MAY / JUNE 2024 # 96

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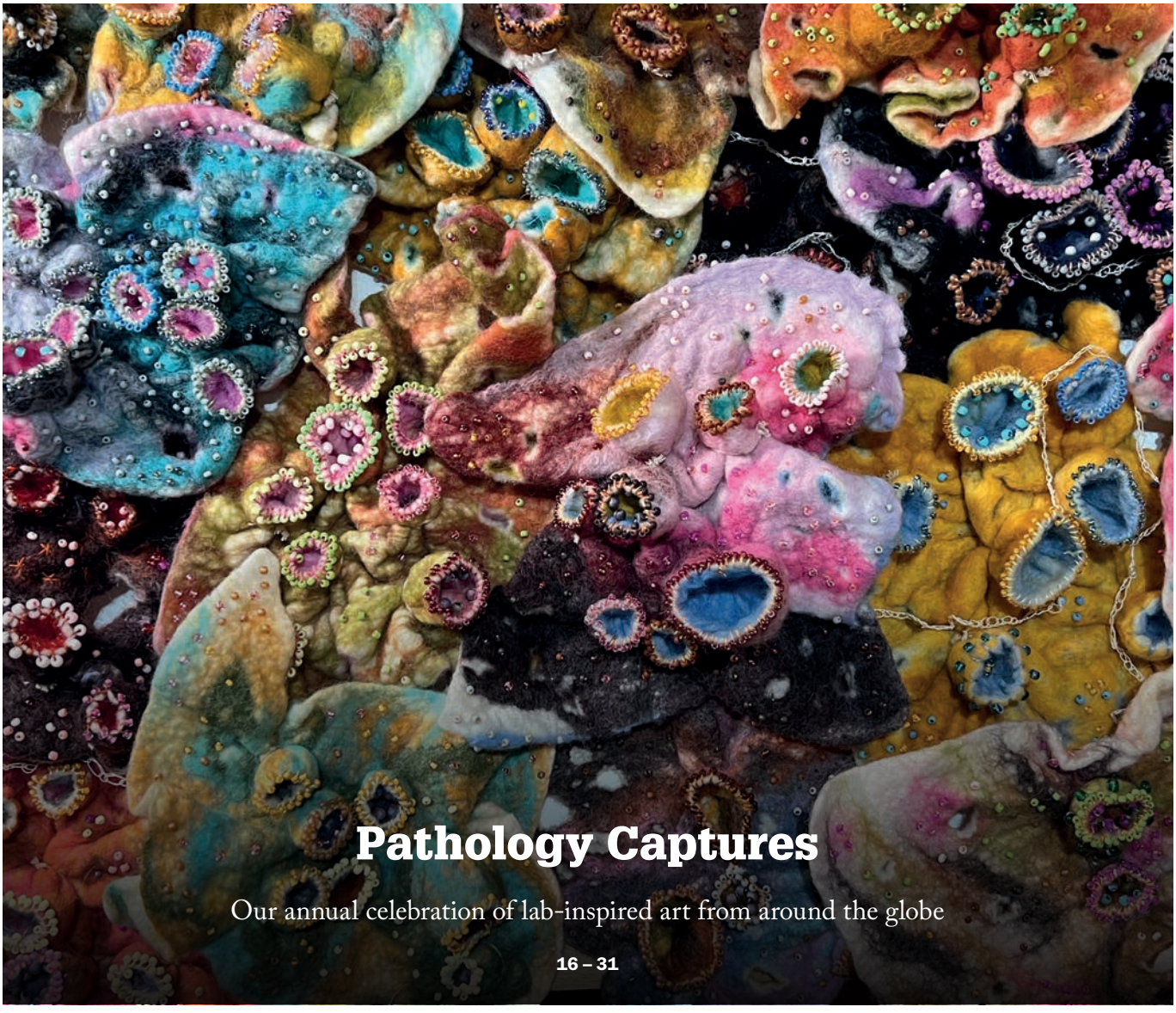

Pathology Captures

Our annual celebration of lab-inspired art from around the globe

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The Collins dictionary defines capture, in a visual sense, as "to succeed in representing or describing (something elusive)." There are so many ways to capture an image! We can paint it, mould it, or photograph it. It can be shown in two dimensions or three. We can use paper, yarn, fabric, or metal. Captures can even be edible! The list goes on – and the contributors to this collection of pathology captures have certainly explored that list. Turn to page 16 to marvel at the images selected for this year's celebrated exhibition of pathology-inspired art created by you – our readers.

We invite you to pause, enter our peaceful gallery, and let the calmness wash over you. Absorb the visual beauty, and admire the variety of creative means used to capture those breathtaking images. Stroll through our virtual corridors lined with paintings, drawings, needle crafts, and more. Emerge refreshed and inspired and, maybe, reflecting on how to capture the images that inspire you in your work – or outside of it.

If further motivation is needed to unleash your own creative juices, turn to page 46 to read our interview with pathology resident and artist Meredith Herman. Combining skills in painting, a passion for histology, and a knack for social media, Herman has managed to turn a lockdown project into a successful – not to mention stress-relieving – side hustle.

In fact, I read with interest that 39 percent of US residents now have a side hustle. And among young adults from the millennial generation, as many as 50 percent have a money-earning project in addition to their day job (1). Before you cry, "How do they find the time?", let's consider the advantages: developing our skills, channeling our creativity, being our own boss, paying off student debts, networking, stress relief…

What about you? Do you put your down time to profitable use? Have you spawned a business from your hobby? If you have an interesting side hustle, The Pathologist would love to hear about it. Write to us at *edit@thepathologist.com*.

Helen Bristow
Editor

Reference

1. *CPA. "Recent Data Study Reveals Most Popular Side Hustle in Every U.S. State" (2023). Available at: https://www.cpapracticeadvisor.com/*

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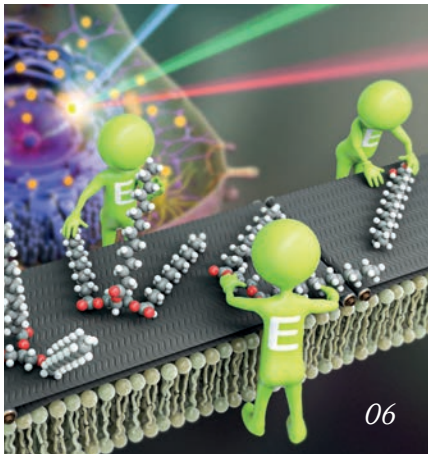

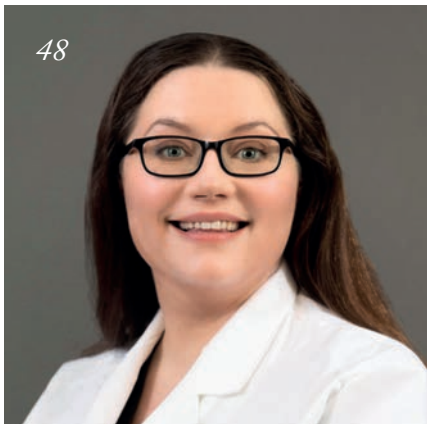

On The Cover

Hand-felted, embroidered, and beaded representation of the lining of the gut, by Anna Dumitriu and colleagues.

Upfront

In My View

From The ASCP

Feature

Foundations

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In Practice

Sitting Down With

Reports

the Pathologist

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Credit: Minhaeng Cho and Chanjong Park

Mic Drop

A new microscopy technique reveals the secrets of lipid synthesis inside living cells

To reach a deeper understanding of lipid droplets and their function, a team of South Korean researchers at the IBS Center for Molecular Spectroscopy and Dynamics (IBS CMSD) developed a two-color infrared photothermal microscopy (2C-IPM) technique (1). Crucially, 2C-IPM offers extended periods of observation and analysis of lipid droplets within living cells – without the need for specially designed exogenous or genetically encoded fluorescent labels.

To learn more about this exciting discovery, we spoke with Minhaeng Cho, corresponding author of this study.

What are the benefits of 2C-IPM technology?

Our 2C-IPM technology simplifies the process of detecting multiple biomolecules in living cells. This technology overcomes limitations associated with traditional fluorescent microscopy, such as photobleaching (the degradation of fluorescent dye). It allows for long-term observation of biomolecules without the need for complex sample preparation involving fluorescent dyes and protein labeling.

Did you face any challenges? How did you overcome them?

Subcellular organelles and associated structures are intricately positioned within cells, which hinders the propagation of laser beams used in infrared analysis. Additionally, lipid droplets exhibit a wide range of sizes and shapes – varying the extent of light scattering and refraction, and posing difficulties in interpreting the obtained microscopic signal. To address this challenge, we repeated experiments under various conditions and established a calibration method.

What's next for this research?

Our study confirmed that 2C-IPM works effectively at observing lipid droplets in Huh-7 liver cells, but we're hoping to take this even further by investigating lipotoxicity in different liver cells. This research is set to deepen our understanding of the role of intracellular lipid droplets in various liver-related metabolic diseases.

What are your hopes for the future of this technology?

2C-IPM also holds potential for infrared spectroscopic analysis of a broader range of biomolecules and functional materials thanks to its technical foundation rooted in measuring infrared absorbance in a specimen. We've already demonstrated the capability of IPM for studying changes in protein distribution throughout the cell cycle in living brain cells. 2C-IPM could help uncover hidden biological phenomena and open avenues in related research fields.

A Matter of Minutes

Mass spectrometry provides forensic toxicologists with a reliable and rapid answer to drug screening

A team of Japanese researchers have developed a reliable method – dubbed RaDPi-U – that can detect 40 forensically significant drugs in urine in less than three minutes (PMID: 38523158). Unlike many mass spec methods, RaDPi-U requires only three relatively straightforward steps. First, 10 microliters of urine are mixed with an internal standard in ethanol for approximately one minute. Second, the resulting solution is pipetted onto a sample plate. Third, the plate is inserted into the probe electrospray ionization and tandem mass spectrometry (PESI-MS/MS) instrument for analysis. The results are automatically reported through an integrated software.

"Rapid and reliable analytical techniques are imperative for forensic toxicologists," explains corresponding author Kei Zaitsu, "We're also planning to expand RaDPi-U to include blood analysis – potentially naming it RaDPi-B – which would be instrumental in therapeutic drug monitoring."

RESEARCH ROUNDUP

A handpicked selection of the latest news in pathology – from ALS research to oral rinse tests for cancer screening

ALS advancements

Francis Crick Institute has partnered with a genomics company to research the mechanisms driving the neurodegenerative disorder, amyotrophic lateral sclerosis (ALS; https://bit.ly/4bOGyyE). This collaboration aims to use DNA break-mapping technology while advancing understanding of genomic instability in ALS – hopefully resulting in improvements in both diagnosis and treatment of the condition.

Swish and spit

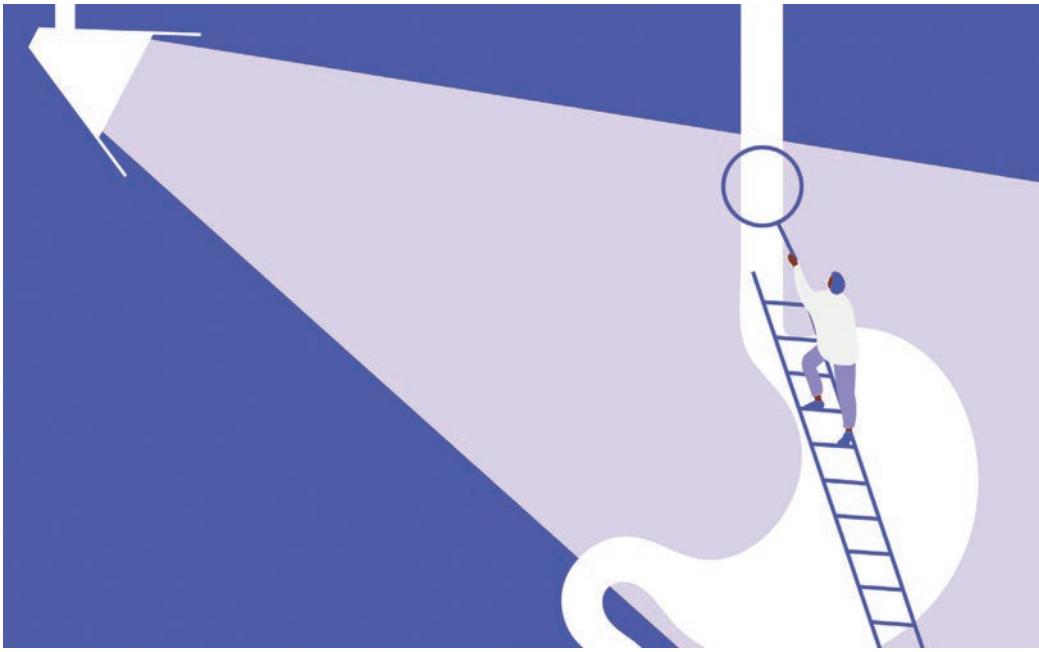
An oral rinse test analyzing bacteria samples from the mouths of 98 patients scheduled for endoscopy reveals distinct differences in the microbiomes of cancerous and precancerous patients compared with healthy individuals (https://bit.ly/3ywFnpd). These findings – presented at Digestive Disease Week 2024 – suggest oral rinse tests could provide early screening for gastric cancer.

The earlier, the better

Newly identified serum protein biomarkers could lay the foundations for early detection and large-scale screening for pancreatic cancer (PMID: 38754433). Using a Mendelian randomization approach, researchers found causal effects of REG1A and REG1B, which are also elevated in lung and esophageal cancer.

Brain tech

Blood biomarkers, when combined with clinical risk score results, have been used to identify large vessel occlusion stroke in patients in a US study (https://bit.ly/3QZRu4n). Moving forward, the researchers hope this technology will allow patients to bypass standard imaging, transforming care for traumatic brain injuries.



Light Fantastic

Raman spectroscopy for esophagus cancer diagnosis

A new test for esophagus cancer diagnosis looks set to drastically reduce discovery time from a couple weeks to less than a minute.

Esophageal cancer, if caught early, is often treatable, potentially during the same diagnostic endoscopy. Rapid diagnosis, therefore, has the potential to revolutionize the field, which is what inspired Alex Dudgeon and colleagues in their latest study, RaPIDE (Raman Probe for In vivo Diagnostics (during oesophageal) Endoscopy) (1).

"Early on, we started treating patients with photodynamic therapy, which proved effective for those with early disease, but symptomatic patients were usually too far advanced to see a positive reaction," says Dudgeon, "Knowing that innovative technology could have a big impact in this area, we set out to develop a technique to improve the identification of early disease."

The team faced a variety of challenges through the COVID-19 pandemic, including furlough and complications during regulatory approvals. However, with support from the University of Exeter, the University of Bristol, and Gloucestershire Hospitals NHS Foundation Trust, they proved triumphant in developing an endoscopic technique for early detection and diagnosis of esophageal cancer.

The technique uses Raman spectroscopy to measure the "fingerprint" of biological molecules present in the sample ahead of advanced statistical methods that help clinicians identify whether the area is cancerous.

"Once proven, this technique would take away the need for tissue removal and could allow for treatment like RFA and EMR immediately – enabling real-time therapeutic targeting and monitoring of response," Dudgeon explains.

As the system is tested in clinical trials to determine its effectiveness in living patients, the team strive to seeking funding for a larger multicenter trial – hoping to develop the diagnostic model for multiple pathologies, "We're planning to explore the utilization of this technique in a range of organs – using the current probe for hollow organs, and a smart Raman needle probe for solid organs."

Reference

1. *ClinicalTrials.gov (2024). Available at: https://clinicaltrials.gov/study/NCT03468634.*

Functional Consequences

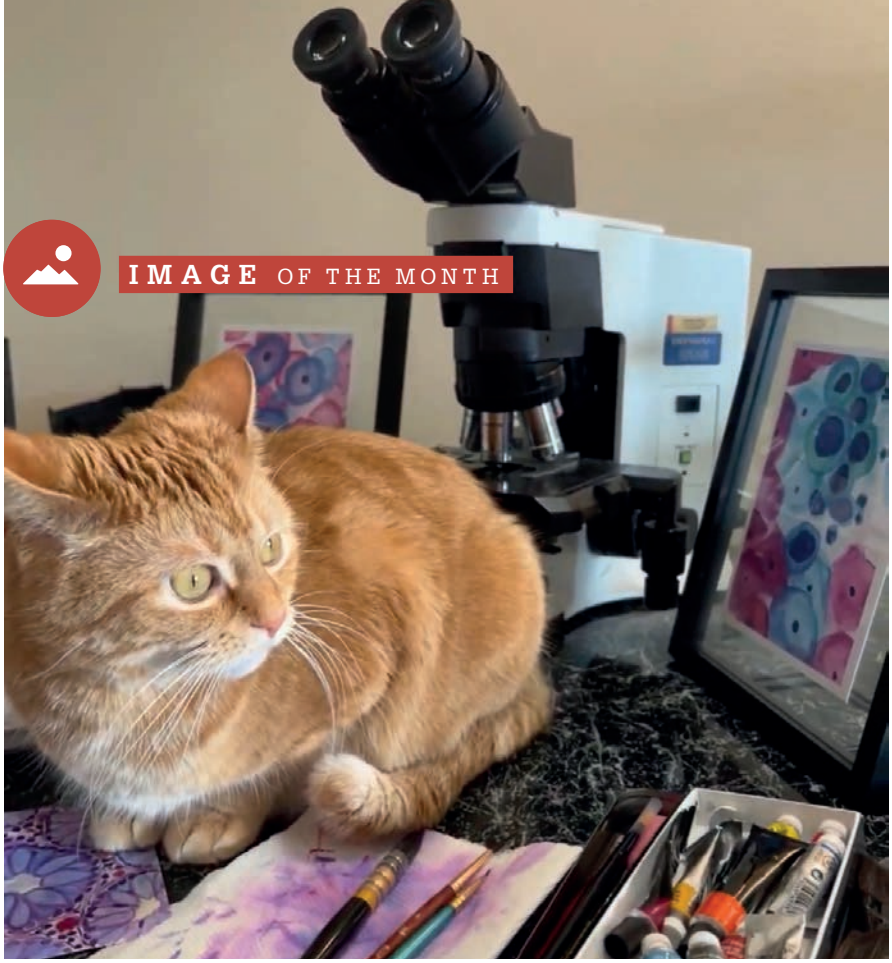
New insights into accelerated epigenetic aging in women with HIV

Researchers behind a US-based study focused on women with HIV have found that epigenetic aging is accelerated compared with women without HIV (PMID:38366369).

Researchers measured DNA methylation age in 190 participants, alongside bone mineral density and physical function assessments. Results confirmed that measures of accelerated epigenetic aging are associated with lower physical function. But no significant associations were found between accelerated epigenetic aging and bone mineral density, despite links being established in a previous study (PMID: 34595517).

"We were surprised to find no relationship between accelerated aging and bone mineral density," says lead author Stephanie Shiau, "Ongoing research is needed to progress our understanding of these results. Deepening our understanding of how aging, HIV infection, treatment, and comorbidities interact with each other is key in maintaining health and quality of life for people living with HIV."

IMAGE OF THE MONTH



Pathology Pet Corner: Brie the Cat

Pathologist Brie ready and reporting for duty! As far as assistants go, this ginger kitty is a cut above the rest. As you can see, she loves to peer down the microscope and help to write up reports – or should that be re-paw-ts? Regardless of the morphology, we'd diagnose a case of cuteness, what about you?

Credit: Meredith Hermann

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

QUOTE of the month

"Not every pathologist will claim they are artistic, but I do believe we all use our right-brain whether we know it or not. I think there is a propensity for pathologists to be more artistically inclined [...] Everyone in the lab has their own hobby and there is often an artistic element to it."

Meredith Herman (see page 46)

In Memoriam: Cyril Wecht

Celebrating the life of the famous forensic pathologist, March 20, 1931 – May 13, 2024

Wecht spent much of his life pressing his view on the circumstances of President John Kennedy's 1963 assassination – that there was more than one shooter involved in the killing. After reviewing reports and videos of the assassination, Wecht concluded that it was "absolute nonsense" for the Warren Commission's report to state a single bullet killed JFK and injured Texas Governor John Connally.

Credit: Image sourced from Pexels.com

This outspokenness led Wecht further into the public eye, writing multiple forensic pathology books and serving as an expert witness on high-profile court cases, including Elvis Presley, O.J. Simpson, and Michael Jackson. However, despite the seriousness of these cases, Wecht was known as a generally upbeat character who enjoyed a hearty laugh at his own jokes.

All of us at The Pathologist offer our sincerest condolences to Wecht's family, friends, and colleagues.

Firefighting Omics

Intense physical activity increases the risk of respiratory infections, according to multi-omic analysis of biofluids

Credit: Images for collage sourced from Unsplash.com and Wikimedia Commons

For some, intense physical activity is a hobby; for those working in firefighting, law enforcement, or the military, it's part of the job – one that can come with health risks. Researchers from Pacific Northwest National Laboratory, USA, set out to quantify that risk using multiomics – and they found that intense physical activity was associated with an increase in respiratory infection risk (1).

In a collaboration with the Los Angeles County Fire Department, the researchers collected blood, urine, and saliva samples from volunteer firefighters before and after an intense 45-minute workout simulating real-life wildfire situations of physical stress.

"We used a method that we developed named MPLEx (metabolite, protein, and lipid extraction), which allowed us to perform the three different omics measurements from a single sample," says Ernesto Nakayasu, Senior Research Scientist and lead author of the study. The researchers used LC-MS and GC-MS to quantify the changes of 3,835 proteins, 730 lipids and 182 metabolites in response to intense activity.

The results revealed signatures of energy expense, tissue damage, and a shift in inflammatory response; a decrease in three pro-inflammatory cytokines and an increase in eight antimicrobial peptides. "The biggest surprise was to discover that high-intensity exercise was associated with an increase in susceptibility to respiratory infections. Usually, exercise is associated with protection from such infections, but it turns out that the high intensity has some detrimental effects," says Nakayasu.

One factor potentially limiting applicability of the findings to the wider population is that wildland firefighters are perennially exposed to specific respirable toxic pollutants that may permanently alter their immune system via immunomodulation and gene expression of key metabolic pathways. "Further epigenetics investigation would help to illuminate this potential bias," wrote the authors (1).

The team is now hoping to mitigate occupational health risk with preventive measures, such as reducing exposure to infection and introducing relaxation techniques (eg. ice bath or hot sauna, hydration, appropriate feeding, sleeping, massage) to aid in recovery. According to Nakayasu, there is also potential to use some of the molecules identified as biomarkers of occupation-associated illnesses. "Then we will combine the different biomarkers to make multi-panel assays that can tell us what specific illness the person is suffering from or even predict the likelihood that such an event will occur."

Reference

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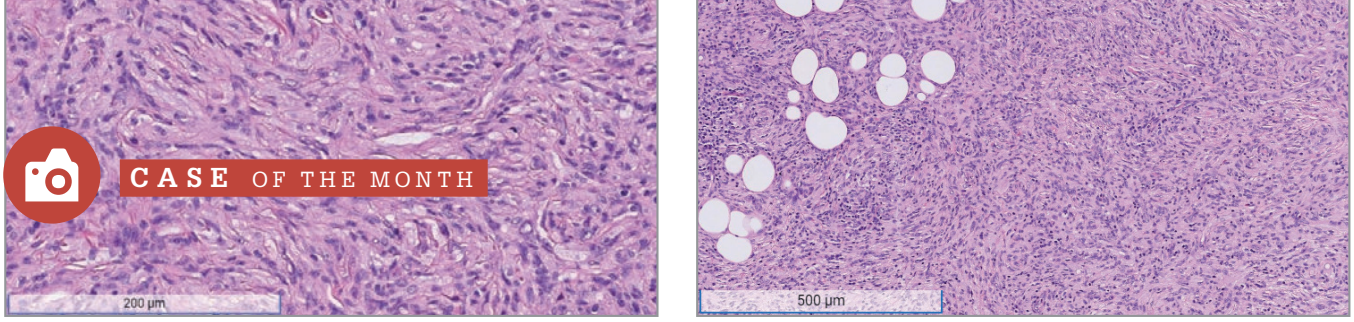
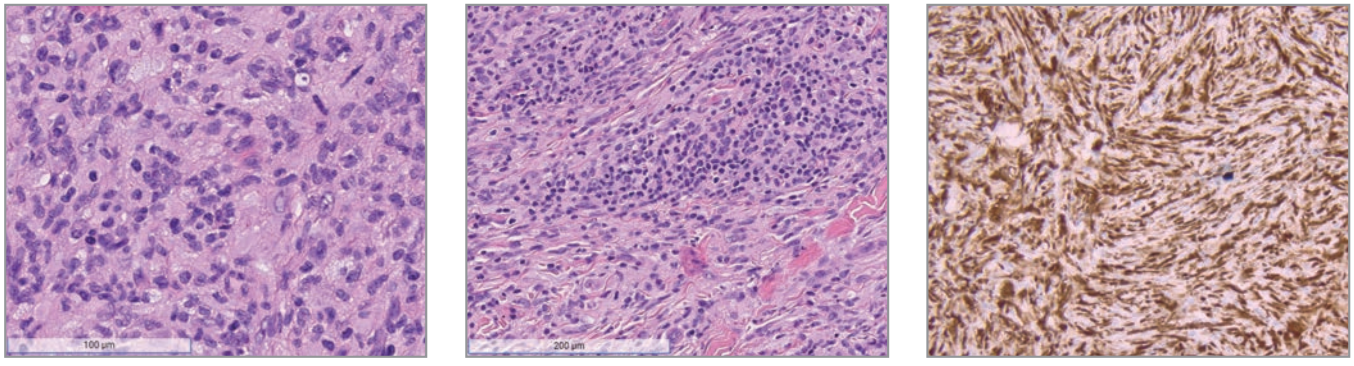
CASE OF THE MONTH





Credit: University of Pennsylvania

Can you identify the correct breast cancer diagnosis?

A 63-year-old woman presented with a left breast palpable lump at 3 o'clock for six months and a family history of breast cancer. Ultrasound examination showed a 0.7 x 0.4 x 0.8 cm cystic and solid superficial mass, corresponding to the palpable mass.

a) Nodular fasciitis
b) Dermatofibrosarcoma protuberans
c) ALK-positive histiocytosis
d) Inflammatory myofibroblastic tumor
e) Fibromatosis-like metaplastic carcinoma

Answer to last issue's Case of the Month…

b) Proximal type of epithelioid sarcoma

In 1961, Laskowski was the first to describe epithelioid sarcoma, which he called "aponeurotic sarcoma". This research was published in Polish (1). Subsequently, epithelioid sarcoma was described by Enzinger in 1970, who also gave it the present name (2). The proximal-type variant, first described in 1997, is an aggressive form of sarcoma with a great ability to metastasize and high capacity of recurrence, even after surgery with radical surgical margins and propensity for early metastasis (3–5).

Proximal-type epithelioid sarcoma occurs in 94% cases in the chest wall, inguinal region, thigh and perineum. Its size at presentation varies from 0.5 to 19 cm (4). To our knowledge, there are only seven previously reported cases of epithelioid sarcoma of the orbit (6).

Histologically distinctive features are: prominence of the epithelioid cell component, a sheet-like growth pattern of large cells with vesicular nuclei and prominent nucleoli, and a frequent rhabdoid morphology (6). Proximal type epithelioid sarcomas can show a typical granuloma-like pattern. Occasionally, a pseudo-angiomatous architecture may be present.

Immunohistochemically, irrespective of the tumor types, the proximal-type epithelioid sarcomas are clearly epithelial-like, with cytokeratin and EMA commonly present. These tumors show cell membrane-based reactivity for EMA. Just over half of proximal type epithelioid sarcoma express CD34, which is an important factor in distinguishing them from carcinomas, which are virtually always CD34-negative.

In conclusion, proximal type epithelioid sarcoma is an extremely rare tumor of the orbit, with a well characterized histology and immunohistochemistry. It is difficult to treat in the head and neck region and the associated mortality rate is high. Aggressive surgical therapy with intensive follow-up is recommended. The prognosis depends on the resection status.

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

See references online

To register your guess, please go to http://tp.txp.to/0624/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.

In My View

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

Ode to WGS

Thanks to a funding boost, whole genome sequencing looks set to make the leap from the research lab to the clinic

By Madhuri Hegde, Senior VP and Chief Scientific Officer at Revvity

The next generation of genomic technologies is already transforming the diagnosis and treatment of rare diseases by enabling researchers to investigate a person's genetic code and develop hyper-personalized solutions. With increased investment, scientists are breaking new ground in genomics – and providing fresh hope for patients in need of diagnosis and access to treatment. In November 2023, the UK Government released a statement committing funds to several different research projects that could bring researchers one step closer to unleashing the potential of genomic technologies in clinical settings.

Among the funding commitments in the UK Government's statement, £51 million was announced for the Our Future Health initiative, which will recruit one million patients to take part in genomic research. Further investment was allocated to Genomics England to launch the Rare Therapies Launch Pad, which aims to generate evidence for new therapy pathways for children with ultra-rare diseases. Additionally, research and development tax reforms were announced to improve incentives for scientific innovation, benefiting companies working in genomic technology.

These upcoming investments are particularly promising for researchers working in whole genome sequencing (WGS) – a key technique used in genomics. Though whole exome sequencing (WES) allows geneticists to analyze the protein coding regions of the DNA, WGS can also detect variants affecting gene regulation and protein function that occur outside of the coding region. WGS provides higher clinical yield than exome sequencing and microarray testing combined, which could help scientists detect thousands of rare conditions earlier, improving the quality of life of patients.

Diagnosing a higher number of highly penetrant conditions

In newborn screening, WGS has been able to identify more cases of lifelong genetic conditions than exome-based screening. Recently, the Journal of the American Medical Association published findings from study – conducted by Revvity Omics – that evaluated the

"WGS provides higher clinical yield than exome sequencing and microarray testing combined, which could help scientists detect thousands of rare conditions earlier."

outcomes of two conceptually different newborn screening approaches: one using genome sequencing as a proactive screening approach and the other using an exome-based gene panel for medically actionable childhood-onset conditions (1). The study is the first real-world proactive screening of apparently healthy children and newborns that provides a side-to-side comparison of the conceptually different screening strategies.

The study found that of the 562 children screened by WGS, 46 (8.2 percent) were at risk for pediatric-onset diseases – of which 22 (3.9 percent) were at risk of developing high penetrance disorders. By comparison, of the 606 children screened with the exome-based panel only 13 (2.1 percent) received diagnoses of potential childhood-onset conditions.

These results indicate that, when compared with a limited gene panel, whole genome sequencing uncovered a significantly higher number of pediatric-onset diagnoses. Many of these diagnoses involved high-penetrance, often neurodevelopmental disorders that would benefit from early intervention and disease surveillance. A gene panel that was limited in scope would have identified just ~20 percent of these high-penetrance conditions, leaving the remaining ~80 percent of conditions undetected.

Potential for population-wide screening

WGS is an increasingly viable technique that holds the potential to evolve from its current use – which is primarily in research – to clinical use.

Ongoing studies should provide further evidence of the cost-effectiveness, feasibility, and clinical utility of genome sequencing in clinical settings, including newborn screening programs. Genomics England has already led the way with the 100,000 Genomes Project – an initiative launched in 2018 that, as the name suggests, sequenced over 100,000 genomes to study their role in rare diseases and cancer. As well as uncovering new diagnoses in 25 percent of participants, the study generated a vast dataset to inform researchers, policymakers, and healthcare leaders of the value of integrating WGS in routine healthcare. Analysis of this data is set to continue for many years to come, helping scientists design screening programs using WGS to bring treatments, diagnostics, devices, and medicines to patients sooner.

Implementing WGS in newborn screening programs can increase the chances of doctors diagnosing rare disorders not detected by biochemical screening, and intervening earlier in the lives of babies born with them – preventing lifelong disability and other long-term health effects. Diagnosing and managing these conditions will not only transform healthcare outcomes for these children and their families, but also save healthcare systems the associated costs.

Though the detection rate of rare diseases is growing thanks to technological advancements in genetics, further studies over the coming years will help inform the development of screening programs and diagnostic tools. The advancements in genomics made possible by the UK's recently announced investments are an important step towards greater adoption of WGS in mainstream medicine in the UK, unlocking potential for more widespread implementation worldwide.

Reference

1. *J Balciuniene et al. JAMA Netw Open, 6, 7 (2023); e2326445. PMID:37523181.*

The Backbone of Diagnostics

Why analytical chemistry, multidisciplinary collaboration, and biosensing technology are all crucial for advanced research

By Luisa Torsi, Professor of Analytical Chemistry at the University of Bari and President of the Regional Center on Single-Molecule Digital Assay, Italy

Credit: Marianna Ladisa Photography

Analytical chemistry plays a pivotal role in clinical research by enabling precise and sensitive detection of biomarkers, facilitating early disease diagnosis, monitoring treatment efficacy, and ultimately improving patient outcomes. For many years, we've been working with electronic devices, particularly bioelectric transistors, to enable ultra-high-performance levels – not only in terms of low detection limits, but also in high reliability.

Advances in biosensors have also provided another avenue for analytical chemistry to positively affect clinical

"Looking into the future of diagnostic and clinical research, it's crucial that we stay resilient in the face of challenges and setbacks in our push for innovation [...] together, we can contribute clinical and diagnostic research that paves the way for future generations."

research – particularly in enabling early diagnosis. However, this progress must coincide with the discovery of new and specific biomarkers. With this in mind, we must take a comprehensive approach, encompassing both nucleic acid and antigen (protein) biomarkers. Improvement in performance levels of sensing devices is particularly notable in immunoassays as their performance is lower in comparison to molecular assays.

Today, we're seeing a plethora of proposed assay technologies for improved diagnostic and clinical research. One of which I've worked closely with: the "Single-Molecule with a Large Transistor" (SiMoT) technology that's being developed at technology readiness level 6 (TRL6). SiMoT can uniquely detect both antigens and oligonucleotides at extremely low concentrations with an accuracy of 96 percent. It's particularly suitable for point-of-care testing, especially for screening asymptomatic individuals, providing fast, reliable, and cost-effective identification of illness. SiMoT can be used for various diseases – we proved its effectiveness in detecting SARS-CoV-2 in saliva (1) and diagnosing pancreatic cancer from a blood test (2, 3).

SiMoT devices consist of a reusable reader and a compact disposable cartridge tailored for early disease diagnosis, offering ultra-portability and handheld convenience. The affordable cartridges work alongside smartphones or tablets, so they can be used anywhere, and the simple nature of the technology makes it suitable for untrained users – even in home settings or in resource-constrained environments. Array technology, on the other hand, is better suited to trained personnel in clinical facilities or smaller laboratories.

Another analytical technology stepping into the clinical spotlight is CRISPR/Cas biosensing, which employs precision gene editing to identify specific oligonucleotide sequences within a sample. This technique harnesses CRISPR's inherent capacity to pinpoint and target genetic sequences within an organism genome or biomarker. It's also been tailored for diverse diagnostic and detection applications. CRISPR systems hold great promise for accurately and sensitively detecting pathogen-specific nucleic acids, which could potentially transform on-site diagnostic and genotypic applications.

One notable advancement is the use of CRISPR-based paper biosensing platforms, which offer an innovative approach to pathogen detection evidence in recent work to detect mycoplasma pneumoniae (4). This newly developed test firstly amplifies the target gene with specific primers before using the CRISPR/Cas9 system for precision recognition, which reduces false negative results. This method is highly sensitive, detecting as few as three DNA copies, thanks to the efficient amplification and ability of the CRISPR/Cas9 system to work at a relatively low temperature of 39 °C.

Of course, these highly performing sensing devices would not be possible without multidisciplinary collaboration. When a project is tackled solely by specialists in one area, it can lead to imbalances in development. For example, focusing only on device performance level may result in a device with limited reliability. The SiMoT project in particular shows the importance of collaboration with other fields.

Looking into the future of diagnostic and clinical research, it's crucial that we stay resilient in the face of challenges and setbacks in our push for innovation. To my colleagues and fellow researchers, both experienced and new to the field, I propose that we advocate for ourselves and others across the scientific community. Without collaboration, we are destined for failure. But together, we can contribute clinical and diagnostic research that paves the way for future generations.

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1. *E Macchia et al., SciAdv, 8, 27 (2022). PMID: 35857467.*
2. *E Genco et al., AdvMater (2023). PMID: 37452695.*
3. *E Macchia et al., AdvMater (2024). PMID: 38108547.*
4. *R Zhu et al., Anal Chim Acta (2023). PMID: 37062563.*

Every Detail Matters

Unveiling the artistry of pathology and laboratory medicine

By E. Blair Holladay

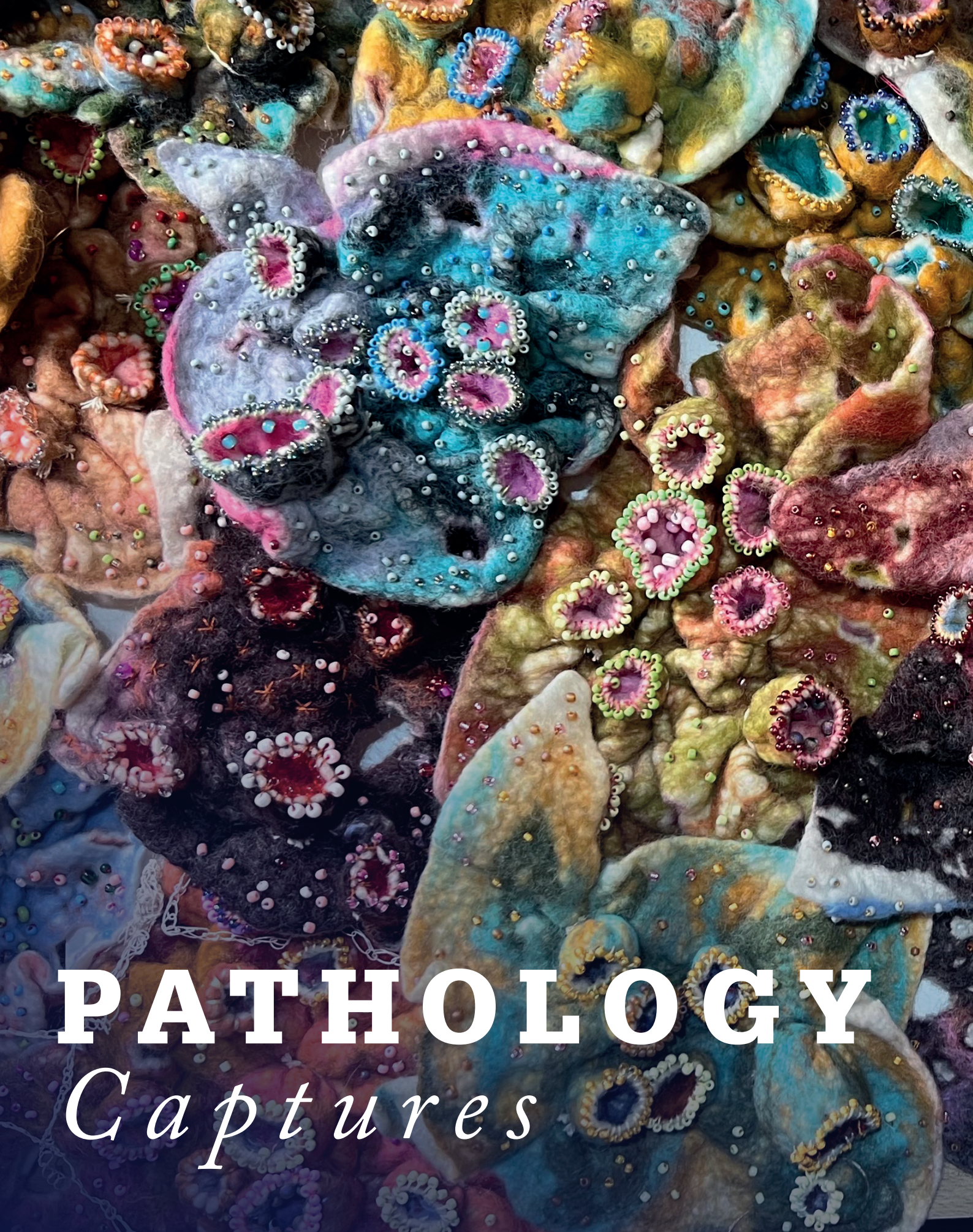
In a medical specialty like pathology and laboratory medicine, precision and accuracy are paramount. They are crucial to ensuring the correct diagnosis – and, ultimately, the correct care for patients.

However, they are not the only elements involved in determining a diagnosis. Under the surface of the test results and data analysis provided by the laboratory lies an artistry that is also important to providing high-quality care for all patients. We cannot separate the visuals from the data; the two go hand in hand. Pathologists and medical laboratory professionals must embrace and hone their unique skill set of blending science and art; this is what solidifies our role as the cornerstone of healthcare.

Attention to detail is a foundational and essential skill of the laboratory – in laboratory work, as in art, every detail matters. Just as a single oversight in exposure could change the quality of a photograph or over-blended paint could leave a garish brushstroke, an oversight in the laboratory could potentially lead to patients not receiving the care they need at the time they need it. Cultivating a keen eye for detail to provide accurate results and, ultimately, better patient outcomes, is not just a matter of following a set of organized steps. It is a matter of understanding why each of the steps is needed, and how those steps blend and work together. The data and the art: hand in hand.

Pathologists and medical laboratory scientists also leverage their artful side through their critical thinking skills when faced with a complex case that requires both analysis and problem-solving. Interpreting test results doesn't always follow a textbook solution, and seeing the whole patient, the whole picture, and bringing a creative mindset to the process can help better inform a diagnosis. Being able to then communicate those interpretations and reasonings for diagnosis is also an art that pathologists and laboratory professionals must hone. In today's healthcare environment, collaboration is key, and effectively communicating with colleagues and patients to ensure test results are understood and integrated into patient care plans is necessary. Clear and concise communication can prevent misunderstandings and facilitate collaboration, leading to better coordination of care and improved patient outcomes.

Pathology and laboratory medicine aren't simply science; the influence of art and science are intertwined. There is an art to what we do, and without that art to complement science, we can never see the whole picture of a patient. Providing high-quality care begins with us, and the laboratory sets the standard for all care teams. Blending our technical skills with creative skills provides us the best opportunity to be better – and to do better – for our patients.



PATHOLOGY
Captures

Fragile Microbiome

Materials: Wet felt, needle felt, beads, embroidery, sterilized gut bacteria from a diverse microbiome.

This hand-felted artwork is richly embroidered and beaded to represent the lining of the gut and the rich communities of bacteria that live inside us and it is also impregnated with their DNA.

Anna Dumitriu, Visiting Research Fellow, School of Computer Science, University of Hertfordshire, in collaboration with Jane Freeman and members of the Healthcare Associated Infections Research group, including academic and clinical members of staff at the University of Leeds, UK

Radiographer's Hand in Pencil

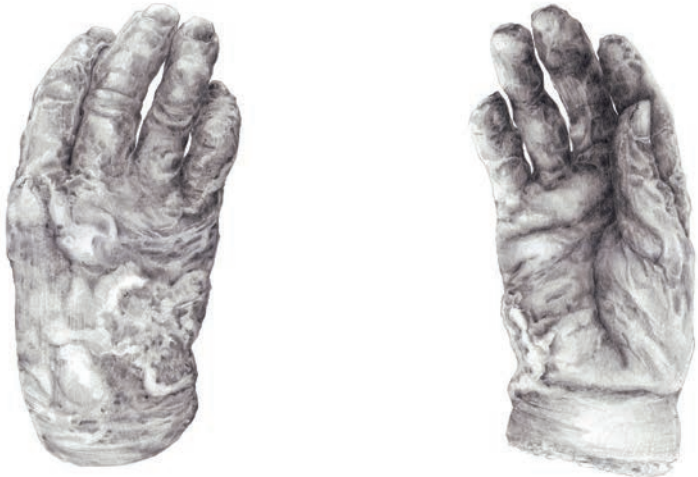
Top

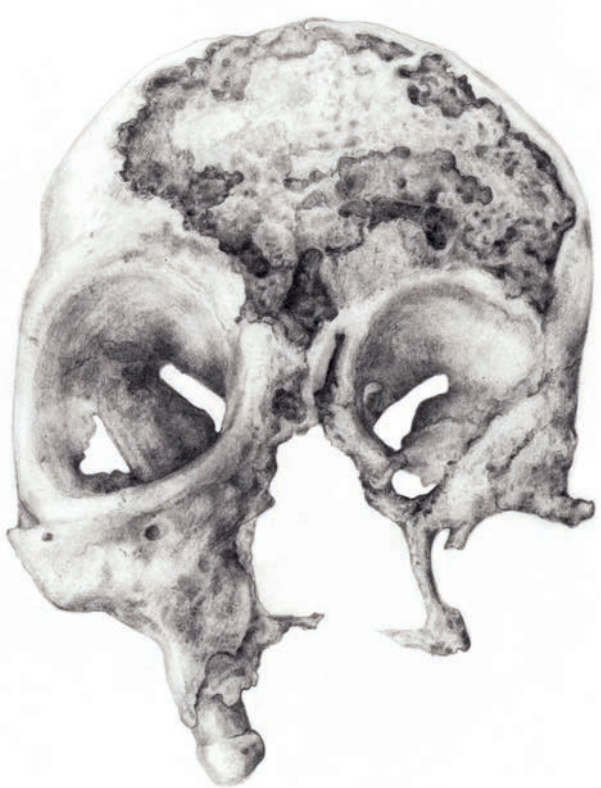
Syphilis Study in Pencil

Bottom

As a student member of the Medical Artists Association, I enjoy spending time at the Gordon Museum of Pathology and these drawings are inspired by some of the specimens on display. Both artworks are on paper and in pencil.

Becki Hiscocks, Freelance Illustrator, Medical Artists' Education Trust, Medical Artists Association, Bristol, UK

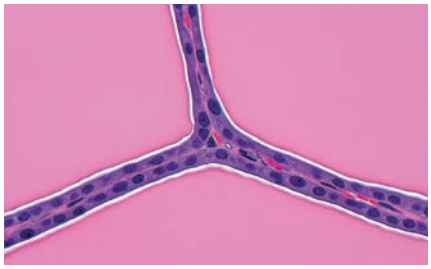


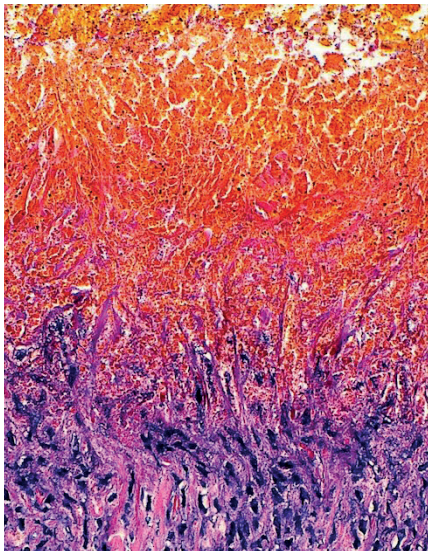


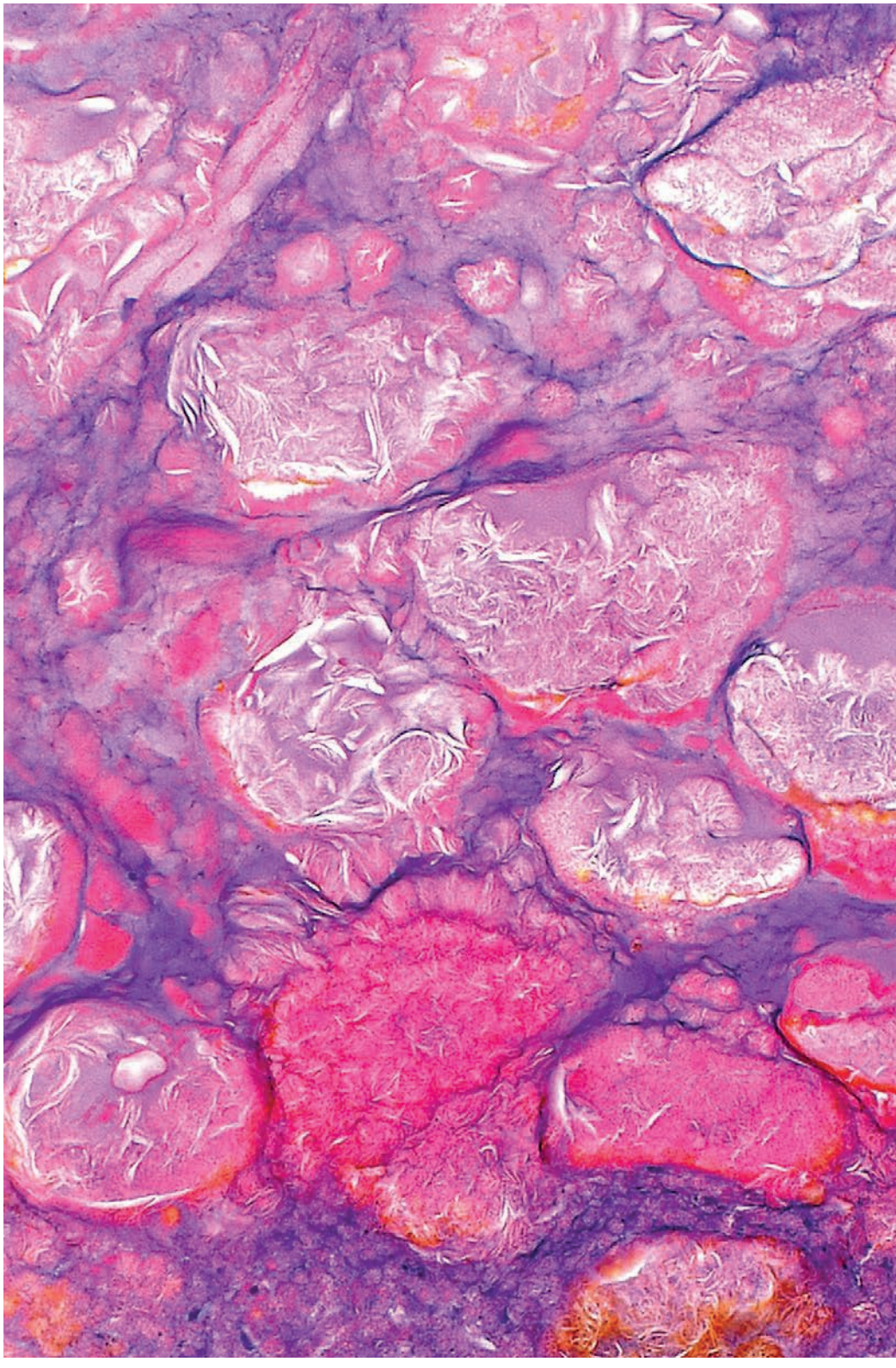
Abstract Anatomy I

In this picture, I explored possibilities to simplify human anatomy to make it unrecognizable to the untrained eye.

Maaia Jentus, Resident in Clinical and Molecular Pathology, PhD Candidate in Endocrine Pathology, Leiden University Medical Center, The Netherlands







Thyroid Intersection

Top Left: Three intersecting thyroid follicles from a multinodular thyroid goiter (H&E stain, 400x magnification).

Tumor in Flames

Bottom Left: Tumor necrosis in a treated hepatocellular carcinoma (H&E stain, 200x magnification).

Saponification

Right: Saponification fat necrosis in a case of pancreatitis (H&E stain, 200x magnification).

Ziad El-Zaatari, Houston Methodist Hospital, Houston Texas, USA

Pentachrome I (Colon)

Top Left

Pentachrome II (Skin)

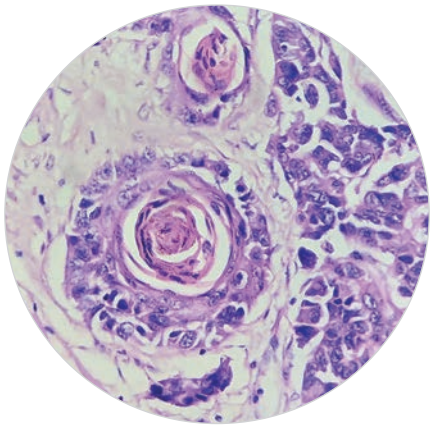
Bottom Left

Pentachrome III (Cartilage)

Top Right

All paintings are painted with watercolor on paper. All references are by Katelin Murphy, who can be found at *@histoqueenofhearts* on Instagram. My paintings are inspired by her pentachrome stains.

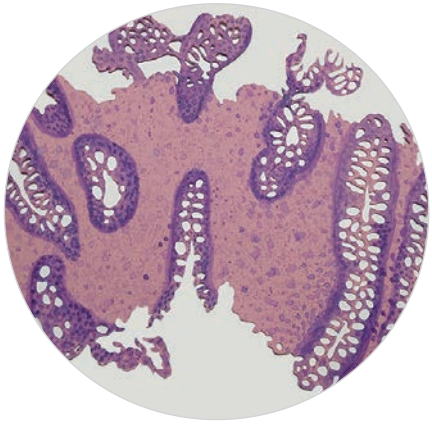
Leonie Schön, Lamellipodium Art



Pink Roses

Keratin pearls in a case of squamous cell carcinoma.

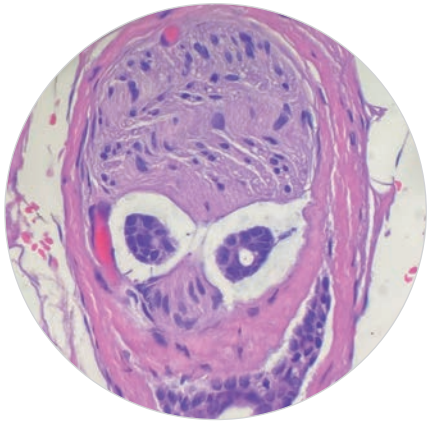
Chitturi Ramya, Assistant Professor, Department of Pathology, Guntur Medical College, India



Intact vs Distorted

Shedding light on lesser-known IBDs with markers, watercolors, and an Xacto knife. This piece was inspired by interest in crypt architecture seen in colitis histologies.

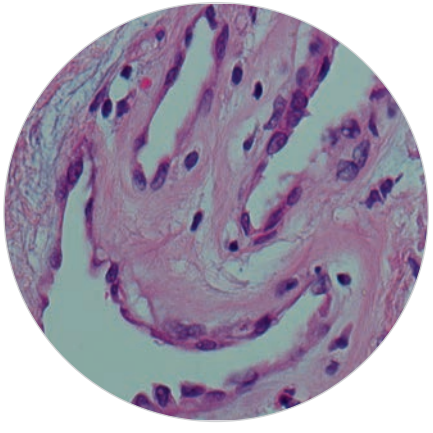
Kaitlyn Niznik, Art Teacher, Hudson Valley, New York, USA



Alien Brain Perineural Invasion

Adenoid cystic carcinoma with perineural invasion.

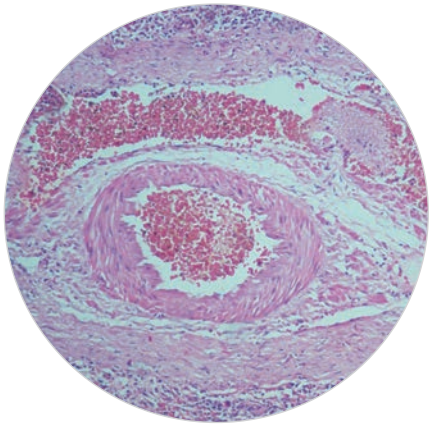
James S. Lewis Jr. Senior Associate Consultant, Mayo Clinic Arizona (Scottsdale Campus), USA



Horror Smile

Photograph of a histology sample.

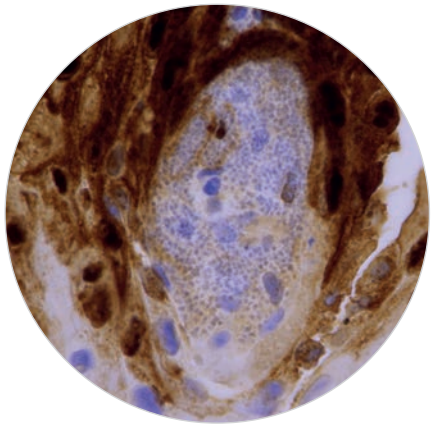
Sanchez Granel German, Laboratorio Quantum, Rosario, Argentina



The Tissue Eye

Photograph of a histology sample.

Sanchez Granel German, Laboratorio Quantum, Rosario, Argentina



Uneasiness

Immunohistochemistry of HSV-1 in an AIDS patient's esophageal biopsy reflecting uneasiness.

Pascual Meseguer Garcia (@Histopatolomon), Head of the Pathology Service at the LLuís Alcanyís Hospital in Xàtiva, Valencia, Spain

Banksy Meets White Blood Cells

Digital artwork of a young girl reaching for white blood cells pictured as balloons. Inspired by the famous Banksy painting.

Misha Dalal, Medical Student, Government Medical College Surat, Gujarat, India

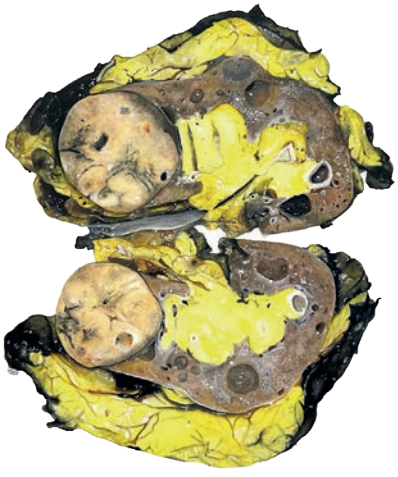
Chordoma

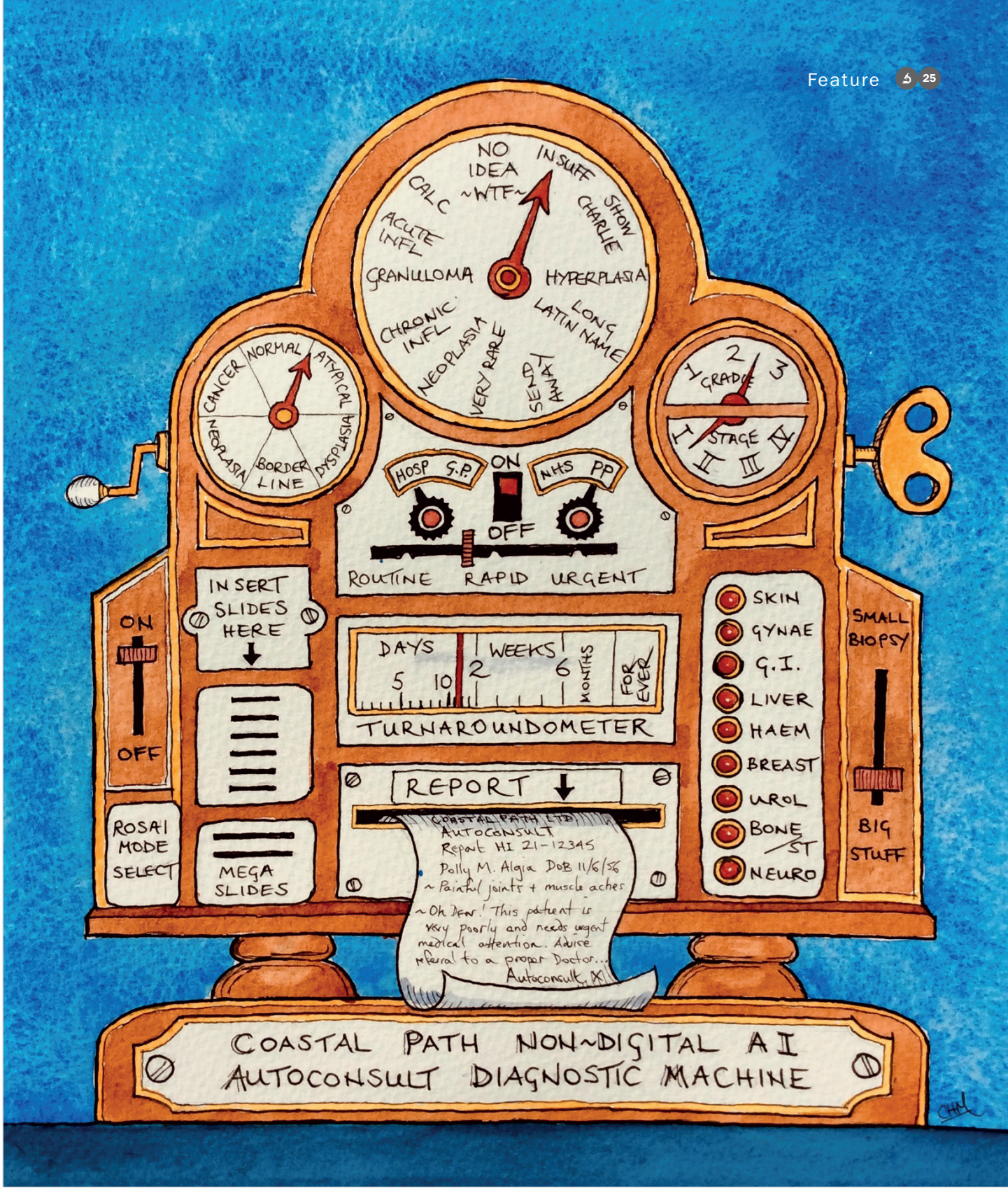
Left: Concept art of a chordoma arising from the sacrum, based on a gross photograph.

Papillary Renal Cell Carcinoma

Right: This is a watercolor pencil medical illustration based on a gross photograph of papillary renal cell carcinoma by surgical pathologist Tiago Oliveira.

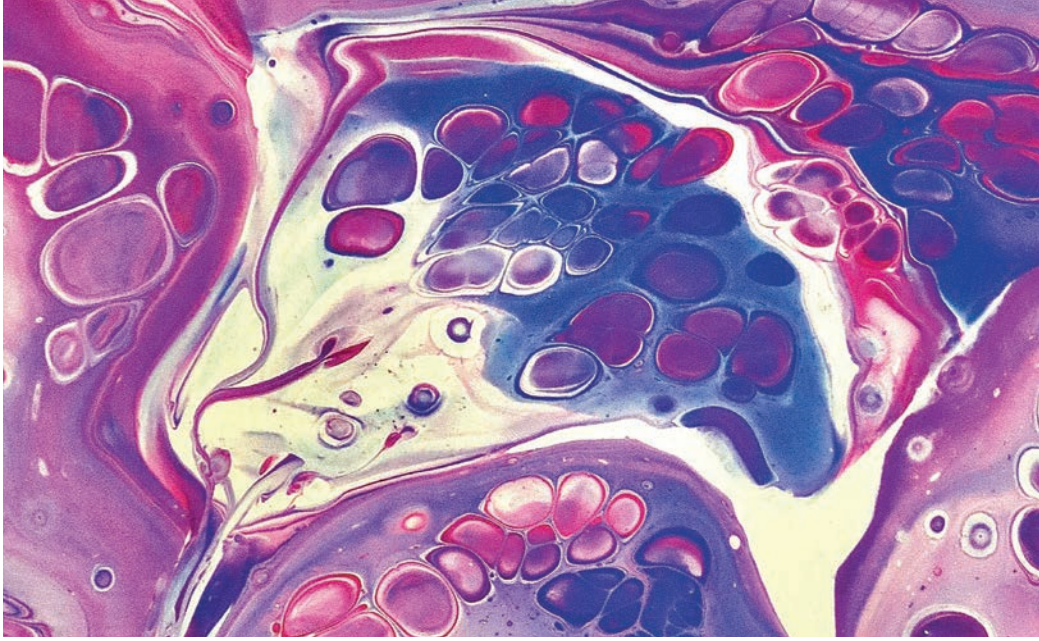
Mariana Duarte Ribeiro, Biomedical Laboratory Scientist at Surgical Pathology Unit of Unidade Local de Saúde Santa Maria, Lisbon, Portugal





Diagnostic Drawings

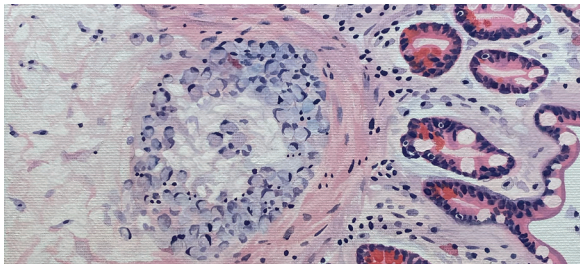
Chris Mason, retired NHS consultant, RD&E, Exeter, UK



SchoolBoy Leukemia

Top Right: My previous work as a laboratory technician at the Curie Institute of Paris inspired me to use art to bring wellness to patients and staff, leading me to create Histosmile – delivering smiles to hospitals through Pouring art. This piece is dedicated to a friend who had leukemia.

Abdul-Azeer R. Raazol, Histosmile, France



Signet-ring Cell Carcinoma Infiltration

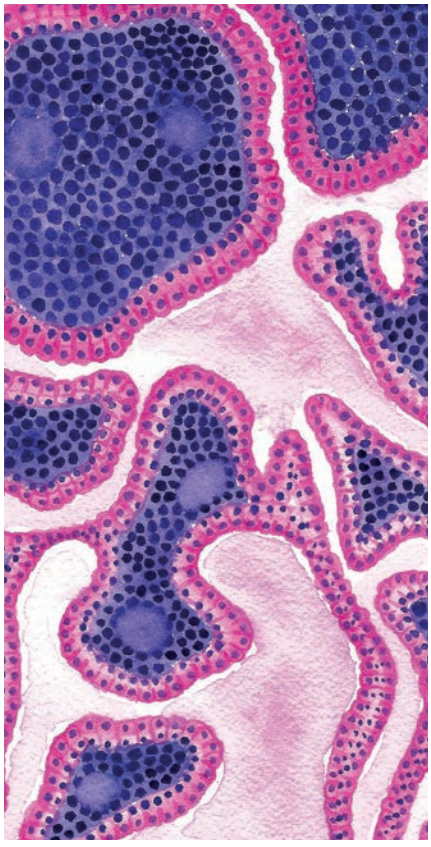
Bottom Right: Realistic style histopathological painting, created during my first pathology rotation as a resident. Fusion of watercolour, acrylic paints, joy, and excitement at the beginning of a new journey in the professional environment.

Anna Poputchikova, Resident, University of Padua, Italy

The Patho Bride

Bottom Left: In India, the wedding lehanga (dress) is the most important attire for the bride in her wedding. This artwork is a version of my dream lehenga that combines my passion and hobby together. A faceless bride signifies the pivotal role of pathologists in diagnosis while staying behind the curtains.

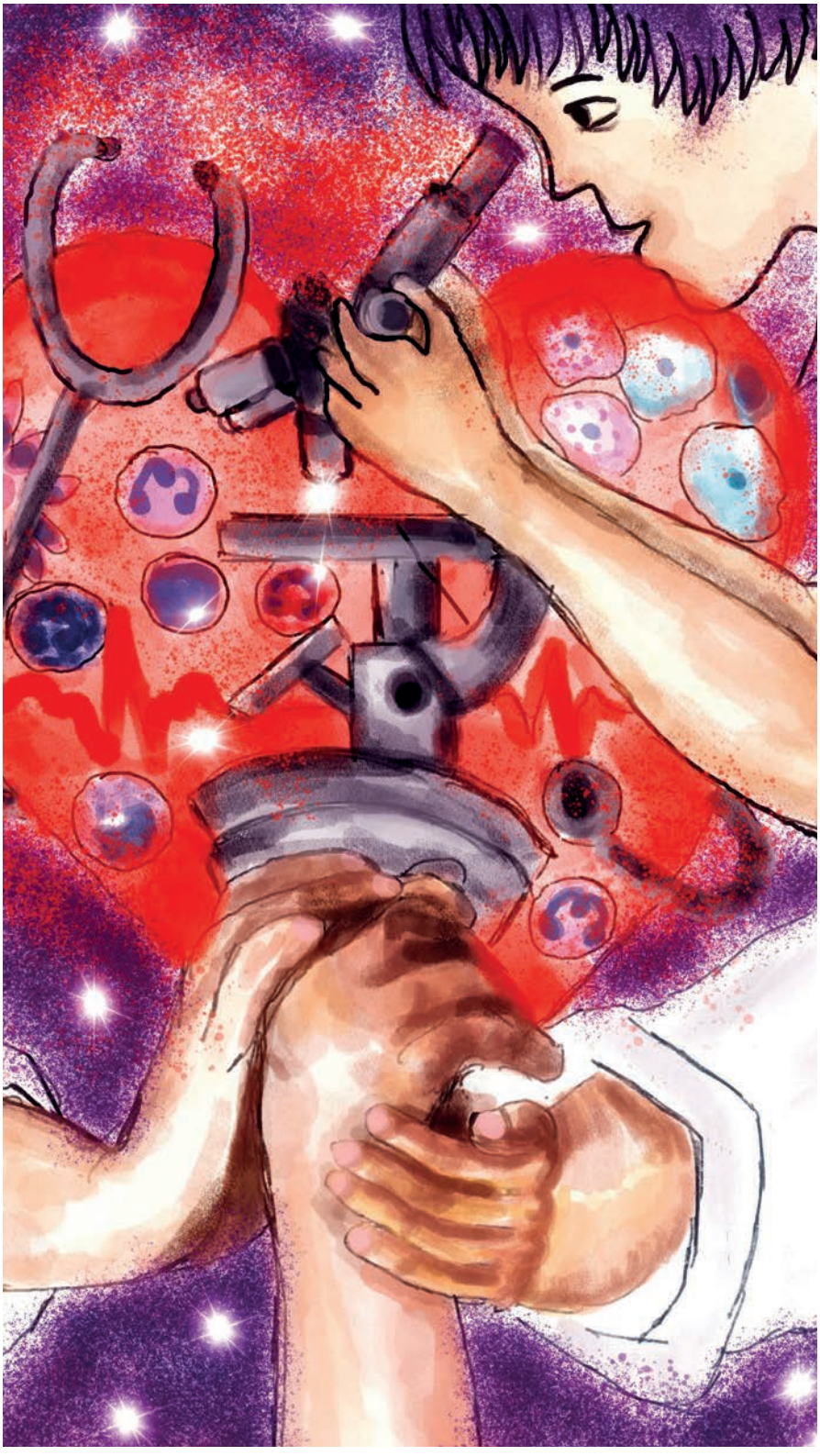
Shruti Shemawat, Mahatma Gandhi University of Medical Science and Technology, Jaipur, Rajasthan, India



Warthin Tumor

Left: My favorite benign tumor of the salivary gland created with watercolor paints.

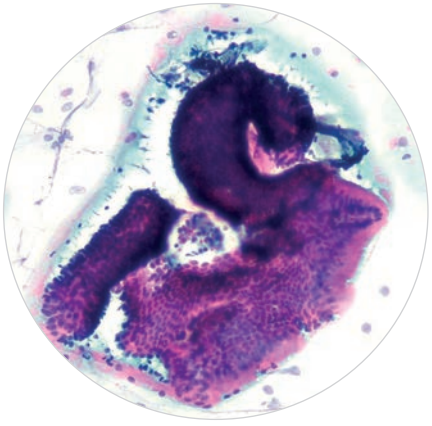
Virginia Fernandez, Pathology Resident, University of Miami Health System/ Jackson Memorial Hospital, USA



Pathology and Patient care

Right: Pathologists care for patients health and life by early and right diagnosis at the right time and place.

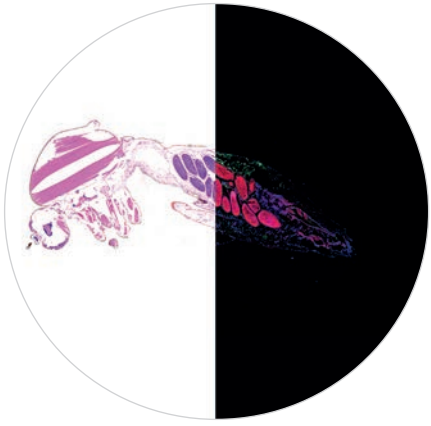
Vasudev Prabhu, Senior Resident, Department of Pathology, Yenepoya Medical College Hospital, Deralakatte, Mangaluru, Karnataka state, India



Cyto-Swan

Spotted in fine-needle aspiration of the pancreas in groups of contaminated normal duodenal epithelial cells.

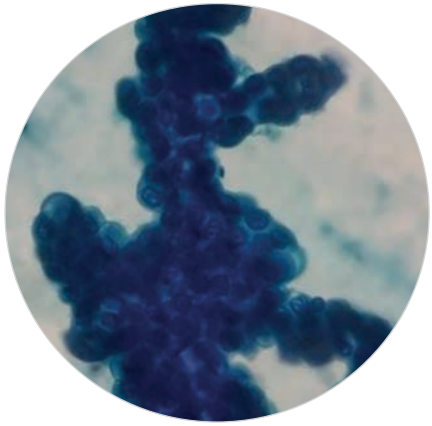
Maria D. Lozano, Department of Pathology, Clinica University of Navarra, Pamplona, Spain



The Dark Side of the Mos

Gravid female Anopheles mosquito from Burkina Faso with H&E staining (left) and a fluorescent confocal image (right).

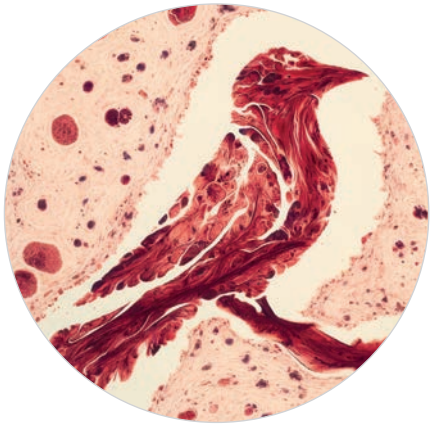
Ewan Parry, Postdoctoral researcher, Sinkins Lab, Centre for Virus Research & Histology Research Service, College of MVLS, University of Glasgow, UK



Dancing Poodle

Cytology image showing a cluster of malignant cells arranged interestingly, with sheer resemblance to that of a happy dancing poodle dog.

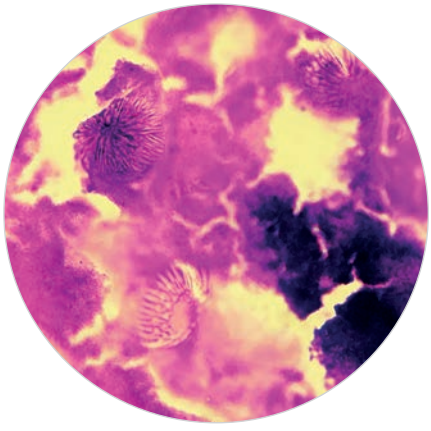
Priya Suneja, University College of Medical Sciences and GTB Hospital, New Delhi, India



Taking Flight

A lambda immunohistochemical stain in the shape of a bird.

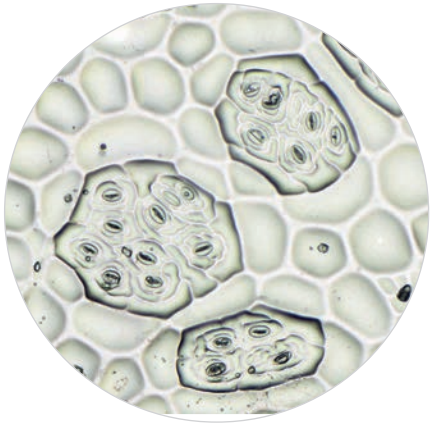
Ahmet Erbağci, Resident, Department of Pathology, Istanbul Medeniyet University, Turkey



Floral Hooklets

Scolex hooklets from a hydatid cyst resembling a flower garden.

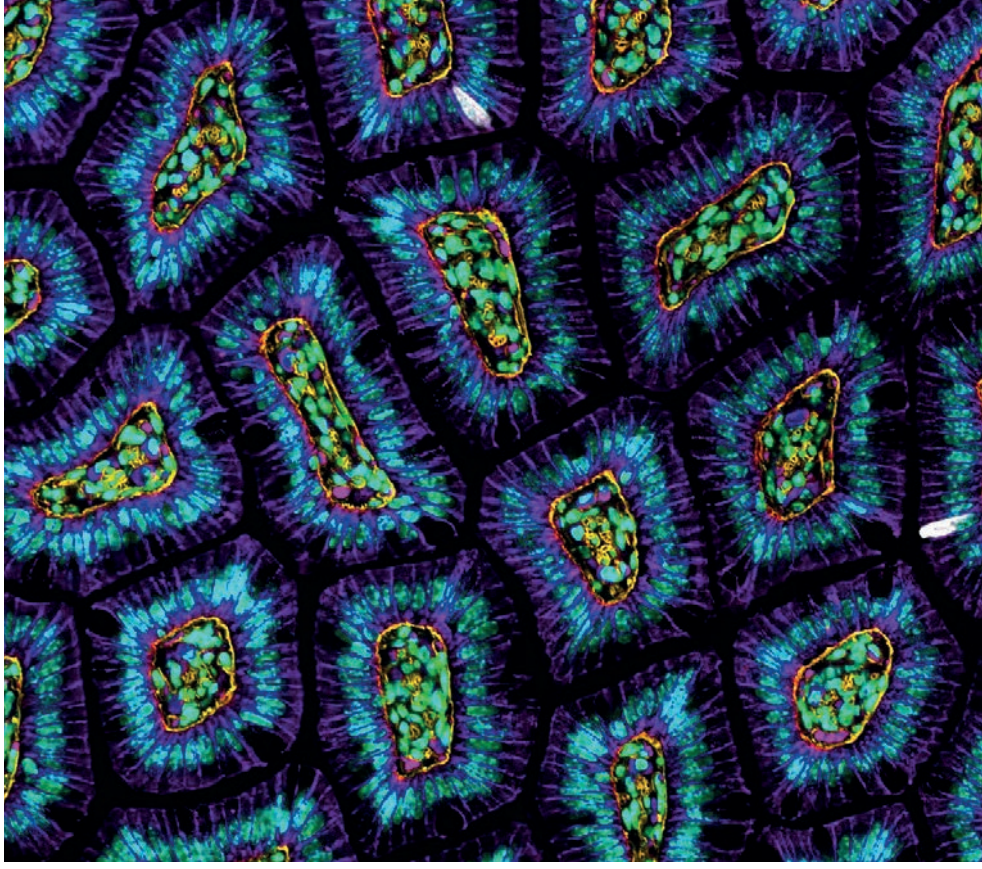
Syed Salahuddin Ahmed, retired Professor and Senior Consultant of Pathology, Delta Hospital Ltd, Dhaka, Bangladesh



"Stomatal universe" of Begonias

Stomata patterns from Begonia collections at the Royal Botanic Garden Edinburgh imaged under 10X magnification.

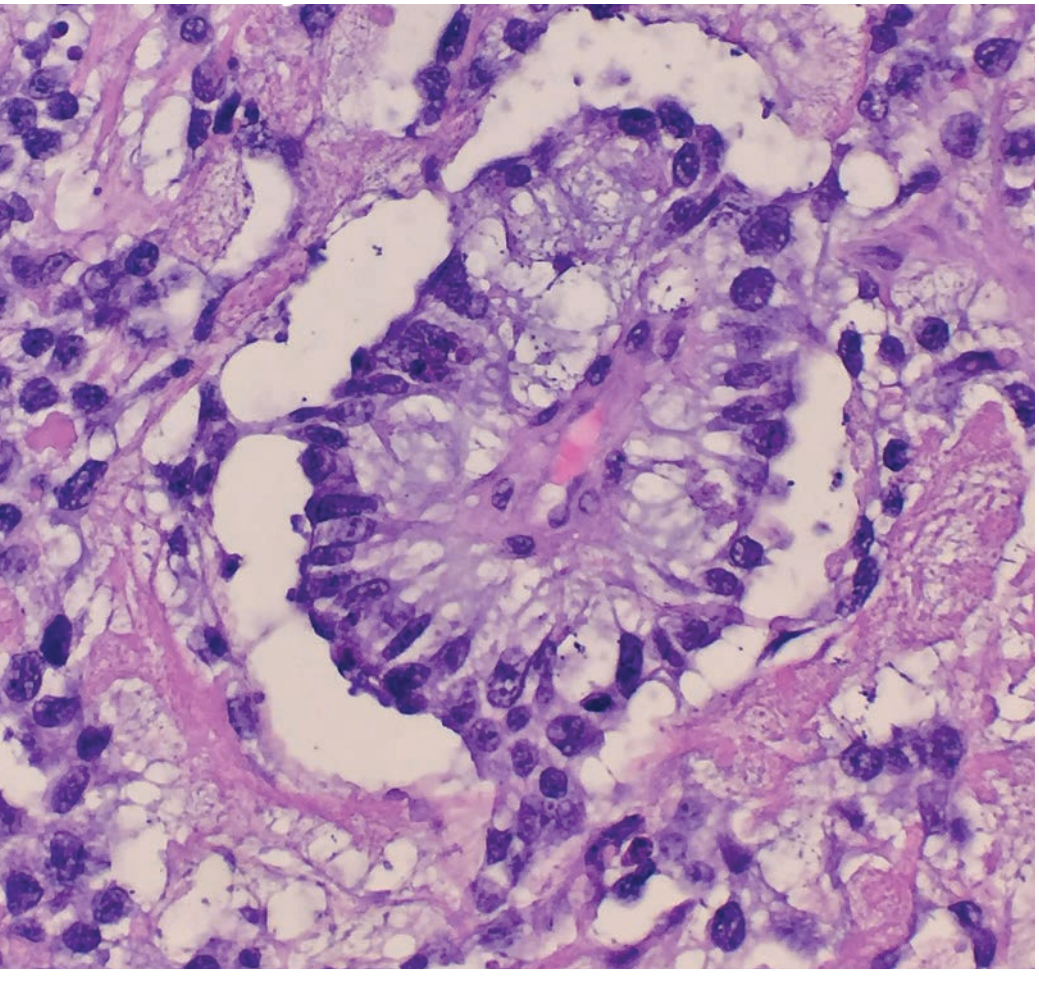
Thu Ly and Rucha Karnik, Karnik Lab, Plant Science Research Group, School of Molecular Biosciences & Histology Research Service, University of Glasgow, UK



Tuft Cells

Top Right: The murine small intestine was immunostained to show rare tuft cells (white). Intestinal laminin in the mesenchyme under the epithelial cells is yellow. The lateral membrane of epithelial cells is purple. Nuclei stained with Hoechst appear cyan/teal.

Amy Engevik, Assistant Professor, Regenerative Medicine & Cell Biology, Medical University of South Carolina, Charleston, USA



Cracking Pathology

Bottom Left and Right: Discover the artistry of Pathology as Schiller-Duval bodies of yolk sac tumor metamorphose into an Easter egg masterpiece!

Woo Cheal Cho, Assistant Professor, Section of Dermatopathology, Division of Pathology and Laboratory Medicine, Department of Pathology, The University of Texas MD Anderson Cancer Center, USA

Crochet Cardiology

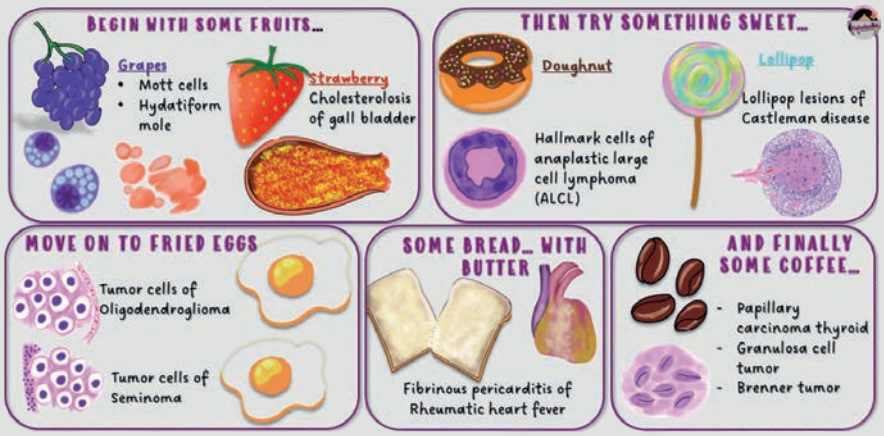
Top Right: My latest medical crochet work. One of my fellow residents defended her PhD regarding the development of the heart, so I gifted her this self-made little thing. It actually wore a graduation cap as well, but the owner removed it. I was aware that I did not fully capture the exact anatomy, however the recipient was still very happy with it.

Frédérique Meeuwsen, Pathology resident, Erasmus Medical Center, Rotterdam, the Netherlands

Through the Looking Glass

Top Left: This is a stained-glass microscope.

Christopher Candela, White Coat Artistry, Michigan, USA



A Pathological Breakfast

Bottom Left: I'd like to introduce you to a whimsical breakfast scene with a twist. It's a delightful exploration of pathology, where you can check out various food-named pathology findings. This breakfast table has everything for a hearty meal: fruits, desserts, fried eggs, bread, and of course, coffee!

Deeksha Sikri, Pathodoodles

Mini-lab cross stitch

Inspired by enjoyment of creating cross stitch designs and the current trend of miniatures of everyday items, this cross stitch was my attempt to recreate and design the lab in miniature. My personal favorite designs are the mini microscope, pipette, and sharps container.

Sophia Chandrasekar, Warbler Works Studio

Timing Matters, and Liquid Is Part of the Future

The importance of timely genomic profiling in NSCLC: a synopsis of an Educational Symposium at European Lung Cancer Congress (ELCC) 2024

In the last 20 years we have seen a seismic shift from the view of NSCLC as a single disease to that of a suite of cancers caused by various oncogenic drivers and specific genetic mutations. Diagnosis has evolved from reliance on histology to genomic-based subtyping, which has guided the development of targeted therapies.

The response rates to such therapies at first line are truly staggering – 60 to 80 percent or more for some EGFR, ALK, and RET targeted therapies (1–3). Five-year overall survival rates are also encouraging with these targeted therapies – up to 60 percent of patients with ALK inhibitors, for example (4). The need to ensure that all eligible patients are identified and offered this targeted first-line treatment as quickly as possible is clear.

The ESMO guidelines support this, recommending testing for all targetable oncogenic drivers is performed for all advanced NSCLC cases ahead of first-line treatment (5). Ideally, targeted NGS panels, covering both DNA and RNA alterations, should be used for this (5).

But is this feasible in practice? In order to review the current and future landscape of genomic profiling in NSCLC, our symposium at ELCC recreated a molecular tumor board for multidisciplinary perspectives. Our speakers were Fernando Lopez-Rios (pathologist from Spain), Francesco Passiglia (medical oncologist from Italy) and Morten Grauslund (molecular biologist from Denmark). Here is what they told us.

The oncologist's perspective – Biomarker testing shortfalls

Sadly, the reality is that the availability of biomarker testing across Europe is highly variable. It is estimated that half of patients with advanced NSCLC are missing the opportunity to benefit from personalized medicine due to gaps in biomarker testing and adequacy (6). Barriers such as no biopsy offered, insufficient samples, tests not ordered, and inconclusive or false negative results are all too prevalent (6). In many cases, turnaround times (TAT) for test results are too lengthy, resulting in disease progression or death of the patient.

Access to NGS testing is also less than ideal. Most patients still receive only single biomarker testing in the real world. Even in the US, less than 50 percent of eligible patients receive multibiomarker NGS testing (7). This can have a detrimental effect on overall survival rates.

Even where NGS testing is available, outsourcing of the service can result in TAT of several weeks. Many patients simply cannot wait this long to start treatment, meaning they may receive less effective therapies, or their condition may advance too far for help. The solution is clear – wider adoption of in-house rapid NGS testing to decrease diagnostic TAT to days rather than weeks.

Finally, given the complexity of interpreting genetic alteration data, assembling all the relevant expertise onto tumor boards is key to timely reporting of genomic profiling in NSCLC.

"The solution is clear – wider adoption of in-house rapid NGS testing to decrease TAT."

The pathologist's perspective – The future is liquid

Studies have shown that overall survival of advanced NSCLC patients improves when broad genomic profiling is performed prior to first-line therapy (8). Integration of biomarker testing into the diagnostic workup is crucial for informed decision making throughout the patient journey.

What can be done to improve accessibility to, and speed of, genomic profiling? With the joint attributes of convenience and speed, wider adoption of liquid biopsy could help break down some of the barriers to multibiomarker reports being available at the time of the treatment decisions (9). Not to mention it is the preferred testing option for the majority of patients. However, workflows for liquid biopsies are rarely optimized, and it is necessary to explore ways to improve the diagnostic TAT with these methods. There are two main ways to achieve this – lean workflows and reflex testing strategies.

A lean workflow starts with efficient blood collection, which, unfortunately, is not yet standardized. Ideally, this would involve two 10 mL samples of carefully drawn blood in EDTA tubes or preservation tubes that are filled to the top. At room temperature, when using EDTA tubes, there should be a maximum of 2 hours between blood collection/stabilization and blood separation. Refrigeration should be used for longer time lapses, up to maximum of 24 hours.

What to test

The ESMO guidelines recommend testing for the following oncogenic drivers at first line (5):

ALK	BRAF	EGFR	EGFR exon 20 insertion	HER2
KRAS G12C	MET	NTRK	RET	ROS1

Reflex testing means performing genomic profiling for all NSCLC diagnosed patients. Truly effective reflex testing would require a change of practice from seeing liquid biopsy as a last resort to using it as a complementary approach to tissue biopsies, or possibly even as plasma first approach (10, 11).

And finally, how should interpretation of broad genomic profiling be handled? Due to its sheer complexity, more and more institutions are now assembling intra-laboratory molecular tumor boards. By bringing together technicians, pathologists, molecular biologists, and clinicians, analysis of the various test results can be most effectively integrated. Experience shows that effective communication has a positive effect on overall survival of patients.

The molecular biologist's experience – Ultra-fast in-house NGS testing is key

In Denmark, the recommended TAT for NSCLC diagnostic testing – including imaging, biopsy, histopathology and biomarker testing – is 24 days. A team at Rigshospitalet in Copenhagen have been studying the effect of in-house NGS testing on TAT.

"With so many patients missing out on effective treatment, can we afford not to invest in rapid TAT and liquid biopsy adoption?"

The team used the Oncomine™ Dx Express Test on the Genexus Integrated Sequencer Dx System, running daily from Monday to Friday, for tests ordered by the pathologists before 12 noon. Molecular results were integrated with histopathology results into one report for the clinician. The study of 544 DNA and 490 RNA samples revealed that their TAT – from test ordered to results reported – averaged just 4 working days.

What's more, the study revealed that the testing workflow time was reduced from 4 days (with Sanger sequencing) to around 20 hours. This is based on running six samples, starting from DNA and RNA, from library preparation to sequencing and results.

The Oncomine Dx Express Test covers the majority of actionable biomarkers recommended in the ESMO guidelines. Conclusive test results were reported for 96 percent of DNA and 99 percent of RNA analyses. Study results showed high performance for both DNA and RNA based biomarkers, and robust assays even with sparse samples. Testing success rates of 95–98 percent were reported, reducing potential re-biopsies and delays.

And was the Genexus Dx System user friendly? Well, whilst lab technicians reported it can be challenging to optimize the chip utilization, they also experienced significantly reduced hands-on time with the Genexus Dx System and, of course, shorter TAT compared to previous systems.

What needs to change?

Tissue biopsy is still regarded as the gold standard for molecular tests, and a cultural shift will be needed before liquid biopsies are widely adopted. That will only be achieved via education. The affordability of liquid biopsies must also be considered. Many institutions currently have insufficient funding to perform both tests.

Similarly, the business case for in-house NGS will need to be strong in order to justify the investment – studies such as the one in Copenhagen will be useful in helping this cause.

Ultimately, with so many patients missing out on effective treatments and considering the overall costs of care, including treatment, can we afford not to invest in rapid TAT and liquid biopsy testing adoption?

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View the whole symposium on demand for free here

To view the intended use of the Oncomine Dx Express Test, visit oncomine.com/express-test.

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Molecular Pathology

No transfusion confusion A genomics-based solution for identifying blood type has been launched in the US (https://bit.ly/3yDmHE1). The array-based assay offers extended blood typing – covering over 40 genes and 260 antigens over 38 blood group systems – to identify both common and rare blood types. The manufacturers commented, "Having access to a scalable, array-based blood typing solution may help blood services effectively screen extended blood types for more precise blood matching." The assay was developed in collaboration with the Blood Transfusion Genomics Consortium, whose vision is to "one day make comprehensive blood typing for all donor and patient blood the standard of care."

Infertility indicators A European collaboration has trained a convolutional neural network (CNN) in the recognition of CD138-positive cells on whole slide images of endometrial biopsy samples (https://bit.ly/3yuSdUT). The study used the CNN tool to assess the relationship between the number of CD138-positive cells and specific reproductive disorders: polycystic ovary syndrome and recurrent implantation failure. The report states: "The algorithm reveals that the occurrence of CD138+ is influenced by PCOS phenotypes and menstrual cycle phases, whereas receptivity status in RIF did not seem to play a role."

Into the imprintome A US study has revealed a new risk factor for Alzheimer's disease (AD) – methylation of DNA regions that regulate genomic imprinting (PMID: 38658973). These genetic aberrations are caused by environmental factors during early development, and could be used as an early warning sign for AD – decades before its onset. The team used whole-genome bisulfite sequencing to examine the methylation pattern of the genome. They identified variations in the area known as the "imprintome" in AD brain samples versus controls. Additionally, the team detected more methylated imprint control regions in the samples from black patients than white patients, which could account for racial differences in AD prevalence.

Subtypical A study published in Nature Communications shows that idiopathic Parkinson's disease (iPD) has two distinct molecular subtypes (PMID: 38684731). Further, these may be differentiated by the level of deficiency in a protein called neuronal respiratory complex 1 (C1). Not only could the findings explain anomalous results in previous iPD pathological studies, but they could also have implications for precision medicine studies for iPD. The report states, "to efficiently translate these findings into clinical practice requires the development of clinically applicable biomarkers, allowing us to classify individuals in vivo."

IN OTHER NEWS

Metastatic colonies
Researchers investigate the link between metastatic cancers and bacteria, using a combination of sequencing techniques to produce a pan-cancer microbiome atlas (PMID: 38599211).

In the family
A new ASCO guideline aims to standardize germline genetic testing of patients with cancer – from patient selection and recording the family cancer history to which multigene testing panels to use (PMID: 38759122).

High-risk melanoma
Study results validating a seven-panel IHC prognostic test for early-stage skin cancer are presented at ASCO (https://bit.ly/4e2TmU5).

Omics funding boost
The Bill & Melinda Gates Foundation continues to support omics research, issuing multiple grants to projects in the field through May and June this year (https://bit.ly/3WSfTwt).

Beyond the Micrometer

Gene expression profiling tests are well validated but underutilized in oncology

By Matthew Goldberg

For many oncology indications, there are innovative treatments and management pathways that offer patients better outcomes than could have been expected even five years ago. But to realize the full potential of these advances, clinicians need to be able to route patients to the management pathway most likely to benefit them.

At present, the clinical and pathologic factor-based staging systems that clinicians use to direct patients to and away from treatment pathways are limited in their prognostic accuracy. Precision medicine tools, such as next-generation sequencing or gene expression profiling (GEP), can provide invaluable, independent information about a patient's tumor. Indeed, this molecular information complements clinicopathologic information obtained during staging to improve diagnostic accuracy, prognostic risk assessment and, in some instances, therapy response prediction.

For example, in melanoma a pathologist will assess histopathological characteristics – such as the depth of a tumor (Breslow depth measured with an ocular micrometer) and whether the lesion is ulcerated – to establish primary tumor stage. This is then used to route patients to a risk-appropriate management pathway. However, we now know that there are differences in gene expression between aggressive melanomas and melanomas that are unlikely to recur or metastasize, even if they have the same histological features. Here, optimized GEP testing results can be used to differentiate between higher- and lower-risk tumors – indistinguishable using gene sequencing panels or the clinical and pathologic factors used in staging.

However, there has been inconsistent evaluation and adoption of GEP testing across oncology. Disparities exist in how guidelines discuss advanced molecular testing across cancer types. In my opinion, careful evidentiary review, consideration, and discussion of GEP testing in cutaneous oncology is needed.

Through my work as a dermatologist and a dermatopathologist, I have come to appreciate some key areas in which GEP testing is underutilized by some clinicians in cutaneous oncology. By clarifying these areas and reviewing the recent literature, I hope to encourage those who have not considered GEP to reassess its benefits for our patients.

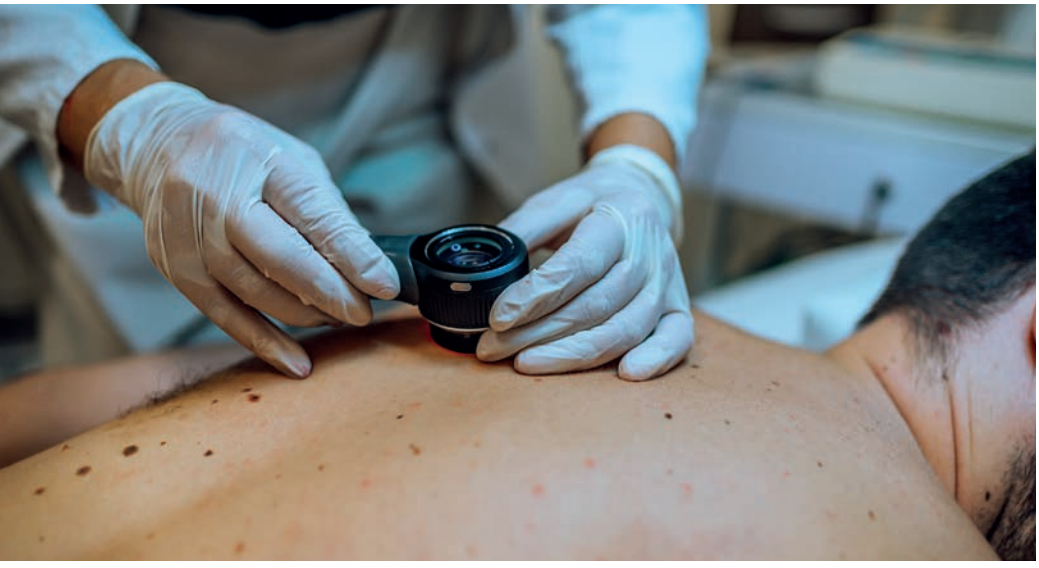
How can GEP tests benefit patients?

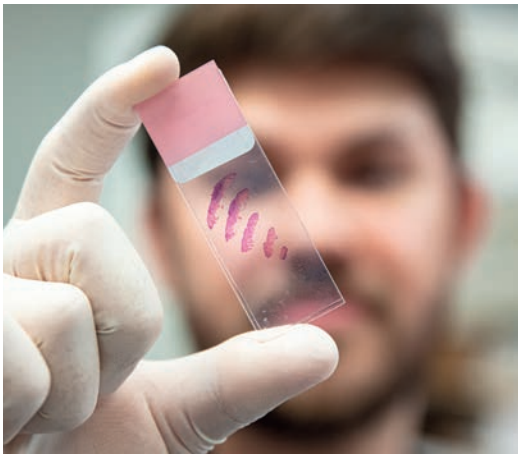
In recent years, GEP tests have been used to improve diagnosis, risk assessment, or therapy response prediction, depending on the cancer and context. Of these, GEP testing for treatment prediction in breast cancer is the most well known, and it is often used as the only point of comparison for other GEP tests. However, it's important to appreciate that the clinical application of therapy response prediction is different from the comparatively broad range of clinical applications for prognostic GEP tests.

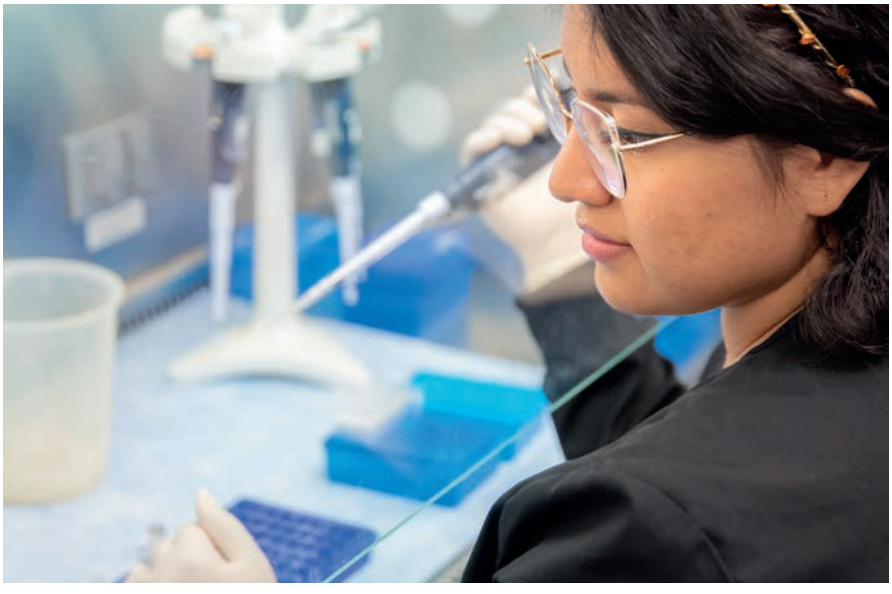
GEP tests whose results directly inform therapy response prediction provide a single action point for clinicians – which systemic therapy to prescribe. Prognostic GEP tests, however, can inform a wide range of risk-aligned management decisions for clinicians who treat both early and more advanced stage cancers. These include frequency of clinical follow-up, sentinel lymph node biopsy decisions, surveillance imaging, and adjuvant radiation therapy.

Both treatment prediction and prognostic risk assessment are critical to improving the lives of patients. For example, a study of more than 4,000 melanoma patients in 2023 demonstrated that patients who received prognostic GEP testing had better survival outcomes than similar patients who did not (1). The survival–benefit association observed by this large study is best understood when contextualized by additional studies focused on specific risk-aligned management decisions.

One such study measured the clinical outcome of patients who were sentinel node negative and either did or did not receive GEP-guided surveillance imaging (2). Critically, this study found that patients with high-risk GEP results were directed by their treating clinician to receive imaging as part of their disease surveillance. As a result, melanoma recurrences were detected earlier, when their tumors were smaller, which led to improved survival compared to the no-GEP group. This study, performed independently from GEP test manufacturers, provides a clear example







in which integrating the information from prognostic GEP testing improved patient risk stratification. It led to more closely risk aligned surveillance approaches that subsequently improved patient outcomes.

Of course, looking at survival outcomes alone does not account for the benefits observed from routing low-risk patients away from inappropriately intensive treatments or procedures – such as sentinel lymph node biopsy (SLNB). A 2023 multicenter, prospective study demonstrated how clinicians use GEP testing in the selection of patients for SLNB (3). Eighty-five percent of the decisions relating to SLNB were influenced by GEP results. And in patients identified as low risk for metastasis by GEP, SLNBs were reduced by 29 percent. Reduction of invasive surgical procedures for patients at low biological risk of metastasis is an important improvement in healthcare outcomes – and demonstrates the need to look beyond the improvement of survival.

It is time to leverage the power of precision

As a dermatologist and dermatopathologist, I recognize the limitations of risk stratification based on clinical and pathologic features alone. I also have confidence that the risk-aligned management decisions that doctors are making for their patients matter. So, when there is an opportunity to improve the accuracy of risk assessment at pivotal points in a patient's care journey, it should be seriously considered. Precision medicine tests, such as GEP, can provide that opportunity when they layer additional, independent information on top of what is already known about a patient's cancer.

Ultimately, those who have not considered using GEP should question whether they are waiting for the future promise of precision medicine at the expense of its well-established current value. For indications such as breast cancer, uveal melanoma, prostate cancer, SCC, and melanoma, the tests are well validated with demonstrated clinical utility. GEP testing is no longer a future prospect – it is already here.

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Infectious Disease

Losing sight of COVID-19 SARS-CoV-2 has been attributed to wide-ranging ocular abnormalities and vision impairment, but understanding remained unclear. In response, researchers at the University of Missouri School of Medicine used a humanized mouse model to learn how our vision is affected by the virus (PMID: 38598560). Their study shows that SARS-CoV-2 is able to breach the protective blood-retinal barrier, infect the cell lining, and has the potential to cause long-term consequences in the eye. Lead researcher Pawan Kumar Singh recommends that those with a COVID-19 diagnosis, "ask [their] ophthalmologist to check for pathological changes to the retina."

Birds > Cows > Humans? The H5N1 influenza virus (also known as bird flu) has been spreading through dairy cows in nine US states – but as of May 2024, tests have shown no sign of the virus in pasteurized milk. However, researchers worry that insufficient collection and reporting on data could hold back efforts to control the virus (https://go.nature.com/3yGsyZh). With a shortfall in testing, despite one infected person being identified and linked with the outbreak, there's a serious risk of bird flu spreading between humans without our knowledge.

Eradicating *E. albertii* The prevalence of pathogenic *E. coli* has caused frequent misidentification of similar bacteria, which is especially damaging with large scale outbreaks of *E. albertii* food poisoning overtaking Japan. To clear up these errors and establish a diagnostic method, researchers led by Shinji Yamasaki and Sharda Prasad Awasthi created a quantitative real-time PCR method (PMID: 38737260). By conducting specimen identification with this technique, researchers discovered that *E. albertii* survived in the human intestinal tract for around four weeks and showed continued presence in feces. These results confirm the ability of this method for detecting *E. albertii* accurately and contribute to elucidating both the source and route of infection.

Lousy lice *Y. pestis* has caused numerous pandemic outbreaks, including the Black Death. Now, a recent laboratory study finds that it's not just fleas and rats at fault for the spread of this virus. Researchers used a membrane-feeder adapted strain of body lice (Pediculus humanus humanus) and showed that they are efficient in transmitting the virus (PMID: 38771885). Additionally, this research showed that *Y. pestis* can infect Pawlowsky glands in body lice, which increases pathogen transmission consistency. These results suggest that body lice were bigger plague spreaders in past pandemics than previously thought.

IN OTHER NEWS

Immunity cell wall
Repeated vaccination and infection of SARS-CoV-2 teaches B and T cells to recognize and target the virus to increase protection (PMID: 38781962).

Sewage takes control
An increase in gastrointestinal illnesses in Massachusetts is linked to untreated sewage overflows in US waterways, BUSPH research finds. (PMID: 38775485).

Rabies revelation
The rabies virus persists in Latin America in a cycle between Desmodus rotundus vampire bats and cattle, but researchers prove that deforestation in Costa Rica raises the risk of outbreak (PMID: 38666690).

CWD barriers
Study of prion diseases with a human cerebral organoids model suggests that chronic waste disease (CWD) is unlikely to spread from animals to humans (PMID: 38781931).

Facing Fungus

What are the diagnostic implications of the alarming rise in fungal infections?

By Ayaz Majid

The prevalence of fungal infections is rising worldwide and those more invasive in nature are of great concern (1). Though superficial fungal skin infections, such as ringworm, are easily treatable, invasive deep tissue fungal infections (IFIs) can lead to high morbidity and mortality rates (2).

The emergence of multi-drug resistant fungal pathogens is certainly cause for concern, with some fungi appearing that are resistant to all types of antifungal medications, either naturally or through exposure (3). In response, clinicians and laboratory staff must remain vigilant, as patient symptoms can often resemble those of non-fungal infections. There should be an increase in diagnostic assessments to promptly and accurately identify the specific fungi causing infection to ensure better patient outcomes and address public health risks (4).

However, diagnosing IFIs is time consuming. Clinical labs often have to test for more frequent viral or bacterial pathogens before they can begin fungal testing. Given the increase of invasive fungal infections, maybe it's time for labs to adjust testing algorithms for efficient screening and diagnostic protocols.

Fungal public health threats

In 2022, WHO released its first list of priority fungal pathogens to highlight the importance in regards to health and creating pathways for patient management (see Figure 1) (5). Four fungal pathogens were rated as critical: *Aspergillus fumigatus*, *Candida albicans*, *Candida auris*, and *Cryptococcus neoformans*. Seventy percent of IFIs were classified as invasive candidiasis, followed by 20 percent cryptococcosis and 10 percent aspergillosis. This rise in fungal infection is traced to global warming, rises in international travel, and increased drug resistance rates.

The *C. auris* challenge

C. auris is also associated with high mortality rates – one in three patients die within a month of being diagnosed with the infection (6). It's often detected in healthcare facilities, persisting on surfaces and transmitting through breathing and feeding tubes. Like other IFIs, immunocompromised patients are the most vulnerable to the dangers of the *C. auris* infection, but healthy individuals may become colonized without symptoms and must be identified and isolated in order to prevent potential spread in healthcare facilities.

To identify colonized patients, healthcare providers should perform colonization screening – taking a composite swab sample from the patient's skin near the armpits and groin, and submitting it for lab testing. Clinical testing with blood or urine must be performed if a patient shows symptoms of an infection with an unknown cause.

Whether screening or diagnosing IFIs, a fast-testing turnaround time with accurate identification is essential for positive patient outcomes. Several approaches for *C. auris* can be seen in Figure 2.

C.auris identification

Culture based phenotypical and biochemical fungal tests take substantial hands-on time of up to 10 days to identify fungal species, and in some cases *C. auris* may be misidentified as yeast through this testing method (7). However, a recently described novel chromogenic agar (CHROMagar Candida Plus) has promising utility for rapid identification and differentiation of *C.auris* from other *Candida species*.

Positive blood culture identification for *Candida* species is less than 50 percent accurate for bloodstream infections and less than 20 percent accurate for intra-abdominal candidiasis (8). Microscopy and histopathology methods require significant expertise and may not be feasible in all labs. However, while detecting fungal antigens could be affordable, user-friendly, and potentially applicable at the patient's bedside, there are currently no immunoassays available for *C. auris*. Additionally, limited sensitivity has restricted development of commercially available immunochromatographic assays for yeast detection (9).

Mass spectrometry techniques, such as matrix-assisted laser desorption/ionization-time of flight (MALDI-TOF), can differentiate *C. auris* from other *Candida* species, but not all reference databases with these devices allow *C. auris* identification. There are FDA-cleared commercial MALDI-TOF systems with updated libraries that allow for *C. auris* identification with quick results, but the initial cost of equipment and training personnel are high.

Molecular tests

Molecular tests provide the promise of accurate alternatives for fungal pathogen detection. Several syndromic or PCR pathogen panel tests are FDA approved and include more than 40 targets associated with bloodstream infections – such as gram-negative bacteria, gram-positive bacteria, yeast with *C. auris*, and antimicrobial resistance genes – allowing for pathogen identification as quickly as an hour from positive blood culture. Other major advantages of these tests include sample-to-answer automation and a high number of targets evaluated in a single test.

Targeted laboratory PCR methods have been reported for detecting *C. auris*, but there are no commercially available FDA-cleared PCR tests for identifying colonized, asymptomatic patients (10). However, PCR has demonstrated

Critical group	High group	Medium group
Cryptococcus neoformans	*Nakaseomyces glabrata (Candida glabrata)*	*Scedosporium* ***spp.***
Candida auris	*Histoplasma* ***spp.***	*Lomentospora prolificans*
Aspergillus fumigatus	*Eumycetoma causative agents*	*Coccidiodes* ***spp.***
Candida albicans	*Mucorales*	*Pichia kudriavzeveii (Candida krusei)*
	Fusarium ***spp.***	*Cryptococcus gattii*
	Candida tropicalis	*Talaromyces marneffei*
	Candida parapsilosis	*Pneumocystis jirovecii*
		Paracoccidioides ***spp.***

Adapted from: WHO fungal priority pathogens list to guide research, development and public health action, Table 3. Geneva: World Health Organization; 2022. License: CC BY-NC-SA 3.0 IGO.

Figure 1. Priority fungal pathogens identified by WHO in 2022 (Adapted from "WHO fungal priority pathogens list to guide research, development and public health action" [2022]).

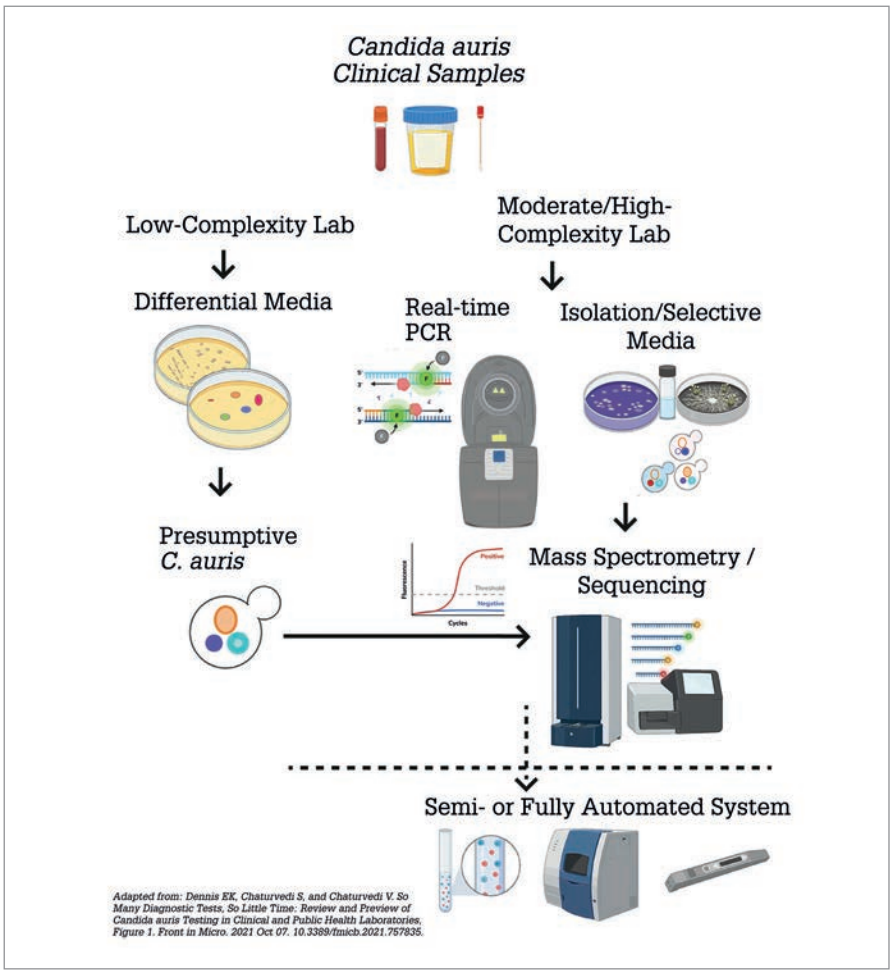

Figure 2. Technologies for C. auris detection (Adapted from E K Dennis et al. "So many diagnostic tests, so little time: Review and preview of Candida auris testing in clinical and public health laboratories." Front Microbiol, 12 [2021]).

improved sensitivity in environmental screening for isolates across, for example, New York healthcare facilities (11).

Importantly, colonization cannot be cured using antifungal medications, and treatment is not required or recommended for people found to be carrying *C. auris* without any symptoms or signs of infection. Commercial FDA-cleared PCR tests highly specific and sensitive to *C. auris* detection will therefore be key to preventing the spread from colonized individuals.

Overall, rapid molecular testing offers an accurate alternative to traditional fungal pathogen testing. PCR-based methods effectively detect fungal strains, even when culture and other tests fail – allowing for timely clinical action. Multiplex panels in PCR testing enable labs to identify various pathogens while distinguishing between similar strains often missed in standard fungal tests. Additionally, molecular tests can pinpoint genetic markers of drug resistance for aiding treatment decisions.

When selecting or developing a PCR method to validate, it's important to consider multiple factors: sensitivity and specificity, lab capacity and equipment, clinical evaluation with appropriate sample type, cost, and turnaround time for swiftly identifying colonized patients.

Looking forward, the rising incidence of emerging fungal infections call for clinical labs to plan for increased fungal testing for screening and diagnosis. Molecular tests can provide labs with accurate scalability, cost-effectiveness, and less hands-on time than traditional approaches for approaching these tasks. Specifically in the US, FDA cleared *C. auris* PCR tests will be pivotal for broader lab availability to identify colonized patients on a global scale and respond to this growing health threat.

Ayaz Majid is Director of product management and specialist in molecular diagnostic tests at Diasorin

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Digital Pathology

Twice the power Lung adenocarcinoma (LUAD) accounts for 40 percent of lung cancer cases, but the current gold-standard diagnostic process can be labor intensive and time-consuming. In response, a team of Chinese researchers propose a "weakly supervised learning" method for LUAD classification on label-free tissue slices with virtually stained histology samples (PMID: 38588884). This method provides a cost-effective and rapid approach to postoperative examinations. Moving forward, other label-free imaging modalities and disease contexts could be developed using this method as a blueprint.

Onco-algorithm A new AI-powered whole-slide pathology foundation model could set a new benchmark in digital pathology. The Providence Gigapixel Pathology Model (Prov-GigaPath) uses large-scale real-world data and novel vision transformer architecture to complete various digital pathology tasks (PMID: 38778098). It was designed with hopes of tackling the scarcity of publicly available pathology data and a resounding difficulty in designing model architecture for capturing global and local patterns across whole slides. This technology demonstrates significant advancements in mutation prediction, cancer subtyping tasks, and vision-language processing. Prov-GigaPath shows potential for enhancing clinical diagnostics and also suggests applicability to broader biomedical domains for self-supervised learning from high-resolution images.

Undesirable clumping Protein clumping is the root of a wide range of neurodegenerative disorders, including Alzheimer's disease. To learn more about its characteristics, researchers at the University of Copenhagen have developed a machine learning algorithm to track clumping proteins in real time (PMID: 38409214). The SEMORE (SEgmentation and MORphological fingErprinting) algorithm automatically maps and tracks important characteristics of clumped proteins down to the nanometer scale in microscopy images. SEMORE also counts and groups clumps according to their shape and size while continuously tracking their development, which can have a major impact on function and behavior. Future developments of SEMORE could support the development of new neurodegenerative disorder drugs and therapies.

AMR mapping A new study uses AI to uncover gaps in global antimicrobial resistance (AMR) research (PMID: 38723455). After compiling a comprehensive database of 254,738 articles spanning two decades, the team discovered significant inconsistencies in semantics and methodologies. Through their sophisticated AI-based analysis, the team developed global maps highlighting where the burden of increasing AMR is most acute. These researchers call for a greater harmonization of research methods, suggesting that culture-based and genomic AMR analysis is crucial for both data integration and holistic health solutions across the globe.

IN OTHER NEWS

Brain tumor subtyping
Researchers create a new AI tool for quick and accurate classification of brain tumors – opening avenues for central nervous system tumor diagnosis in clinics (PMID: 38760587).

AI immunophenotyping
Machine-learning-based CD8 immunophenotyping models identify patients with non-small cell lung cancer that could benefit from immunotherapy (https://doi.org/10.1089/aipo.2023.0008).

Open source analysis
DL4MicEverywhere – an open source platform for microscopy image analysis – launches to address challenges in computing resources for life sciences research (PMID: 38760611).

Mutating data
Machine learning methods offer rapid and effective diagnosis of mutations in gliomas, but inconsistent standards remain a barrier in clinical applications (PMID: 38539436).

Portugal's IMP Diagnostics, a Digital Case Study

Family-owned IMP Diagnostics pioneered digital pathology integration into private practice workflows

By Rob Monroe

Part three of our "Journey to Digital Pathology" series

Isabel Macedo Pinto first glimpsed the future of pathology more than 10 years ago.

"I was in a meeting and overheard two colleagues conferring on a complex case. I am intrigued by difficult cases, so I was drawn to their conversation," says Macedo Pinto, who founded IMP Diagnostics more than 25 years ago and currently serves as co-CEO and Medical Director. "To my surprise, one colleague was attending our symposium in Barcelona and the other was in another country, yet they were reviewing an image together in real time. I immediately thought: "This is the future. We need to transform IMP to be digital.'"

Headquartered in Portugal, IMP Diagnostics is a private, family-owned, high-volume reference laboratory business with a central headquarters based in Porto and facility in Lisbon. More than 120 pathologists, lab technicians, cytotechnicians, and support team members provide comprehensive molecular and anatomic pathology services, accepting and reporting out cases from Angola, the Cape Verde Islands, Mozambique, and, of course, Portugal. IMP also has an R&D department that focuses on computational pathology.

João Sousa Pimentel oversees IMP's strategy and technology, and serves as co-CEO and Head of Business Development. "IMP is structured for clinical excellence, efficiency, and growth. Subspecialized diagnostic units are the backbone of this structure, including gynecologic pathology, perinatal and placental pathology, breast pathology, gastrointestinal pathology, dermatopathology, and uropathology," explains Sousa Pimentel. "We manage 250,000 cases annually, of which 135,000 are histology cases, 95,000 are cytology cases, and 20,000 are molecular pathology, with the number of molecular cases growing rapidly."

The beginning of the journey – preparation to implementation

IMP began readying for digital pathology well before implementation. The process included planning the project's feasibility, raising funds, and assembling the digital pathology team.

"We wanted to be sure fundamental elements were in place so we would be ready for full digital implementation when the time was right," recalls Sousa Pimentel. For example, during the preparation phase, IMP integrated a 2D-barcode-based tracking system, which is critical for full digital pathology implementation.

"The digital pathology project team wasn't big, but it was diverse. It included an overall project leader, a clinical lead to involve pathologists' insights from the beginning, an IT representative to serve as point person with our tech vendors, and a business lead to oversee financial investments," explains Sousa Pimentel.

As part of its diligence activities, the IMP team talked to hardware and software vendors and visited labs incorporating digital pathology. "I strongly recommend visiting with vendors and labs to see digital in everyday use. Doing so helped us gain an understanding of key considerations we would need to address, such as workflow modifications," Macedo Pinto advises.

The IMP team also monitored digital pathology hardware and software development, regulatory actions, and publication of clinical evidence. Sousa Pimentel pinpoints three catalysts that, ultimately, compelled IMP to advance from a preparation phase to implementation.

The first catalyst was a 2017 presentation by Google CEO Sundar Pichai about machine learning in histopathology. "It was meaningful that the top person at Google took time at the company's global developer meeting to address machine learning in pathology. We felt it was time to embrace digital or be left behind. So, we started looking even more closely at implementation," says Sousa Pimentel.

The second catalyst involved two related, but distinct, events. "The year 2019 brought two defining moments in digital and computational pathology," Sousa Pimentel continues. "A peer-reviewed paper was published documenting the performance of a clinical grade AI algorithm. That same year, the FDA granted breakthrough designation for the software referenced in that paper. The paper provided credible evidence of efficacy, while the FDA action underscored regulators' belief that the software was ready for clinical use."

The halfway point – a stepwise approach

From the outset, Tavares and his IT colleagues had a goal to implement digital into IMP's existing workflow without causing significant disruption to the pathologists. They knew IMP needed an approach to managing a huge amount of digital data in a manner that enabled the system to respond quickly and smoothly.

"Even a minimal change in workflow affects a lot of people," notes João Monteiro, IMP's Laboratory Director. "In the histology department alone, there are more than 25 technicians. Everyone

should work the same way to get the best result, whether it's cut thickness, slide disposition or organizing the workflow."

To achieve this, IMP took a stepwise approach. The organization acquired the FDA-cleared high-throughput scanners, an action the team considers the 'official' kick-off of the implementation process. Scanner installation was followed by an in-house assessment of requirements for IT integration and initial vendor negotiation, with the LIS–IMS integration completed in six months. Concurrently, an initial test scanning phase was undertaken involving the digitization of 2,963 slides (44 percent archive material and 56 percent current, routine cases), followed by the incremental digitization of the routine workload. IMP opted to begin by scanning single subspecialty areas and then scaled up to full digitization.

"The stepwise approach meant pathologists and the technical team could learn and adapt to digital over time, and that was central to our success," says Diana Felizardo, a pathologist hired in 2020 to serve as IMP's Clinical Lead of Digital Pathology and Unit Head of R&D.

"People accustomed to working with a microscope can be a little afraid of digital. We found the learning phase essential to creating an ease and familiarity with digital for our colleagues. Now, the pathologists report that they not only like digital but are also comfortable working with the technology. They don't want to go back to the microscope because the microscope is not as practical in today's work environment," says Felizardo.

"Many pathologists' initial reaction to digital is concern but, once they see that it works, they realize it can be a very good thing. We can do different – often better – tasks with digital pathology," adds Felizardo.

IMP is documenting the impact of digital across the practice and finding that although digital pathology deployment in the private setting has its challenges, it also provides compelling opportunities, including easier and faster case delivery to the pathologists. This is extremely relevant for IMP, as they have two Porto buildings, as well as two laboratories in different cities, meaning that physical slides need to be transported between sites. Digital also allows simpler case sharing between colleagues located in different places and enables remote work.

On the horizon – computational pathology enhances patient care

Digital pathology deployment lays the foundation for the integration of artificial intelligence (AI) tools, which will ultimately contribute to improving patient care.

"AI requires access to digitized pathology slides, which are generated using whole-slide scanning," explains Vivian O. Tan, a computational pathologist with clinical diagnostics developer and supplier Leica Biosystems. "AI tools can be key in increasing workflow efficiency and improving diagnostic quality."

AI applications in pathology are already in use in clinical and research settings. There are digital tools available to assist diagnosis that can facilitate many pathologists' tasks, such as measurements and annotation of regions of interest. State-of-the-art AI approaches can be used for advanced tasks, including prediction of survival and therapy response, which, if rigorously validated, can enhance clinical decision-making in the future.

Tan further explains, "AI enables researchers to identify biomarkers that can be useful in the clinical setting to aid in treatment decisions. AI can identify morphologic features on H&E that correlate with molecular changes, for instance, that may be associated with drug benefits for specific cancers. All of this is made possible by AI. And digital pathology is the substrate for AI."

Sousa Pimentel says, "At IMP, we think of digital pathology as a vessel. It can take us from point A – enabling diagnosis largely in the way pathologists currently work – to point B – diagnosis with AI."

The organization is making this a reality with an ambitious digital pathology/AI agenda. IMP implemented digital pathology in parallel with computational pathology, starting with a research project to build algorithms for the detection of colorectal and cervical cancers in scanned images. IMP is also building a digestive cancer algorithm to aid pathologists in analyzing histopathology images of colorectal carcinoma and other GI cancers in a more accurate manner.

"Digital pathology has transformed our current diagnoses into more exact and complete forms of diagnoses, and it will continue to do so as more AI algorithms are developed," reflects Macedo Pinto, who believes AI will both enable an economic return on investment and make pathologists even more vital to patient care.

She continues, "There is potential for an economical return in addition to the clinical return. If I can provide a diagnosis more rapidly and leverage AI to make the diagnosis more precise and comprehensive, colleagues will select IMP as their partner. They're more likely to send us their biopsies and specimens because of the in-depth insights we can provide."

Looking ahead to the next decade? Macedo Pinto says, "AI will enable us to better serve clinicians and their patients. It is our commitment to them that drives us at IMP to continue to innovate. We never forget that each slide we review represents a human life. For this reason, we seek to maximize the excellence of the diagnostic services we provide, every day, for every case. We need to be exhaustive. We need to be exact. We need to give these precious diagnoses to our patients."

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

Profession

Your career
Your business
Your life

Paint What You Know

The growth and benefits of #pathart

By Helen Bristow

What's a pathologist to do when, every time they look into a microscope, they are blown away by the beauty they see? Go home and paint it, of course!

Meredith Herman, pathology resident at the University of Michigan, creates beautiful paintings inspired by the images she sees in her daily training. We found out how the worlds of science and art have collided in her life.

What was your route into pathology?

From a young age, I was always artistically inclined and developed fine motor skills quickly. I would draw and color for hours, even holding art exhibits for my family when I was four years old. I continued to flourish in art through grade school, but started thinking more seriously about careers in high school. I must preface that I am the first in my family to go to medical school or pursue work in the laboratory. I realized that I enjoyed science and when I got into college at Michigan State University, I found my way into the laboratory science program. In this program, I was taught how to be a medical laboratory scientist in the hospital laboratory.

I remember my first course in lab methods, where we learned how to make peripheral smears and perform a blood cell differential under the microscope. I was captivated by the smallest of life forms in our body and the details that made them unique – I loved it.

Fortunately, I was connected with my mentor in college who also was a pathologist, and he helped me realize pathology could be a good fit for me. And so, I went into medical school knowing I wanted to do pathology, which is rare. I was the weird one who just loved being in histology lessons and studying the cells. I followed my passion and found immense support from the pathology community, and now that I am in pathology residency it feels like I am living the dream!

Can you remember how you felt when you first looked down a microscope?

When I first saw human cells under the microscope I thought it was magical – seeing life in its simplest life form was truly captivating.

But did you surprise yourself when you selected science instead of art?

As a child, I dreamed of being a fashion designer or an art teacher. Being a doctor or scientist never crossed my mind. At that age I didn't think science was very artistic. But when I started looking more into it in college, I thought, "Wow. There are a lot of visual components, details, and pattern recognition in this field." I was particularly gifted at art, so I took that as a hint to pursue it more because it did come naturally. In retrospect, it makes total sense that I landed in medicine, especially pathology, because having a visual and artistic aptitude have helped me grow into the specialty.

So how did your pathology art come about?

Sadly, I stopped painting in college – and even in medical school. During those years, I was focused on doing well in classes. But then COVID-19 hit. When everything shut down and went virtual I thought, "What am I going to do with all this down time?" When life slowed down and I had more time for myself, I realized that I missed art and needed it back in my life. As an artist, ideas and inspiration come spontaneously and I get an urge to create. My first painting after my artistic hiatus was a microscope with pathology in the background. I went to the craft store, picked up a few materials and started painting.

When I finished, I thought, "This is pretty good!" I wondered how I could share it with others. I found the Royal College of Pathologists' Art of Pathology Competition (rcpath.org) – and the closing date was only a week away, so I just submitted it right on time. My entry was awarded an honorable mention. This made me realize that, even though I hadn't painted anything in a long time, perhaps I still had some talent and I should keep going. I kept practicing with watercolors during my third and fourth year of medical school. And every time I was planning what to paint, the inspiration was obvious – pathology.

I wanted to know if anyone else liked what I was creating, so I decided to put it out on Instagram and made some videos for TikTok. It really took off! I sensed some real interest and excitement about my work. So I just kept doing it!

Have you had any formal art training?

I did take some oil painting lessons before I started residency – mainly fine art and landscapes. It was fun and taught me many skills – color theory and composition, for example – that I still use and apply to my other paintings. But everything else is self taught. I took it upon myself to learn different techniques and always practice and make time for painting every day.

How would you describe your artistic work?

My medium is primarily watercolor on paper, but I also do some oil paintings. I try to illustrate what I see under the microscope – what our tissues and cells look like microscopically. And try to illuminate the patient experience, as well as disease diagnosis. I throw in some regular histology as well. I feel like my art should be described as "where science meets art." I think it's a skill to be able to blend those two things artistically. People don't usually get to see their cells under the microscope, so that's what I'm able to bring to them. And if people comment that the images are beautiful or mesmerizing, I can ask, "What makes it beautiful? What catches your eye?" For most people it's just that they have never seen cells and tissues as art, but now they can see the beauty.

How else do you get your work seen?

I sell my work via an online store. Occasionally I do commissions. I also donate pieces to good causes; I donated a painting to a fundraiser for breast cancer and plan to do more. I get to use my work in a philanthropic way, it's my hobby, and it's my side gig – it's a win–win situation.

Tell us about the pathology art community – and how you connect with them.

#pathart has been used for quite a while on social media – both for real laboratory images that people find particularly beautiful or representative of a disease, and for painted images. The hashtag is already used widely on X (formerly Twitter) and Instagram, and is starting to gain more traction on TikTok. More people are becoming interested and there are more emerging artists as a result – both painters and digital artists. Pathologists and laboratory scientists alike enjoy art and have always shown support in my artistic pursuits.

The platform I use depends on the media I want to share. If it is a process video, I will create it on TikTok (*@meredithkheman*). If I have a static photo of a painting I did or want to make a trendy short reel, I post it on Instagram. It is important to be present and accessible on social media. I like to connect with other artists and engage with my followers. I frequently get messages from people around the world about how my art inspired them to paint or create something pathological. I think it is important to also support other artists with shared interests by promoting their content, interacting with them, and collaborating with them!

What advice would you give to other artists who would like their work to be seen?

The first step is to put yourself out there. Don't be afraid to publish your work and to show it around. You'll find a very supportive community. It's also good to show your process; for example, make a video and put it on TikTok, Instagram, X, YouTube, etc. Experiment with different platforms and styles and find the way you want to express yourself.

In your experience, do laboratory medicine professionals tend to be artistically inclined?

There is a visual aspect to pathology. We need to be detail-oriented to pick up patterns to connect pieces, and to have puzzle-solving capabilities. Not every pathologist will claim they are artistic, but I do believe we all use our right-brain whether we know it or not. I think there is a propensity for pathologists to be more artistically inclined; however, it doesn't have to be painting – I've seen people doing woodworking, sculpture, and pottery. Everyone in the lab has their own hobby and there is often an artistic element to it.

What does the artistic process mean for you, personally?

It's very relaxing – but it's also essential to my wholeness as a person. I can't believe there was a time when I didn't paint. I just put it off and thought, "I have to study, I have to do other things." But I realized that doing art is important for my sanity in a stressful profession or with a stressful school workload. It's also my business, so I have orders to fulfill. More generally, I think it's very healthy to have a creative outlet. My husband finds it funny that I go to work and then get home and go straight to my other work. But when I get an idea for a painting in my head, I just want to work on it straight away and get it out there. I have an art studio set up at home so that everything is ready to go. I take my art seriously just as I take my residency training seriously.

In Practice

Technologies and techniques
Quality and compliance
Workflow

For Work and Play

Embracing artificial intelligence: a pathology resident's perspective

By Caitlin Raymond

Artificial intelligence (AI) has been making headlines for some time, and recently large language models (LLMs) like ChatGPT have been causing quite a stir among pathologists – myself included. Can ChatGPT be used to write notes? Will it help me write papers? Is it coming for my job?! I decided to learn as much as I could about ChatGPT and LLMs in general to discover the truth.

Firstly, I learned exactly what LLMs are: an algorithmic prediction of text trained on a large body of data. ChatGPT, for example, produces a response to a prompt by predicting the first word, then word 2 from word 1, then word 3 from words 1 and 2, and so on. LLMs are a useful tool for a large variety of uses, such as creative text generation, summarizing and outlining text, organizing data, writing code, and even gameplay.

Learnings

Secondly, I examined some of the drawbacks – which have been widely publicized. Importantly, LLMs aren't infallible and their output must be fact-checked. Although they're algorithms, the data they are trained on contain biases which will influence the output. Additionally, LLMs cannot access information past its training, meaning that responses can quickly become

outdated. And, finally, there are limits to both the size of the prompt and the generated output.

Overall, these tools come with restrictions despite the powerful assistance they can provide to residency, and should be used with such understanding. Continuing with my research, I looked into prompt patterns, which allow you to tap into the extensive training dataset of an LLM, control the output for improving consistency, and increase information allowance in a limited prompt size. For example, I used prompt patterns to develop an educational question-to-question game about platelet disorders. There are a variety of courses available for prompt engineering on LLMs and I recommend diving into those within your budget. You might even find that you can reimburse the cost with your residency book fund.

Applications

After conducting all this research, I chose to embrace LLMs and incorporate them into my workflow, both in my residency and in my personal life. I find ChatGPT 4.0 particularly useful in writing code – so much so that I pay for a subscription! I also use ChatGPT to produce outlines of my writing so I can double check the flow and structure of a document. In my studies, ChatGPT has also helped me create several games for studying difficult material.

Additionally, I use Consensus and Elicit LLMs to perform literature searches and generate research ideas. Consensus has plugins available for use within the ChatGPT interface to search verified scientific literature. However, I particularly enjoy using Elicit, as it generates a 1–2 sentence summary of every paper it returns for your search, extracts data from uploaded PDFs, and – my personal favorite – produces a list of key concepts from the literature for any research question you ask. Did I mention it does all this for free?

In my personal life, ChatGPT is ideal for planning weekly menus and grocery lists, especially for developing new recipes that fit with our dietary restrictions. I also use another LLM called Google Bard, which generates date night ideas that cost less than $50. The training data cut-off for Google Bard is more recent, meaning that the ideas it suggests are more up-to-date than other LLMs.

Other considerations

Having said all this, I don't use LLMs in two key areas: writing notes and papers. LLMs are still a young technology and the medicolegal framework for their use in clinical documentation is still in its infancy. With so much uncertainty and risk, I still choose to handwrite all my clinical notes. Similarly, there is a raging debate about the role of LLMs in producing scientific manuscripts. The exact guidelines vary by journal, but the overall consensus is that LLMs cannot be given authorship and their use must be disclosed. Given the overwhelming negative view of LLMs and the risk of backlash, I have decided to steer clear of this debate and write my own manuscripts.

With all this in mind, will LLMs and AI in general replace pathologists? As Toby Cornish and David McClintock state in their Critical Values article (1), this is very unlikely. However, pathologists familiar with and comfortable using AI and LLMs will almost certainly replace those who are not. AI is a powerful assistant tool for practicing pathologists, with the potential to transform the disease screening process and help with staff shortages – it even has future potential to generate clinical documentation. AI instrumentation is already in use in many core laboratories and expansion is definitely on the horizon. Indeed, some enterprise-wide electronic medical record systems are already incorporating AI to generate certain types of patient communication.

"AI is a powerful assistant tool for practicing pathologists, with the potential to transform the disease screening process and help with staff shortages – it even has future potential to generate clinical documentation."

With all these potential benefits, and the almost certain inevitability of its adoption, I would urge all pathologists to become familiar with AI and LLMs during their training.

By Caitlin Raymond, MD/PhD
Resident Physician at the University of Texas, USA

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Future Thinker

Sitting Down With… Anil Parwani,
Vice Chair of Anatomical Pathology at
The Ohio State University, Wexner Medical Centre

What drew you to a career in medicine?

As a child, I really liked science – and I had a very curious mind. My dad noticed my interest and converted our garden shed into a laboratory for me. I would spend hours there, perfecting my animal dissections in preparation for my biology exam.

I decided to further my studies in the US, and enrolled for a biology degree course. My research projects were in infectious diseases, and this led me to a PhD, developing a vaccine. After that I went to medical school.

I really enjoyed doing research, but I was keen to find a discipline that combined research with patient care. It was also noted that in every rotation I did, I was drawn to the lab to look at my patients' samples under the microscope. I liked the "detective work" that was involved. It became clear that pathology was the perfect fit for me.

How did your interest in digital pathology evolve?

In the early 2000's, a couple of years into my residency, the first slide scanners became available. My department had one for research, and I was excited by its potential in terms of sharing images with different users. We set up a website and shared some static images on it for training purposes and it soon became a part of my daily practice.

I took a job in Pittsburgh, which was at the centre of informatics at that time. During my 10 years there, we managed to set up telepathology networks, and share slides across the state – and even across countries. A whole slide image scanner was installed in China and we set up a service consulting on cases with pathologists over there.

Recognizing this potential, I started working with the FDA and the CAP to develop the regulatory frameworks for digital sign-out of cases.

What have been your greatest achievements?

I am proud of being part of the movement to make digital pathology available for primary diagnosis in the US. Initially, the FDA considered whole slide imaging to be a high-risk technology. I was part of a group of pathologists who secured a meeting with the FDA to address this. We managed, with the help of the DPA, to start a conversation about the regulatory issues surrounding the use of whole slide imaging for clinical use and create a roadmap towards approval.

Our team at Omnyx designed a study with some slide scanner manufacturers to test the hypothesis that digital slides were non-inferior to glass slides for diagnosis. We were able to present the results to the FDA and were involved in several discussions with them that eventually led to the first approval of a slide scanner for use in primary diagnosis in 2017.

When I moved to The Ohio State University, we set up a digital pathology workflow and were the first hospital in the country to sign out cases digitally. That was in 2018. I remember the day well – I signed out the case on this very monitor on my desk, with my colleagues crowded around me, observing. It felt very momentous! Since then, many thousands of patients have benefited from the availability of digital pathology for primary diagnosis and consultations.

What do you think the pathology lab of the future will look like?

I think we're in the knowledge age of pathology right now. We start with data – that leads to information – and from that comes our knowledge. And, in the future, AI will take us into the wisdom age. We must remember to separate artificial intelligence from real intelligence, real experience, and the ability to learn from our mistakes. We can rely on AI to take over tasks that are very manual or very labor intensive, and to do them well. But we must see the work as a partnership, with each side sticking to what it's good at. We must continue to use our wisdom. We might be able to liken the future to the highways, where we will find a combination of self-driving and non-automated cars; in the lab there will be some processes with AI copilots, and some without.

I also predict that the specialties that are highly dependent on imaging will start to merge because of AI. Diagnostic teams will consist of pathologists, radiologists, and oncologists all working together on cases. There will be a collection of tools and skill sets, which will be highly customized, comprising the patient care team. In fact, diagnostic imaging might become a specialty in its own right.

In terms of tools, the technologies we need already exist; we need to ask how we can safely and ethically incorporate them into the workflow.

What advice would you give people aspiring towards pathology leadership?

Engage with the people around you, communicate your vision, and keep dreaming.

It's also important to identify the problems you're trying to solve, create the right team around you, and work towards specific goals. Problem-solving is not just about throwing money at it – throw your vision at it.

With your goals laid out, establish the steps needed to achieve them, and make sure you have buy-in from your team. Also, accept that it might take time. It took 12 years from the time I dreamed of digital sign-out to the time I achieved it!

For people following in my footsteps, it will be important to keep looking at technology developments, and applying those to the future vision. The question should be "how can I transform the pathology practice of the future?"

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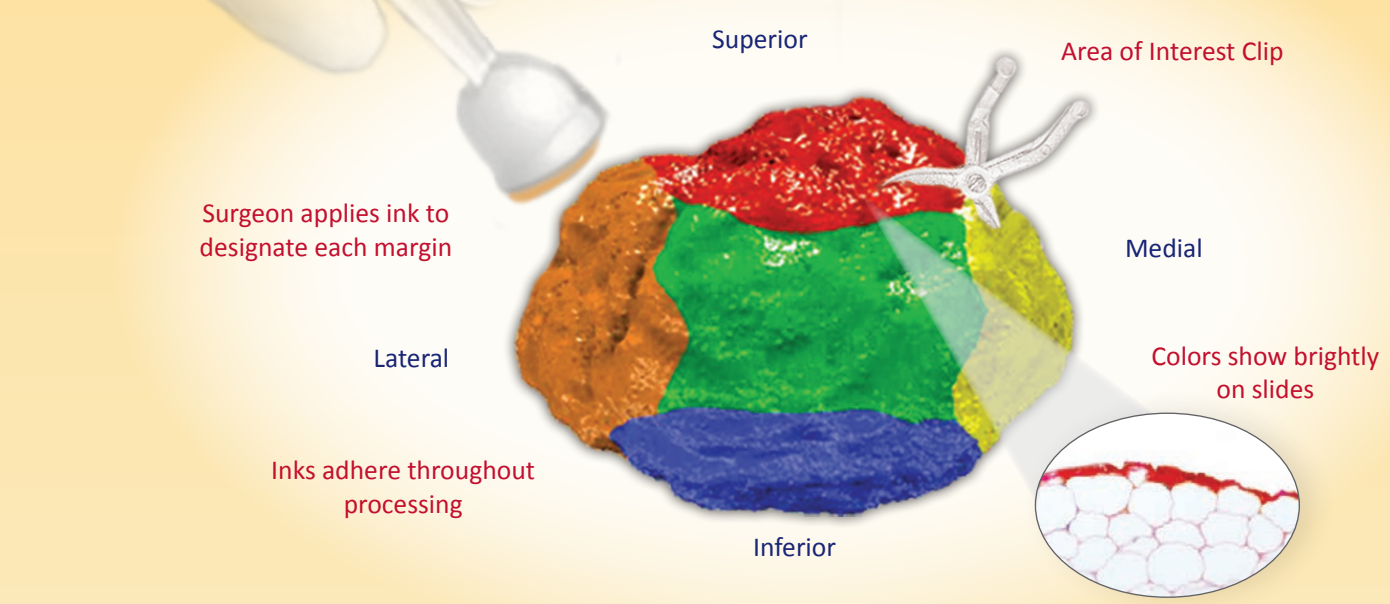

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