.

Why do initiatives like MatchToPath.com matter?

Initiatives like MatchToPath.com play a crucial role in addressing pathologist shortages by raising awareness about pathology as a specialty and providing information about training pathways, career opportunities, and the importance of pathology in healthcare.

By providing centralized resources and information, these initiatives also make it easier for prospective trainees to navigate the path to becoming a pathologist, potentially increasing the number of applicants to pathology training programs.

How is the RCPA addressing recruitment gaps?

The RCPA continues to advocate for funding to help increase the number of pathology training programs, address workforce shortages, and promote the value of pathology in healthcare delivery through engagement with government bodies and healthcare organizations.

MATCH DAY
STATS 2024

How many pathology residencies are being filled in the US?

In the US, Match Day is the annual event when all medical residency applicants find out where, and in what specialty, they will train. The National Resident Matching Program shared the results for the 2024 residency programs, and we have picked out the headlines for pathology.

Interestingly, pathology is among the top five specialties for attracting international medical graduates. It might also be encouraging to see that the number of pathology placements on offer has been on an upward trend since 2020, though it peaked in 2022, and fill rates have been consistently over 95 percent.

Pathology post-graduate year one positions offered and filled, 2024

Number of places offered
628

Number of places filled
621

Percentage of places filled
99%

Pathology positions filled by applicant type (N=621)

Bar chart — Number of PGY-1 positions filled:
- MD senior: 263
- MD graduate: 24
- DO senior: 89
- DO graduate: 13
- US IMG: 61
- Non-US IMG: 171
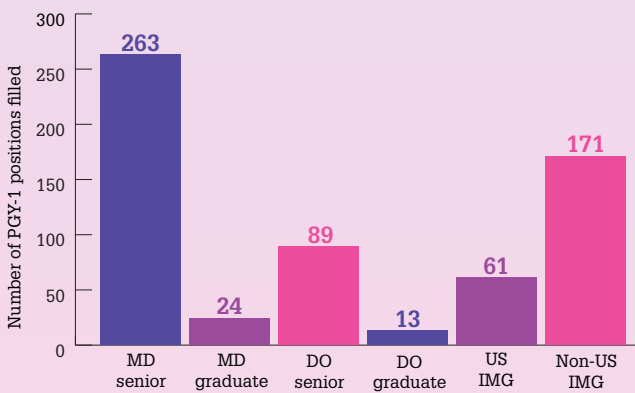
DO, doctor of osteopathy; IMG, international medical graduate, MD, doctor of medicine; PGY-1, post graduate year one; US, United States

Pathology positions offered and filled by year

Bar chart — Number of pathology PGY-1 positions (Offered / Filled):
- 2020 (97% filled): 603 / 587
- 2021 (96% filled): 611 / 589
- 2022 (98% filled): 631 / 619
- 2023 (99% filled): 613 / 607
- 2024 (99% filled): 628 / 621
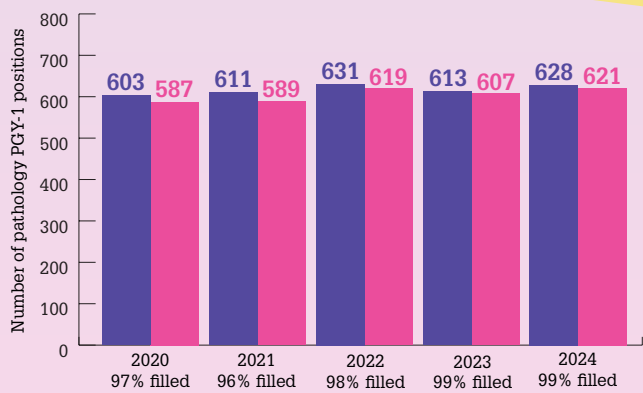
PGY-1, post graduate year one

Offered ■ Filled ■

In Profile

Exploring the relative merits of comprehensive genomic profiling and targeted panel testing in precision diagnostics for oncology

For today's precision oncology, both comprehensive genomic profiling (CGP) and targeted panel testing are fast becoming widely available – and are delivering rapid results. But which test should be ordered when? We asked Vera Paulson, an anatomic pediatric and molecular pathologist at the University of Washington School of Medicine, to clear the mist on the distinctions between these two NGS techniques.

Could you briefly explain the differences between CGP and targeted panel testing?
CGP allows us to sequence hundreds of genes at the same time on a single test. We can evaluate mutational signatures as well as things like microsatellite instability. This can be useful for screening for conditions such as Lynch syndrome, for example, where the choice of immunotherapy depends on microsatellite instability or tumor mutational burden.

In contrast, targeted panel tests tend to be more limited in scope. They focus on a specific subset of genes – sometimes just a handful – that are involved in specific cancer types.

How should health professionals choose between CGP and targeted panels in the clinic?
For clinical trials, where enrollment is dependent on a very specific mutation, then using a targeted panel might get you the answer faster. However, if you have a cancer that's not responding, or if the targeted test is negative, you might want a more comprehensive panel. CGPs may also be indicated in the case of rare cancers, or when less common mutational signatures are of interest. The most important advice I can offer is to ask your molecular expert.

To what extent are CGP and targeted panels complementary to one another?
Over the course of a patient's treatment, both assays might be employed at different time points, particularly when initial tests are negative or inconclusive. For example, after a negative comprehensive panel test, we might subsequently run a targeted sequencing panel, or vice versa.

Key points

- Targeted panels are designed to be cost-effective and provide fast turnaround time.
- CGP provides a broad overview of the genomic alterations in cancer.
- It's important to note that no one test is perfect.

What considerations should be made towards CGP and targeted panels in relation to hematological and solid tumor cancers?
Hematology uses molecular testing for what's known as an integrated diagnosis, based on both IHC and the specific molecular alterations. Hematologists also frequently use molecular testing to monitor disease, for which they need assays with very low thresholds for variant detection.

Different CGP assays may be geared towards solid brain tumors or hematologic malignancies. It's important to ensure that your comprehensive test is testing what you need.

Solid tumors frequently have a more complex mutational signature for which a more comprehensive assay might be useful.

M-AMR-01309

CGP		Targeted panels	
Strengths	Weaknesses	Strengths	Weaknesses
Broad overview of alterations due to genomic coverage	Can be more expensive – not always covered by insurance	Typically have a shorter workflow	Can overlook complex mutational landscapes
Identification of mutational signatures for rare alterations that can qualify patients for targeted therapies	Potential for incomplete coverage of potential regions of interest, leading to false negative test results	Identification of specific alterations that are well established in a particular cancer type	Potential to miss rare alterations of significance
Utility in diagnosis of cancers of unknown primary	More likely to identify variants of unknown significance	Fewer variants of unknown significance	Potential for false negative tests where there is low tumor content
Confirmation of sufficient tumor content in biopsies			

Table. Strengths and weaknesses of the two approaches

ASCP 2024
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Chicago, IL | September 3-6, 2024

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Glioma-omics A spatial proteomics study published in Science Advances has identified protein changes unique to glioma tumors (PMID: 38363834). The researchers analyzed blood samples from in and around glioma tumors using liquid chromatography–mass spectrometry methods to map proteomic patterns. The analysis revealed protein shifts unique to the glioma tumor microenvironment. "Our data offers a landscape view of the molecular changes induced by glioma, which may provide useful diagnostic and therapeutic clues in the ongoing battle against this deadly disease," said corresponding author, Suming Chen. The strategy used could be applied to mechanistic studies of other tumors.

The fab four Researchers in China have identified key plasma biomarkers for predicting dementia in healthy patients years before onset (PMID: 38347190). The long-term prospective study interrogated proteomic test results of more that 50,000 patients without a dementia diagnosis, who were recruited to the UK Biobank study between 2006 and 2010. Four of the 1,463 plasma proteins studied showed strong association with dementia: GFAP, NEFL, GDF15, and LTBP2. In the paper, which was published in *Nature Aging*, the authors wrote, "Our findings strongly highlight GFAP as an optimal biomarker for dementia prediction, even more than 10 years before the diagnosis, with implications for screening people at high risk for dementia and for early intervention."

Beyond colonoscopy: Part 1 Results of a study into a blood test for colorectal cancer have been published in the *New England Journal of Medicine* (PMID: 38477985). The ECLIPSE study detected cell-free DNA in patients with colonoscopy-confirmed colorectal cancer. The test identified more that 80 percent of the confirmed cases, and showed particular sensitivity for early-stage colorectal cancers. Corresponding author William Grady, said, "Colorectal cancer is now the third most common cancer for people under the age of 50. Having a blood-based test for people to take during routine doctor's visits could be an opportunity to help more people be screened."

Beyond colonoscopy: Part 2 Another study, also published in the *New England Journal of Medicine*, has identified colorectal cancer via next-generation sequencing of stool samples (PMID: 38477986). The test, which uses multitarget profiling, identified 93 percent of colorectal cancers confirmed by colonoscopy. Sensitivity was shown to be superior to a commercially available fecal immunochemical test. "Improving specificity of non-invasive stool-based screening tests while maintaining high sensitivity is a critical step in advancing the detection and prevention of colorectal cancer and minimizing the potential for unnecessary follow-up colonoscopies," said corresponding author Thomas F. Imperiale.

IN OTHER NEWS

Adverse effects
Epigenetic study, using mSTARR-seq, identifies link between DNA methylation patterns and human response to environmental factors (PMID: 38407202).

Go large
Health economic study finds that whole-genome sequencing could be more cost-effective for diagnosis of pediatric genetic disorders than whole-exome sequencing (PMID: 38277144).

The blood biomarker challenge
As researchers uncover optimal biomarker for dementia prediction, two studies are set to take place in the UK with aims of developing blood tests for diagnosing Alzheimer's and other forms of dementia on the NHS within five years (https://bit.ly/4cLJNIy).

So and pso
Mice heterozygous for an Ikbkb gain-of-function mutation mimic psoriasis pathology; doubling the gene dose escalates to psoriatic arthritis – results that warrant further investigations in humans, says the Australian-based team (https://go.nature.com/3TxGLif).

Proteomes and Predictions

How advanced spatial phenotyping can help predict tumor sensitivity and resistance to immunotherapy

By Niyati Jhaveri and Arutha Kulasinghe

Immunotherapies, in particular immune checkpoint inhibition (ICI), can lead to remarkable outcomes for a subset of solid malignancies. But overall response rates remain frustratingly low, with success primarily in patients with non-small cell lung carcinoma (NSCLC), renal cell carcinoma, and melanoma (1). Given these odds, predicting which patients will benefit from immunotherapy is of paramount importance. Stratifying likely responders and non-responders can offer a range of important benefits, including guiding treatment decisions and selecting patients for clinical trials.

Predictive approaches hitting their limits

Predicting patient response to ICI currently relies on PD-L1/PD-1 immunohistochemistry (IHC), next generation sequencing (NGS), and assessment of the tumor mutation burden (TMB) status (2). The US Food and Drug Administration (FDA) has granted approval to multiple drugs based on these assays as the triaging tool for patient eligibility (3). These assays, however, are limited in their predictive power because they provide bulk measurements across an entire tissue sample – measurements that are not representative of a dynamically changing TME.

The findings of a recent meta-analysis (4), suggest an improved diagnostic benefit when spatial relationships and protein co-expression on cellular subpopulations are assessed – and that

measuring cell phenotype and functional states is likely to provide a real-time view of the dynamically changing TME.

Shedding light on tumor heterogeneity

Spatial biology, especially spatial phenotyping, is a powerful technique for quantifying protein co-expression on immune cell subpopulations and assessing their spatial arrangement within the microarchitecture of the TME (5). The technique combines ultrahigh-plex protein detection, high-throughput workflows, and powerful analysis algorithms, enabling more than 100 biomarkers to be visualized, characterized, and quantified in a single tissue sample at single-cell resolution – while preserving whole-slide spatial context.

The ability to map the spatial proteome reveals the disruption of the normal organization of immune, epithelial, stromal, vascular, and other cell types, offering the potential for a more detailed view of tumors and visually revealing the factors driving sensitivity and resistance to immunotherapy.

Unlike conventional, low-plex assays (which are limited to analyzing a handful of biomarkers per sample), mapping the spatial proteome of a tumor can uniquely answer the following important questions, such as where and what types of cells are present in the TME and what factors drive sensitivity or resistance to treatment?

Seeing resistance for the first time

Several studies have used highly multiplexed spatial phenotyping of the tumor immune microenvironment to improve the stratification of patient responses to immunotherapy (6, 7). We recently authored a peer-reviewed publication that described mapping of the spatial proteome of head and neck squamous cell carcinoma (HNSCC) to visualize tumor resistance to ICI with ultrahigh-plex whole-slide imaging for the first time (8). ICIs are used to treat recurrent/metastatic HNSCC with a durable benefit observed in approximately 30 percent of patients. Current biomarkers for HNSCC,

however, are limited in their ability to accurately predict responses to therapy and guide patient treatment regimens.

Our study optimized and applied an ultrahigh-plex, single-cell spatial protein analysis on formalin-fixed paraffin-embedded cancerous tonsil tissue from a patient who initially responded to ICI treatment but whose cancer ultimately progressed. The study used a panel of 101 antibodies targeting immune biomarkers as well as those related to metabolic, proliferation, invasion, apoptosis, stress, and survival pathways. By combining analysis of the spatial organization of the tumor/immune environment with functional metabolic profiling, an unprecedented visualization of patterns of treatment sensitivity and resistance was revealed.

A high degree of heterogeneity within the tumor was revealed and offered unique insights into the pattern of clinical response and subsequent progression of the cancer. Though spatial phenotyping and CN analysis based on immune and structural markers revealed multiple tumor-immune CNs within the tissue sample, analysis of metabolic and functional phenotypes revealed a more nuanced profile across all cell types contained within the sample.

The tumor mass consisted of four distinct regions based on histological examination of the tissue, expression of epithelial markers, and spatial metabolic phenotyping (see Figure 2).

The distribution of immune-related cell phenotypes within the four tumor regions was explored in greater detail and compared with a small region of normal tonsil tissue that was present in the patient sample. Overall, the study demonstrated the presence of both immune activation-induced death and tumor progression in the same HNSCC sample. These heterogenous regions and competing microenvironments may underpin differential responses to ICI therapy observed in HNSCC and other types of cancer.

Our approach represents a significant advance in ultrahigh-plex spatial mapping of the human proteome and highlights the potential utility of this technology for identification of clinically significant biomarkers, disease stratification, and understanding the underlying basis of therapeutic responses. By screening large cohorts of patients, new spatial biomarker signatures associated with therapeutic response and resistance will be revealed (9), setting the stage for better and more accurate screening tools and companion diagnostic assays for patient stratification.

Providing complementary information to current diagnostic techniques, I believe the power and potential of multiplexing and spatial biology to be immense. Ultrahigh-plex spatial approaches will continue to bring greater clarity to the complex tumor/immune cell environment, providing information on areas of therapy sensitivity and resistance, and guiding treatment decisions. Ultimately, these assays will be most valuable when advanced into the clinical setting for deeper patient stratification and determination of effective treatments based on unique spatial signatures.

Looking toward the future, as digital spatial data are imputed onto H&E images, it becomes interpretable by pathologists, making the knowledge more accessible and actionable, and democratizing spatial information for the field. As these integrated, data-rich sets provide an improved guide for selection of therapeutic regimens on a patient-by-patient basis, we can move the needle forward for precision medicine.

Niyati Jhaveri is Discovery Applications Manager, Akoya Biosciences

Arutha Kulasinghe is Clinical–oMx Lab Head, Frazer Institute, Faculty of Medicine, The University of Queensland, Australia

See references online
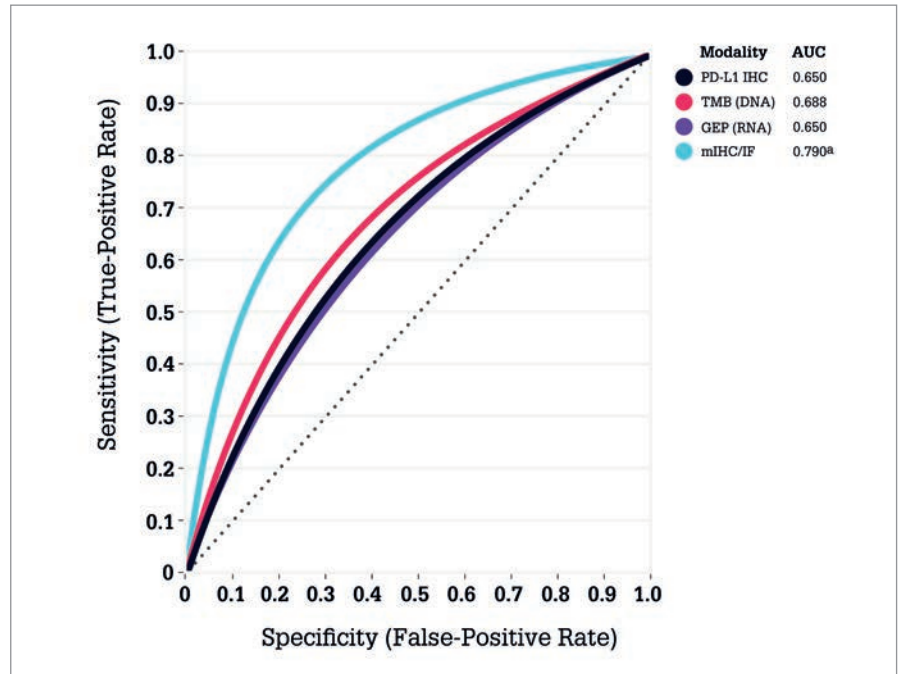
Figure 1. A meta-analysis of different diagnostic techniques for predicting response to PD-1/PD-L1 checkpoint inhibitor immunotherapy showed that multiplexed mIF/mIHC methods had higher predictive value than currently used assays, including PD-L1 IHC, TMB, and gene expression profiling. The "a" indicates statistical significance (P < 0.05), Hanley and McNeil method (4).
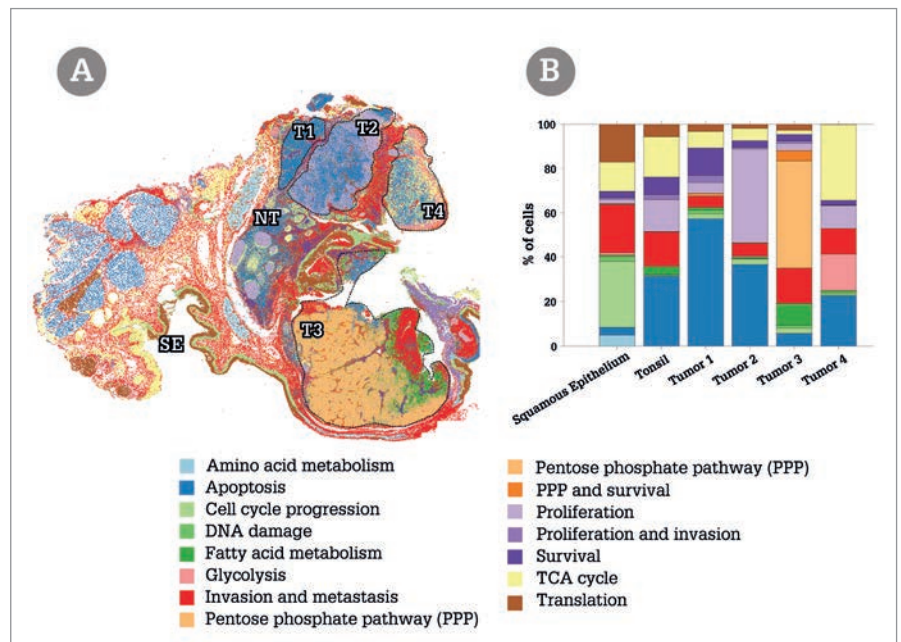
Figure 2. Whole-slide single-cell spatial phenotyping of a human FFPE head and neck squamous cell carcinoma with an ultrahigh-plex antibody panel reveals four distinct tumor regions with varying metabolic and stress profiles (8).

Dry Run

Outsourcing antibody panels is key to standardized flow cytometry

By Sandra Hernandez

Flow cytometry is the benchmark for delivering rapid and accurate analysis of hematologic malignancies, such as lymphoma and leukemia. However, pathology laboratories face several complications when using in-house antibody panels with wet reagents, including reagent waste, time-consuming validations, and batch-to-batch variations. Today, life science companies can offer standardized dry-antibody panels to transform flow cytometry networks. We are already starting to see the direct impact of these panels in flow cytometry laboratories; for example, at Cabell Huntington Hospital in West Virginia, where individualized cancer care is a priority.

For Jennifer McCallister, the medical technologist in the Cabell Huntington Hospital's cancer center, working in a small setting is what fuels her passion. "The beauty of a small setting is I get to know my patients closely from collecting their bone marrow samples through preparing slides for pathology tests and tracking their outcomes and journeys," she explains. "Also, the opportunity to discuss their results directly with expert hematopathologists has added a lot to my experience."

McCallister has witnessed the expansion of the hospital's flow cytometry capabilities since 2004. Initially working with four-color flow cytometers for several years, the hospital gradually upgraded to six- and eventually ten-color flow cytometers. These upgrades enabled a much more accurate population identification and

the detection of low-level abnormal specimens. However, the short shelf life of wet reagents remained a significant setback. "We could validate our cocktails for only 30 days, which was often not enough to complete long-term flow cytometry experiments," she says. "There were also times where we ran out of reagents before the month was up. Even worse – when we ended up not using the entire cocktail, we had to throw expensive reagents away." Cabell Huntington Hospital is one of the many

clinical facilities dealing with reagent waste because of antibody redundancy, reagent expiry, and reagent surplus.

Pre-optimized dry antibody panels can provide a remedy for the technical and workflow challenges, including the waste of reagents. Reagent stability is particularly important for prolonged and consistent flow cytometry assays. The transient durability of liquid reagents often requires the preparation of new batches at different time points or locations for the same assay, which

pipetting, multicolor flow cytometry analysis, and data transfer could all be automated. Because the panel was quality control tested and CE and FDA approved, it could instantly be integrated into the flow cytometer without additional validation. "Time saving is the highlight of a dry panel," McCallister says, "It eliminates the strenuous pipetting process, so I can analyze more patient samples per unit time. After running a gated analysis on our flow cytometry software, I can drop it into the pathologist's working folder, where he can directly access it from his computer." The result was a combination of enhanced confidence over results, streamlined data sharing, and faster turnaround for patients.

But what about cost? At first, the benefits of dry antibody panels may seem inconspicuous; after all, their initial purchase might cost more than preparing a cocktail. However, when other important factors are considered – such as the number of clinical samples per month, the cold shipment of reagents, the frequency of cocktail preparation, and the number of control tubes required for each cocktail – the cost of using liquid reagents multiplies rapidly. On the other hand, dry antibody panels present long-term benefits by eliminating the need for cold storage and frequent cocktail preparation.

In my view, pathology laboratories should seriously consider the shift towards dry antibody panels to standardize their flow cytometry assays for rapid and accurate results. And if cost is holding you back, I urge you to search the internet for the "DURA Innovations Cost Benefit Calculator" and plug in your own numbers. You may be surprised by what you find.

Sandra Hernandez is Global Clinical Flow Marketing Manager, Beckman Coulter Life Sciences

inevitably leads to variation. In contrast, dry antibody panels possess long-term stability with a shelf life of 12 months at room temperature. This makes them ideal for multicentric or long-term studies, as the same panel can be repeatedly used.

The pathologists at Cabell Huntington Hospital replaced liquid reagents with dry antibody panels containing reagents for lymphoid (B-cells, T-cells) and myeloid (M1, M2) antigens. This allowed them to store antibodies at ambient temperature for 12 months. Furthermore, the duration could be extended up to 18 months for custom dry panels. An added benefit was the ease of transport at room temperature, mitigating the risk of reagent waste due to temperature excursion.

Besides durability, dry antibody panels provide various other advantages for flow cytometry workflows. For McCallister, automation was the most enticing aspect of using pre-optimized dry panels. The panel enabled a workflow where reagent

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Credit: Shutterstock

New directions for healthcare applications Deep tech company XPANCEO announce the discovery of new properties of rhenium diselenide and rhenium disulfide. Both materials were found to have different principal directions of absorption and refraction – allowing for more control of the light propagation direction without traditional technological steps used in materials like silicone. These unique properties open exciting opportunities in healthcare, such as the development of highly efficient biochemical sensors and earlier detection of dangerous disease and viruses like cancer and COVID-19.

Fast and deadly In its rapid risk assessment, the European Centre for Disease Prevention and Control (ECDC) reported the number of *Klebsiella pneumoniae* (hvKp) sequence type (ST) 23 cases in EU and EEA countries has doubled since 2021. The ECDC states that life-threatening hvKp infections may occur in young and healthy individuals, and that the risk of further spread across healthcare facilities is high: "The severity of hvKp infections combined with their resistance to last-line antibiotics makes the infections difficult to treat. It is important to detect hvKp early and prevent further dissemination in healthcare settings in EU/EEA countries to avoid further establishment of hvKp carrying carbapenemase genes as a healthcare-associated pathogen."

Meningitis movement The World Health Organization confirms 30 deaths in Gombe State, Nigeria, are linked to three cases of meningitis that are part of seasonal outbreaks (PMID: 38443668). Following the Ebola and COVID-19 outbreaks, the Nigerian Centres for Disease Control are keen to keep on top of infectious diseases and this news sparked action from health officials across the country. Yobe State in particular recently took action and quarantined over 200 people in an effort to curb the spread of meningitis.

Avian flu attacks Antarctica The first signs of avian influenza in the wider Antarctic region appeared in October 2023, but now the virus has spread further across the mainland – so much so, that Antarctic penguin studies have been disrupted (PMID: 38491182). Only researchers specializing in infectious disease are permitted to access animal colonies in this region and several projects have been canceled in hopes of reducing the spread of the virus. Further discovery of influenza in dead skuas near Argentina's Primavera research station has heightened fears, "We must be prepared to protect both the Antarctic fauna and the human beings working there," said virologist Antonio Alcamí.

IN OTHER NEWS

PrEPare for safety
Clinical studies in South Africa reveal that the monthly dapivirine vaginal ring and daily oral pre-exposure prophylaxis (PrEP) are safe for HIV prevention among cisgender women throughout pregnancy (https://bit.ly/4cMPNAB).

Streptococcus soars
Japanese researchers race to identify the cause of a rise in dangerous bacterial streptococcal infections as the number of cases soar to record levels (https://rb.gy/icndla).

It all boils down to…
Researchers point to 10 nonkeratitis Acanthamoeba infections that are linked to using unboiled tap water for nasal rinsing (https://shorturl.at/aqEWY).

WHO's next?
World Health Organization recommends using next-generation sequencing for the rapid diagnosis of drug-resistant tuberculosis (https://bit.ly/3TRzxG3).

Bacteriophage Boost for TB Management

Are phage-based diagnostics the next big thing in the fight against tuberculosis?

By Pranabashis Haldar

It is estimated that up to one quarter of the world's population may have latent tuberculosis (TB) infection without developing any illness; 5–10 percent of this group will have progressive infection that eventually develops into active TB. Currently, it is difficult to identify those with latent TB who will progress to pulmonary TB – a disease that causes significant lung damage and can, without treatment, be fatal.

Thankfully, a promising new type of bioindicator for bacterial infection is emerging that identifies the organism in a blood sample. It uses bacteria's naturally occurring enemy – a phage – to hunt down live bacteria and lyse them, allowing the DNA to be identified with qPCR.

Benefits of phage-based diagnostics

Bacteriophages are viruses that infect bacterial cells. They are highly specific, with each phage preying on a single type of bacteria. The bacteriophage infects a bacterium and uses its own genomic machinery to replicate itself. This leads to lysis of the bacteria, breaking down the thick cell wall and releasing the phage and bacterial DNA, which can then be used for analysis.

There are several phage-based diagnostics for *Mycobacterium tuberculosis (Mtb)* in development, but most are confined to sputum or liquid cultures. It is difficult for children and immunocompromised individuals to bring up sufficient sputum for

analysis, so there is a need for a molecular diagnostic that can determine *Mtb* in the blood – providing a simple, effective way to screen at-risk populations.

Recently, we've been putting a phage-based assay to the test to see whether it can accurately detect TB disease and predict progression.

Clinical study (1): Can a phage-based test detect bacteria in the blood of those with active TB?

At the University of Leicester, UK, we conducted two studies using a phage-based test. The first study investigated if the phage-based assay could detect bacteria in the blood of people with active pulmonary TB or people with incipient infection.

We recruited people with suspected disease and identified a cohort with microbiologically confirmed active pulmonary TB. A smaller cohort of people who presented to the clinic with non-TB acute respiratory illness was also recruited.

We then recruited household contacts of the active TB cohort, including

those who were IGRA-positive (latent infection) and IGRA-negative as healthy controls. Neither group had active TB and were shown to be asymptomatic with normal chest x-rays. They were followed up for 12 months after the assessment, with chest x-rays at three-month intervals.

The phage test was performed before people started treatment, and we found that it was highly sensitive and specific for pulmonary TB; 11 out of the 15 people with pulmonary TB were positive with the phage assay. The phage-negative participants tended to have disease of limited extent with fewer symptoms and lower level of systemic inflammation, suggesting that the infection was being controlled before they were seen in the clinic.

None of the people in the non-TB respiratory disease control group were positive on the phage assay. Somewhat surprisingly, three out of the 18 people we identified with latent infection were positive with the assay and, of particular interest, two out of those three people went on to develop TB after seven months.

We could verify this because they were seen at three-month intervals and had no evidence of TB prior to that time point.

This suggests that detection of *Mtb* in the blood of people with latent infection may be an indicator of incipient TB and able to identify those who are likely to progress to full disease. This was a very intriguing observation, albeit in small numbers of participants.

Clinical study (2): Can a phage-based test indicate progressive TB infection?

Building on the first study, we conducted a second that explored whether or not *Mtb* detected in the blood by the phage assay was associated with progressive TB infection.

Only 5–10 percent of people with latent infection will develop TB, but if we were to use active TB as an endpoint for our study, we would need to recruit very large numbers. We overcame this by using PET-CT as a highly sensitive imaging tool to visualize the trajectory of infection.

We recruited a cohort of healthy household contacts of pulmonary TB patients. The contacts were all asymptomatic with normal chest X-rays. They underwent a PET-CT baseline scan and, if it was positive and showed metabolic activity that could be sampled, they went on to have a bronchoscopy and sampling. If this was positive for *Mtb* they were treated for either having early disease or being at high risk of TB.

If the baseline PET-CT scan did not show anything that could be sampled or if the sampling was negative for TB, they were monitored with a second PET-CT after three to four months.

By comparing the first and second scans, we were able to categorize people as:

1. Stable; indicating no significant change in PET-CT appearance.
2. Progressive PET-CT change (indicating progressive infection).
3. Resolving PET-CT change (indicating resolving infection).

Those classified as stable or having resolving changes with no evidence of a positive mycobacterial culture were then observed for 12 months. Those with a progressive change were considered to be at high risk of developing disease and given treatment.

After the baseline PET-CT scan, four out of 20 participants had positive *Mtb* microbiology with sampling from regions of increased PET-CT activity and received treatment. For the remainder who went on to have a second PET-CT scan, two out of 16 contacts showed significant progressive PET-CT changes and were given treatment.

In total, we identified six people with potentially progressive latent TB infection who fit the criteria for incipient TB. All participants to the study had a baseline phage-based test, and we found a significant association between having a positive phage assay result at baseline and being subsequently identified with probable incipient TB. This correlation supports our observations from the first study that being positive on the phage test is a risk factor for progressive infection at risk of developing to TB.

Promising potential

When combined with qPCR methods, phage-based technologies offer a highly specific and sensitive approach to developing pathogen-directed markers of TB. The existing diagnostics for TB are inadequate to meet the minimum WHO target product profile thresholds to support disease elimination – proving that faster, more sensitive tests are required that do not rely on sampling sputum from the site of infection.

Using phage-based diagnostics, it is becoming increasingly possible to detect *Mtb* in the blood of a large number of people with TB infection – supporting future development of effective blood-based, pathogen-directed biomarkers

"Using phage-based diagnostics, it is becoming increasingly possible to detect Mtb in the blood of a large number of people with TB infection."

that are low-cost, rapid, and potentially deployable in low-income settings. These biomarkers will likely reflect impaired pathogen containment within granulomas, which is thought to be the core basis for progressive TB infection.

Pathogen-directed biomarkers may complement current host immune markers for evaluating TB infection phenotypes, allowing us to discriminate between individuals who do – and potentially don't – require treatment for their TB infection. This combination is a powerful tool to have in our arsenal, if we are to drastically reduce TB cases and deaths by 2030.

Pranabashis Haldar is Clinical Senior Lecturer at the University of Leicester, UK and Principal Investigator in the Respiratory and Infection Theme of the Leicester NIHR Biomedical Research Centre

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2. JW Kim et al., *Lancet Microbe*, 5,2 (2024). PMID: 38244554.

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June 11, 11:00 ET

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Foundation
Digital Pathology

A sMASHing discovery Metabolic dysfunction-associated steatohepatitis (MASH) therapies have previously been hindered by a lack of human translational models and limitations in fibrosis analysis techniques – until now (PMID: 38467661). A team of researchers across Switzerland and the USA combined digital pathology with artificial intelligence analysis to create the FibroNest image analysis platform. Applying the FibroNest to their MASH three-dimensional (3D) InSight human liver microtissue (hLiMT) model, researchers demonstrated that using measurements of fibrosis, alongside analyzing the secretion of fibrotic biomarkers and studying gene expression, opens avenues for fibrosis drug discovery.

Neglected no longer Despite being a vital part of the immune system, there is no standardized method for assessing the structure and function of the thymus. In response, researchers created an integrated and orthogonal digital pathology approach that allows for morphometric analysis of the thymic epithelial cell (TEC) network. This pipeline is versatile and applicable to different conditions affecting the thymus – from acute involution to autoimmune diseases like myasthenia gravis – and opens avenues for investigating thymic function and disease in basic and translational immunology labs (bit.ly/3PB3Yi8).

Illuminating multidimensional pathology Pathologists are starting to explore the possibilities of 3D pathology for analyzing complex 3D tissue structures and imaging thick tissue that isn't possible with slide-based methods. Researchers at Optica Biophotonics have progressed this ideal by incorporating a swept illumination source into an open-top light-sheet microscope. Compared with previous microscope designs, this new system quadruples the field of view and doubles optical sectioning without compromising volumetric imaging speed (bit.ly/4cyj1Ty).

UNIfied digital pathology With hopes of improving evaluation and annotation of images in computational pathology, researchers introduce UNI – a self-supervised model trained on a dataset of over 100,000 diagnostic images across 20 major tissue types. UNI introduces new capabilities, such as resolution-agnostic tissue classification and disease subtyping. The technology should allow for more efficient and accurate AI models for diverse and diagnostically challenging tasks and clinical workflows (PMID: 38504018).

IN OTHER NEWS

Keep it simple
Deep learning from histopathological H&E slides provides a simplified process of predicting protein-based subtypes of upper tract urothelial carcinoma.

In the cloud(s)
Royal Philips and Amazon Web Services (AWS) collaborate to bring digital pathology to the cloud – allowing for secure, scalable digital pathology solutions.

A biomedical boost
Danish pathology departments find that involving biomedical laboratory scientists and technicians in digital pathology offers improved quality assurance and development.

Express yourself
Inspired by picture-making neural networks, researchers create a biomedical model using RNA expression profiles to generate synthetic digital pathology images in various cancer tissues.

See references online

Learning the Language

The importance of AI fluency in the era of digital and computational pathology

By Eric Walk

The field of pathology is rapidly moving toward a digitally enabled future where all pathologists access, view, diagnose and manage cases using whole slide images (WSIs) and artificial intelligence (AI) algorithms. As this transformation progresses, it will continue to be critical for pathologists, laboratory professionals, and other key decision makers to become fluent in the evolving language of AI and digital pathology (DP); after all, we will be charged with making informed decisions about which specific digital and AI pathology solutions best meet the needs of our practice environment.

Achieving this fluency will not require the knowledge to code AI applications but will require the acquisition of foundational levels of knowledge in the areas of DP infrastructure as well as underlying AI, machine learning, and neural network approaches. The focus should be on understanding the strengths and weaknesses, training requirements, and level of supervision associated with each approach. The depth of knowledge should be similar to what pathologists and lab professionals already know about other testing methodologies in routine use such as immunohistochemistry (IHC), next-generation sequencing (NGS), and polymerase chain reaction (PCR). The goal should be a level of familiarity and comfort in critically assessing different AI solution options and matching specific pieces of digital pathology software, AI algorithms and other tools to current and future needs in their laboratory environment.

Digital and AI pathology infrastructure

The core components of a DP infrastructure include a digital slide scanner and either a basic digital image viewer or full image management system (IMS; see Figure 1).

The IMS also enables the use of AI pathology applications, either natively/directly integrated or via so-called contextual or "pop-out" integrations. It is important to understand the difference between these two scenarios; they may have significant implications for i) real-world ease of use, and ii) the flow of complete data from AI algorithms to the IMS and then to the LIS and pathology report. IMSs with natively integrated AI applications allow immediate and direct use of AI tools within the same diagnostic viewing environment. Whereas, without direct integration, AI applications rely on launching a separate application window where the AI is visualized. From a data flow perspective, IMSs with natively integrated AI solutions by design have the required fields to accept data from the AI application for delivery to the IMS for reporting. A potential limitation with non-native AI algorithm integrations into an independent IMS is a mismatch in either functionality (for example, the AI requires overlay capability not present in IMS) or data field quantity, leading to potential limitations in reporting. Additionally, the creation of AI-IMS application programming interfaces (APIs) may be required, at additional cost and timeline impact, to enable full functionality of a non-native AI application with an IMS.

AI and machine learning methods

AI is a broad field of many methods focused on the use of machines to replicate the intelligence of humans.

- **Machine learning (ML)** is a subset of AI that specifically uses algorithms and statistical constructs to learn from data and improve performance on specific tasks.

- **Deep learning (DL)** is a subset of ML that uses deep neural networks to process and analyze vast amounts of data to identify patterns and make predictions. Several specific types of deep neural networks have been used to create histopathology-specific AI applications that have the potential to improve the efficiency, turn-around time, reproducibility and accuracy of pathologist and histotechnician workflows (see Figure 2 online).

Let's dig a little deeper into AI model types and their applications:

- **Convolutional neural networks (CNNs)** are supervised ML models trained on large amounts of labeled data that can identify the presence of trained structures in previously unseen data sets. CNNs are hypothesis-driven, meaning one needs to know what the model should be identifying. By design, they will not discover any new associations within the data set or identify structures not present in the training data. Several CNN-based algorithms have been created to identify PD-L1 positive and negative tumor and/or immune cells and output the relevant PD-L1 scoring metrics. Another common CNN algorithm application is tumor detection for quality control, NGS sufficiency, and case prioritization purposes.

- **Graph neural networks (GNNs)** exist between CNN- and MIL-based models in that they are moderately supervised, relying on some identified features but also have the ability to discover new associations in the data set. This approach

Key Elements of A Digital & AI Pathology Infrastructure

Laboratory Information System (LIS/LIMS)
The *LIS/LIMS* orchestrates management of critical laboratory data, including patient information, testing requests, and results.

Whole Slide Scanner
The *whole slide scanner* generates a high-resolution image within seconds to minutes from an unstained or stained glass slide.

Image Management System (IMS)
The whole slide image is uploaded to an *IMS*, which serves as a digital repository for pathology images that pathologists can use to retrieve and search cases as well as run embedded AI.

Artificial Intelligence
With the creation of a digital image, *artificial intelligence* can be applied to the images to augment and enrich clinical decision making across a multitude of different use cases.

Digital Pathology Applications
Diagnostic: Primary digital diagnosis, remote diagnosis
Consultations
Tumor board
Education

AI Pathology Applications
Workflow: auto-QC, reflex ordering, smart case distribution, sorting & load balancing
Diagnosis: Assisted diagnosis, biomarker quantification, report generation, pathologist assist tools (LLM/LMM)
Prediction: CDx quantification, genomic alteration prediction and screening

Data Storage
Slide must be stored in either **on-premise storage or cloud storage**. This robust storage infrastructure accommodates the safe retention of patient images and associated data.
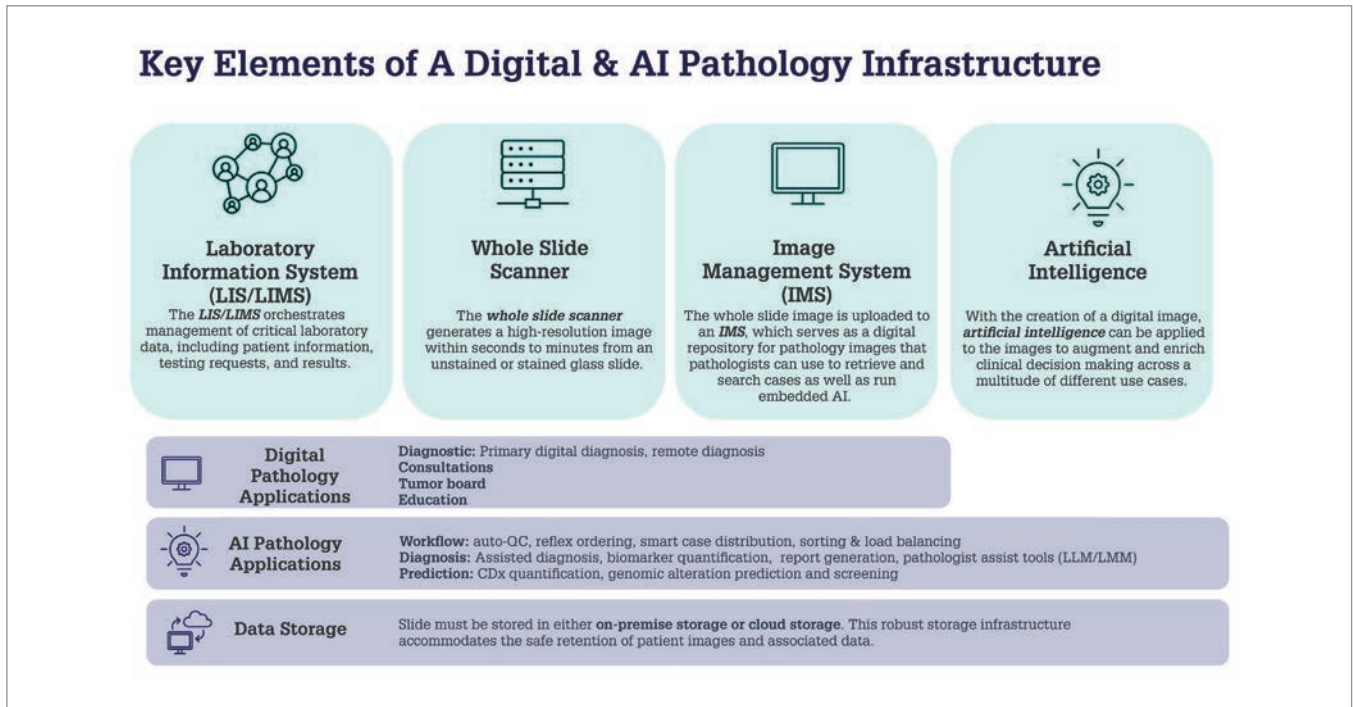
Figure 1. Key elements of a digital and AI pathology infrastructure

is based on the creation of graphs, which consist of "nodes" connected by "edges". In histopathology, the nodes are typically morphologically identified cell types such as lymphocytes, tumor cells, etc., but can also be cells identified by IHC expression. The edges can be any relationship between cells but are typically the distance between cells.

- **Multiple instance learning (MIL)** is a weakly supervised, hypothesis-seeking methodology that does not use labeled data but instead can discover patterns in a data set that correlate to an endpoint or characteristic of interest. A pathology example is molecular biomarker prediction where the model is trained to identify cellular and/or tissue-level morphologic patterns in the hematoxylin and eosin (H&E) slide that correlate with a specific gene alteration (for

example, a point mutation). MIL has also been used to directly predict drug response from H&E.

- **Generative adversarial networks (GANs)** Generative AI methods create novel output data based on input data and a ground truth. In a GAN model, there are actually two models, one generating novel output and a separate discriminator model comparing the output of the first model with the ground truth. In histopathology, GAN models can be used to transform the WSI output of one scanner model to visually match the output of another scanner model, which can be valuable to cross-train an algorithm to be generalizable to multiple scanner types.

Continuous learning and the future

Pathologists and other lab professionals should take advantage of the abundant sources of information online and in the

literature to establish and build their DP/AI pathology fluency, one layer at a time. Challenge yourself to learn more about topics not covered here such as self-supervised learning (SSL), zero-shot learning (ZSL), transformers, foundation models, and visual language models (VLMs).

VLMs represent the cutting edge of this field and an indication of where it will go in the future. The vision is that these generative AI tools will serve as pathologist assistants during the diagnostic process; for example, to create a differential diagnosis and refine it with recommended additional IHC and molecular testing. In addition, these tools could assist the pathologist in the creation of the pathology report, including drafting the microscopic description, synoptic diagnosis, and any relevant clinical decision support information. Importantly, pathologists should remain in control and be the final decision maker, choosing when and how to use VLMs – or any other AI tool.

Eric Walk is Chief Medical Officer, PathAI

TU Munich, a Digital Case Study

Technical University of Munich bridges the gap between research and clinical care

By Rob Monroe

Part two of our "Journey to Digital Pathology" series continues in Germany

When Katja Steiger started working in the Collaborative Research Center at the Technical University of Munich (TU Munich) more than 10 years ago, she was a rare species of pathologist: a translational pathologist – focusing on the translation of laboratory findings into clinical practice.

"The Collaborative Research Center was searching for pathologists with animal models experience," Steiger recalls. "I applied for the job because I'm trained as a veterinary pathologist but have always worked on both animal and human medicine. This experience made me a slightly exotic person at the time."

At TU Munich, five veterinary pathologists and seven technical assistants have joined Steiger at the Collaborative Research Center in the last decade. This team complements the 20 pathologists at TU Munich's Institute of Pathology, a department responsible for diagnostic pathology that receives more than 30,000 clinical cases annually.

"The Technical University of Munich built a large facility for comparative experimental pathology that supports animal pathology for translational research as well as comparative animal–human studies," notes Steiger. "We

work up tissues and read the slides for the researchers that are working in cooperation with us. In this setup, digital is fundamental to our work."

The beginning of the journey – assisting education

In 2012, TU Munich began its digital journey with a foundational project for the European Council. The aim of the project was to teach biology PhD candidates and postdocs about pathology in animal models – an initiative that necessitated digital slides. "We scanned the slides in Munich and sent them by hard drive to Finland," Steiger recollects with a smile. "It was basic, but it worked. We continued with this protocol for a few years."

Steiger emphasizes that slide digitization is key in the research setting. "We've learned how important it is to have slides available to researchers; digital images make this possible. When

images are digital, we don't have to sit at the microscope together to work together. We can be in different locations at TU Munich – or even working remotely – and access the same slide at the same time, or even sequentially, to facilitate dialogue, exchange information, and annotate the images digitally."

From that initial project, the TU Munich team developed an affinity for digital. "In our research environment, people started to ask, 'Can we digitize the slides from our mice? From our animals? Or can we get H&E sections from human patients to compare them?'," Steiger continues. "Over the next four or five years, we were able to increasingly respond to these requests, which resulted in expanding our capabilities in comparative experimental pathology with a variety of models, such as xenografts, genetically engineered mouse models, and genetically engineered pig models. Using digital pathology, we could do a

"Computational pathology, including augmented (or artificial) intelligence, has potential benefits across clinical and research, such as enhancing biomarker discovery."

standard pathological workup and easily compare the findings, especially from the genetically engineered models."

The halfway point – impact on cancer research

By 2016, the volume of requests for digital images compelled the research team at TU Munich to purchase a high-throughput scanner. In 2019, the organization added another as demand for digital continued to grow. "In concert with the expansion of digital slides, we implemented a database so people could access their slides. This was used quite often," Steiger adds. "We are situated in the pathology department so we have full access to the archive, making it easy to compare these findings to cancer cases of real human patients. We can pick up the slides and the blocks, and we can provide, for example, biomarker validation."

The COVID-19 global pandemic outbreak in 2020 further accelerated TU Munich's adoption of digital on a broader scale for both clinical and translational needs. "We had the digital foundation in place and an established collaboration with our technology vendor so we could act fast to support pathologists' needs during the pandemic," Steiger recollects.

Steiger's unit now supports a range of translational cancer researchers working closely with the clinical pathology team. Approximately 30,000 slides per year are digitized for research purposes with storage provided by the organizations' lab administration center.

On the horizon – better patient outcomes

TU Munich continues to learn how digital pathology can benefit the institution and its patients, including exploring how it serves as a gateway to computational pathology. The organization recently added a dedicated computational pathology professor for both research and clinical pathology.

"Our computational pathologist frequently interacts with the deputy director of the institute, who is responsible for the lab. Together they focus on performance. What are the network requirements? What are the errors? What can we change to make the process faster and better? They also talk to the pathologists to ensure the approach is working and to gain their feedback and ideas," Steiger notes.

Computational pathology, including augmented (or artificial) intelligence, has potential benefits across clinical and research, such as enhancing biomarker discovery.

"AI can play a role in biomarker research through computer-aided morphologic assessment," notes Vivian Tan, a computational pathologist with Leica Biosystems. "What fascinates me about AI is the ability of deep learning to extract a significant amount of information from an H&E image that can increase our understanding of tumor biology, which can translate into the clinical setting to facilitate patient stratification and treatment planning."

Even as Steiger looks ahead to future applications of digital pathology, she reflects on what she has learned over the past decade. Her top advice? Think early and often about data management: a catch-all term for a set of topics including data throughput. "For example, if you want to scan on a server and provide slides on a server, you need the network environment. At TU Munich, having two high throughput scanners for the research team allowed our pathologists to have the first connection," she explains.

Digital storage is another important component of data management. "TU Munich's data management approach recognizes Europe's regulatory requirements are varied and evolving. For example, the European Union requires storage of research data for at least 10 years while here in Germany there is a local regulation that data must be stored locally, not in a cloud-based system," Steiger notes. "As a result, we require a storage room and personnel to manage our data, and we must keep revisiting our needs to ensure we plan for appropriate storage capacity and have an ability to easily store and access images."

Steiger also notes that engaging with colleagues "top-down and bottom-up" is vital to ease adoption and expansion of digital technology across a distributed organization. "You need the support of people in leadership positions as well as the technical people involved day to day. If both those groups are supportive, it's easier."

In the end, she concludes, "All our efforts are in service of increasing knowledge on all sorts of conditions and improving public health."

Rob Monroe is a pathologist currently serving as Chief Medical Officer for Leica Biosystems and Chief Scientific Officer, Oncology, for Danaher Diagnostics

Business Case Beginnings

When it comes to laboratory improvements, project management always starts with justification

By Helen Bristow

First there is the vision – interconnected laboratories running seamless workflows with their shiny, new systems. But next comes the question of funding. How do you convince those who control the purse strings to pay for it all?

We posed that question to Mike Langford, Principal Scientist at Spire Healthcare, an independent hospital group in the UK. In 2020, he was tasked with connecting a network of 39 private hospitals and two centralized histology labs via digital pathology workflows. With the system now successfully rolling out, he is well placed to share his experience of turning vision into reality.

When putting together a business case, where do you start?
You should start by describing the problem. For Spire, the problem started with turnaround times. If clinicians hold a clinic, say, every seven days, we need assurance that pathology results, including immunohistochemistry (IHC), hit this target every time.

These targets were challenging when using physical slides. In our network, there can be up to 250 miles between hospitals and the main laboratory, which results in unavoidable time lost to transporting samples. Return of prepared slides from the lab back to a site, with onward transport to the pathologist's location, creates an additional step – which can be removed by sending digital images.

When pathologists asked for additional testing, such as IHC, the slides followed the same journey all over again. We also found that specialist cases were being referred out of Spire for second opinions, which further slowed reporting. This was frustrating as Spire had the expertise but lacked a clear process to refer in house.

We also recognized the potential for AI to assist in making the whole pathway faster. So, our benefits statement was clear – digital pathology will support improved turnaround times, open rapid case sharing for second opinions and multidisciplinary teams, and allow introduction of AI tools.

When it comes to "selling" the project proposal, it's worth focusing on more than the technology itself. In our case, this was not a project about digitizing a slide – we could do that 30 years ago – it was a complex project about digitalization of pathology, improved processes, connectivity, efficiency, and great teamwork. The fiscal case, of course, needed to be shown, but digital pathology is more about quality and standardization of process.

Future proofing also came into the business case. We are in transition – "digital pathology" will soon just become

"pathology" again as the tools available become standard.

What else did you need to consider for the business case?

Having carefully stated the problem, you then need to propose the solution. Some of the details that went into our plan were:

- **Executive buy-in** – Sponsorship and a clear understanding of the vision at the highest organizational level were fundamental.
- **Leadership** – Development and release of time for the project and operational teams in histopathology and IT was essential to ensure ownership of the operational changes throughout the laboratory.
- **Staffing levels** – Digital processes add some extra in-laboratory steps, so new headcount targets were proposed.
- **Seamless launch** – Pathologists are hundreds of miles apart, so it was essential to be able to digitize everything, ensuring that macro images and request form images were all together from Day 1 of going live.
- **Single workflow** – We had to ensure that we could link patient data in our laboratory information management system (LIMS) with the digital image, which required an additional IT interface. At the next upgrade of our LIMS, a key consideration will be integration with other systems, including digital imaging, voice recognition, and AI.

Who did you include on the project team?

First came the sponsor – that was my role – with a bird's eye view of the organization. I needed to work closely with a lab lead who was invested in the fine details of delivery.

Finding an experienced project manager was essential – this was the most complex project that our PMO had ever undertaken. We also had an IT solution architect who attended every meeting and brought together technical IT teams for each step.

There is a huge cast behind the main team, of course – ops managers, IT specialists, quality, finance, procurement, and so on.

What contingency measures did you include?

Problems and setbacks are inevitable in any large project. Therefore, it's essential to build some contingency into the proposal. In our case, the first slide scanners we trialed were not accepted and we had to restart the evaluation and contracting process from scratch.

On the subject of contracting – it always takes longer than expected. Despite revising the timelines for the second wave of scanners, progress on implementation slipped a year behind predictions. But what we lost in time, we gained in knowledge of the impact on lab operations. We found that digital pathology would add a half to a full day to our lab process, so we needed to be efficient. We learnt a lot about our histology pathway and what needed to change, and what we needed digital suppliers to offer. Now, with certain IT components not talking to each other, time has had to be added for tailoring the software to meet Spire's needs.

My advice would be to set out in the proposal the elements over which you have control, and those over which you have only influence. It will be the latter that are more likely to go wrong and delay overall delivery.

What sort of objections did you encounter to the business case? Did it have to be revised?

A business case may need to go through several iterations before the project is agreed. For our project, we recognized that release of funds is challenging when you're competing with capital spend on other assets, like CT and MRI scanners. We found that balancing the project cost against that of a major investment, such as an MRI scanner, was a good way to illustrate the spend.

We also looked at the total cost of ownership. Adding a slide scanner adds cost to each slide that is digitized. In addition, the ongoing storage costs are cumulative and hundreds of times more expensive than glass slide storage. We have made some predictions, but we will need to find more intelligent storage options and only retain key images.

How do you measure success?

Gaining feedback from end users is crucial to assessing a project's success. When Spire went through that process, we found that those pathologists who had used the new systems found them beneficial – just removing the burden of glass slides was a big win for them. But they did recognize the system needed improvements. In particular, they would like a single digital sign on. This will be especially important when AI is introduced, as that would be another screen to open.

What are your top tips for project sponsors?

- Get the right team – from blue sky thinkers to the very detail-oriented.
- Choose an experienced project manager to take ownership of the plan, and a steering committee to hold the project to account.
- Constantly engage stakeholders – sharing good news and bad.
- Choose the right suppliers (they might not be the cheapest!).
- Accept that it will take as long as it takes – it is hard work to install new systems and change processes to fit.

Navigating Digital Scholarship and Professional Growth

How can new-in-practice pathologists leverage the power of social media to enhance traditional academic work?

By Katrina Collins, Xiaoyin "Sara" Jiang, Nicole Riddle, Adam L. Booth, Mirian Ramirez, Laura Torbeck

In the ever-evolving landscape of modern academia, scholarly contributions now extend beyond traditional avenues. Social media and digital engagement are very much on the rise – certainly not hindered by a world in lock down in the COVID-19 years. Pathologists, recognizing the transformative influence of digital scholarship, are increasingly using new and emerging platforms to expand their knowledge, connect globally, build reputations, and stay informed about the latest developments in their field.

Historically, in academia, digital scholarship has been viewed as a peripheral interest rather than a significant contribution – a pathway to traditional scholarship rather than a distinct form in its own right. But there is a growing recognition of its significance, with efforts to blend it seamlessly with traditional scholarship. New-in-practice pathologists are urged to embrace this transformative shift, particularly within the framework of promotion and tenure expectations. It can help guide their career trajectory, ensure job stability, and

provide access to crucial resources.

Accepting digital scholarship in promotion and tenure dossiers demands an acknowledgment of its intellectual rigor, impact, and significance. To actively participate in this shift and showcase the impact of digital scholarship, managing metrics associated with online presence is key. So how can pathologists optimize their online footprint, ensuring their digital efforts contribute meaningfully to scholarly impact?

Understanding digital scholarship

Digital scholarship involves employing digital tools, technologies, and platforms for research, data analysis, archiving, and the online dissemination of scholarly work across diverse academic fields. It encompasses a broad spectrum of activities aimed at leveraging the potential of digital resources in academic pursuits.

The domains traditionally linked with digital scholarship encompass digital humanities, digital sciences, digital social sciences, digital art, and data science. However, all academic

disciplines actively use digital materials, tools, and methodologies to construct scholarly work. In fact, digital scholarship transcends disciplinary boundaries and fosters multidisciplinary collaboration. Just as the internet transformed access to data and information, today's digital scholarship tools significantly amplify our capacity to share and collaborate.

Computers, along with other digital tools and software are crucial for all aspects of the academic tripartite mission, encompassing education of healthcare professionals, innovative biomedical and clinical research, and the delivery of top-tier patient care. Since these are already routine practices in daily workflow, it makes sense to take a more intentional, thoughtful, and critical approach to understanding the capabilities the digital realm can afford us with scholarship.

Digital scholarship adds a layer to scholarly endeavors that traditional analog approaches struggle to support effectively. This extension greatly expands the scope of scholarly pursuits, fostering a more creative exploration of research

goals and facilitating more uniquely designed outcomes. Given that humans are inherently attracted to novelty, presenting research in innovative ways can also stimulate increased curiosity and interest. As noted, digital scholarship tools and platforms naturally lend themselves to collaborative initiatives, making them ideal for projects and community engagement.

Integrating digital scholarship

There are numerous ways digital scholarship can be incorporated into research, teaching, and publication. Creativity and innovation are a hallmark of digital scholarship; opportunities abound to build on these ideas and create your own pathway. Below, we present four practical approaches for weaving digital scholarship into both individual research endeavors and collaborative networking efforts.

1. Diverse metrics for scholarly impact and effective metrics management

- Track traditional citation counts on platforms like PubMed and Scopus to gauge academic influence and recognition within the scholarly community.
- Use alternative metrics to monitor the online visibility of your research; track mentions, shares, and discussions on social media, news outlets, blogs, and other online platforms (for example, ResearchGate, X, LinkedIn, PlumX).
- Use visualization tools or graphics to represent metrics (including likes, shares, reposts, reach, engagement rate, followers).

2. Real-time collaboration and interactive engagement with peers

- Connect with other researchers beyond your usual established network – across diverse departments and geographies, including those you may have never have met in person – to write and publish papers, articles, or books.
- Actively engage in collaborative platforms, such as ResearchGate, ORCID, or LinkedIn, to connect with peers, share expertise, and contribute to discussions.

3. Innovative educational approaches

- Develop e-learning in the form of online courses, webinars, or interactive tutorials. This pursuit not only enhances your role as an educator but also contributes to the advancement of medical knowledge, aligning with the evolving landscape of medical education.
- Create and curate digital archives or repositories that store and provide access to research data, documents, and multimedia materials.
- Participate in (or organize!) virtual conferences and webinars, leveraging digital platforms to facilitate scholarly discussions and knowledge exchange.

4. Integrate feedback

- Recognize that active engagement on various platforms requires time and effort – and then strive for a balance between the quantity of metrics and the quality of research. Prioritize impactful contributions over sheer volume.
- Periodically analyze the documented metrics to identify trends, patterns, and areas for improvement.
- Acknowledge and celebrate achievements, recognizing milestones and positive feedback received from the academic community, collaborators, or other stakeholders.
- Encourage constructive feedback from the research community and help promote a supportive environment where researchers can learn from one another.

As the trend towards digital scholarship grows, mastering the tools and skills needed to succeed will become increasingly important. Embracing continuous exploration and adaptability is essential in this dynamic landscape. By integrating all strategies, new-in-practice pathologists can effectively turn their digital work into scholarship, thus contributing more robustly to the academic and professional community.

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Applying the 2023 ASCO-CAP guideline updates for HER2 testing in breast cancer

With the emerging clinical significance of HER2-low breast cancer, this article explores the latest best practice guideline recommendations for HER2 IHC testing and reporting in your clinical practice.

Introduction

HER2 expression in breast cancer is currently categorized as HER2-negative and HER2-positive (1). HER2-negative breast cancer makes up 85% of all cases (1). However, 60% of HER2-negative breast cancers can show low levels of HER2 expression (1,2). Defined as HER2 IHC 1+ or 2+ with negative ISH, these tumors are often referred to as HER2-low, and classed as a subset of HER2-negative breast cancers (1).

Over the years, the ASCO-CAP guidelines for HER2 testing in breast cancer have evolved to keep up with the changing HER2 landscape to ensure clinical care teams are well equipped to make optimal care decisions (3). In 2023, ASCO-CAP published a guideline update with a specific focus on recognizing and reporting HER2 IHC 1+ or 2+/ISH- (HER2-low) tumors (4).

Although HER2-low has not been recognized as a distinct subtype of breast cancer, it is a clinically meaningful classification of HER2 expression (5). Identifying HER2-low tumors may have an impact on patient care; hence, the importance of standardizing assessment of low levels of HER2 expression has been recognized in the most recent guideline updates (4,6).

Training is advised for pathologists to implement guideline updates in practice (7,8). However, this can be challenging considering access to quality resources can vary between laboratories (9,10). Online educational platforms, such as *HER2Know.com*, provide access to a range of educational materials to help pathologists implement best practice recommendations for assessing low levels of HER2 expression.

Key best practice recommendations from the 2023 ASCO-CAP guideline update

Test ordering
- All newly diagnosed patients with breast cancer must have a HER2 test performed (4)
- Patients who then develop metastatic disease must have a HER2 test performed in a metastatic site, if tissue sample is available (4)

Pre-analytic considerations
- Pay careful attention to pre-analytic conditions and follow guidelines for optimal tissue handling requirements (4)

Interpretation
- Use controls with a range of HER2 expression, including with HER2 IHC 1+ staining (4)
- Examine HER2 IHC at 40X magnification when distinguishing between HER2 IHC 0 from 1+ staining (4)

Second opinion
- Consider second pathologist review when results are close to the 0 versus 1+ interpretive threshold (4)

Reporting
- Always report semiquantitative (discrete) HER2 IHC scores (4)

- Include a footnote in the pathology report on the therapeutic implications of the results (4)

Considering previous results
- Medical oncologists can also consider historical HER2 IHC results (from prior or concurrent primary samples, or other metastatic sites) as there may be heterogeneity in HER2 expression levels between samples, and/or metastatic cancer tissue samples may suffer from pre-analytic conditions that are better monitored in primary breast tissue samples (4)

How to report HER2-low
ASCO-CAP guidelines and CAP template both recommend including semi-quantitative HER2 IHC scores in the pathology report (4,6). It may also be considered to report intensity, pattern of staining, and percentage of cell staining along with the IHC score to provide a detailed description of the result (11). For reporting HER2 IHC 1+, IHC 2+/ISH- results, ASCO-CAP recommends including a footnote in the pathology report which could aid communication between the pathologist and the clinical care team (4). Highlighting the most significant information in the pathology report can help ensure treating physicians have a clear understanding of details that affect decisions about patient care. Although ASCO-CAP currently suggests it is premature to use the term 'HER2-low' in the report, the CAP reporting template acknowledges its value in their suggested template (6).

Conclusion
Recognizing HER2-low tumors can have clinical implications, and so it is important to standardize assessment of tumors with low levels of HER2 expression.

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HER2Know.com can support pathologists in evolving their clinical practice by providing peer-led educational resources for assessing HER2 IHC at the low end of expression.

Visit HER2Know.com and start exploring the resources today.

ASCO, American Society of Clinical Oncology; CAP, College of American Pathologists; HER2, human epidermal growth factor receptor 2;IHC, immunohistochemistry; ISH, in situ hybridization.

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Digital Directions

Sitting Down With… Marcial García Rojo, principal investigator in the EUROtelepath EU project, principal researcher with AIDPATH, and head of pathology at the University General Hospital of Jerez de la Frontera, Spain.

How has the field of digital pathology changed in the last decade?
Digital pathology has evolved considerably, with better whole slide imaging (WSI) scanners, cost-effective storage solutions, interoperability, and more intuitive software. The main impact of digital pathology in my clinical practice is related to increased efficiency, workflow optimization, better traceability, and decreased interobserver variability. Increased efficiency comes, for instance, from reducing the time that it takes to access previous studies or faster slide reading. Workflow optimization is mainly a consequence of redefining many processes in the lab, such as improvements to and standardization of microtomy, staining and coverslipping, or reducing the need to repeat slides.

With digital pathology, it is easier to guarantee that the slides correspond to the correct patient, and we can make sure that the complete slide has been revised. Additionally, teleconsultation with the rest of the team in the department or with external colleagues is significantly easier and faster.

When we interviewed you back in 2014, you talked about the need for validation and standardization in digital pathology. Has anything changed?
In validation, the main changes are related to clinical guidelines released by scientific societies and digital pathology associations, and the introduction of In Vitro Diagnostic Regulation (IVDR) in the European Union – a framework governing the production and marketing of in vitro diagnostic medical devices with the goal of ensuring safety and effectiveness.

In relation to standardization, Digital Imaging and Communications in Medicine (DICOM) WSI standards are being implemented by scanner, and picture archiving and communication system (PACS) vendors. However, only a few hospitals worldwide are using DICOM to store their digital slides. The situation with regards to "Integrating the Healthcare Enterprise" (IHE) guidelines, which define the standards we should use between different actors (pathology information system, scanners, viewer, storage repositories), is even worse. I'm not aware of any institution that has implemented the IHE Anatomic Pathology General Workflow Technical Framework, even though it has been available since 2010.

What are the main hurdles that remain for the implementation of digital pathology?
Today, the initial costs of digital pathology implementation are the main barrier. Making the case for digital pathology and convincing our managers of its cost efficiency and how it saves lives, is still difficult, but not impossible.

Focusing on technology, we still need to optimize storage technology. WSI scanners should be able to accept slide racks from stainers. Scanning speed could also improve. Correct tissue detection or focusing is still an occasional issue with some scanners, and the generation of DICOM files natively from the scanners (scanners using DICOM modality worklist) is still under development.

What are your views on the pace of integration of digital technology?
Many things have changed since 2014. Scanning technology is better today. Some private and public health institutions are aware of the importance of digital pathology to make precision and personalized medicine a reality. Nowadays, we see on average about 15 percent of hospitals with fully digital pathology in surgical pathology, and the figure is steadily increasing. In cytology, complete digitization is becoming a reality now thanks to new cytology scanners.

Where do you see your lab in 10 years? "I think I'll be fully digital," you said in 2014. In my case, frankly, no. We suffered a delay due to the COVID-19 pandemic, and we expect to finish the digitization process this year. But we have many examples in Spain that have become fully digital in surgical pathology. First, it was Granada, with four hospitals working in an interconnected manner. Then, it was Catalonia, with eight hospitals, and the Quiron Hospital group successfully connected their hospitals in Madrid and Catalonia. Recently, complete digitization has become a reality in three northern regions in Spain – Castilla y León, Navarra, and the Basque Country.

How do you see the field of digital pathology evolving over the next decade?
I expect that, in the next 10 years, digital pathology will be a requirement for pathology department accreditation – and most of these departments will be fully digital, including cytology.

Part of the process will also be implementation of artificial intelligence (AI) algorithms. Otherwise, we run the risk of increasing the technology gap between pathology departments (and between patients). I believe AI will become a driver for the adoption of digital pathology.

Are you hopeful about the future of digital pathology?
Ten years ago, we were not able to foresee the disruptive technology of AI. Deep learning has opened our eyes, and now we can think of the integration of AI algorithms able to detect automatically if a tissue slide contains cancer, perform an efficient cervical cancer screening in cytology, help in grading and classifying tumors, predict the prognosis for each patient, and more. So, yes, I'm hopeful!

The year 2024 marks The Pathologist's 10th anniversary. Bibiana Campos Seijo sits down with García Rojo to discuss the advancements in the field of digital pathology in the last decade.

Our 2014 interview with García Rojo, The Digital Pathologist's View, is available at bit.ly/3xsfiHb

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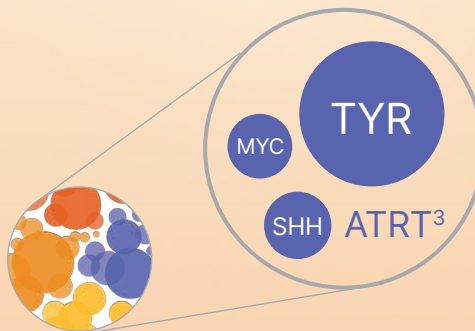
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