MARCH/APRIL 2022 # 83

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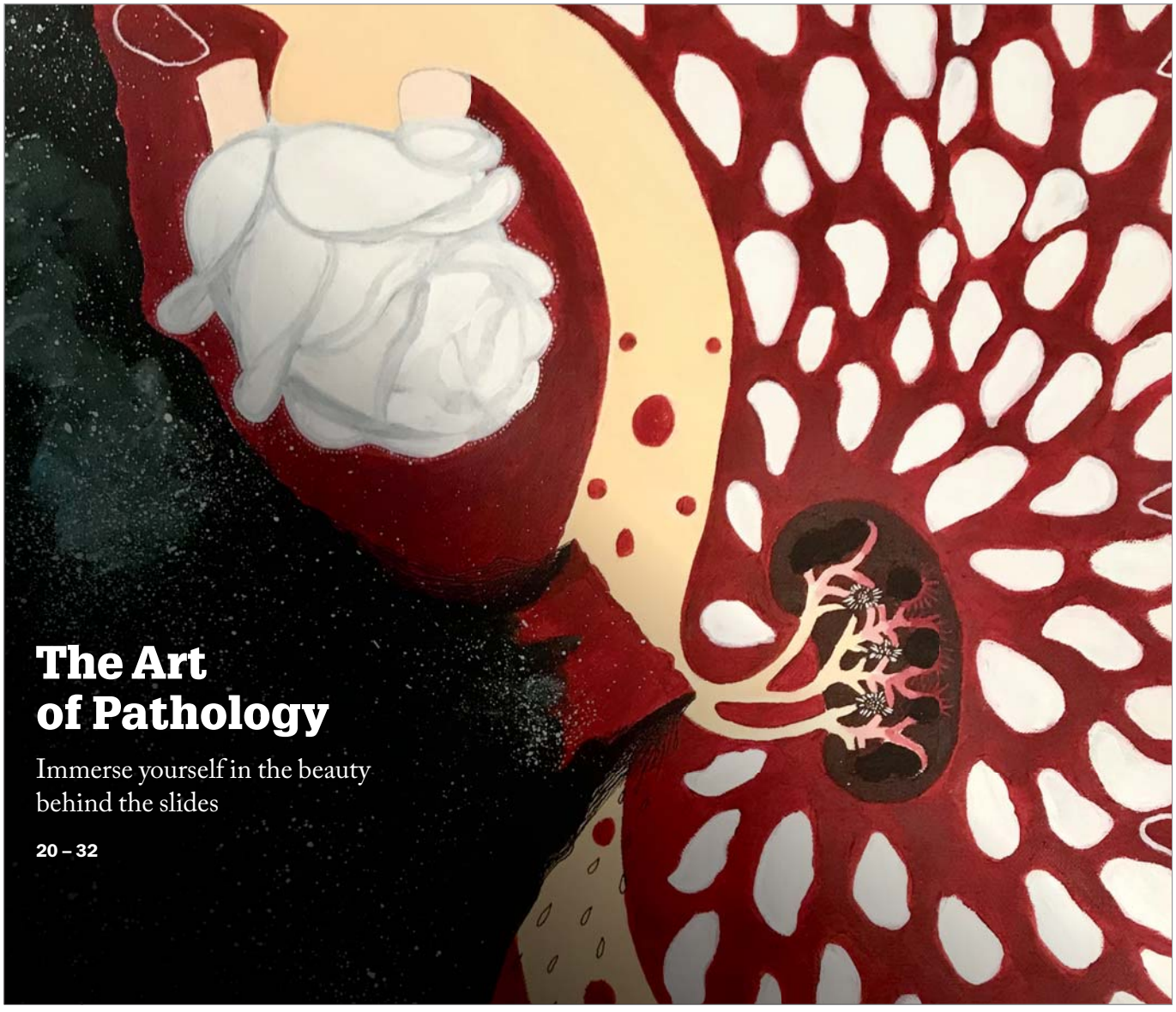
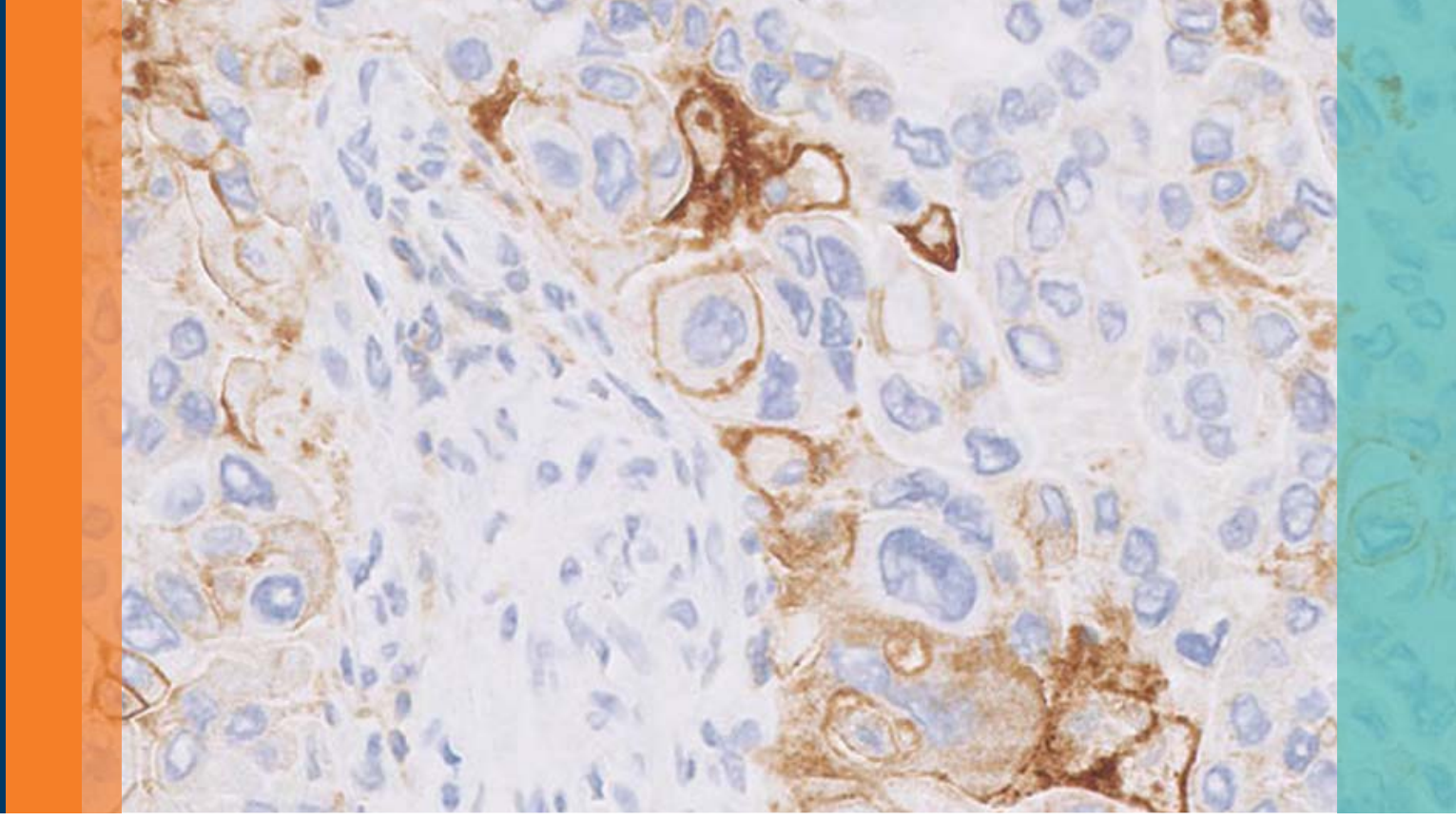


The Art of Pathology

Immerse yourself in the beauty behind the slides



PD-L1 IHC 22C3 pharmDx Combined Positive Score (CPS) Training

3 Remote sessions to choose from:

April 21 | May 17 | June 15 — Time: 1:00 pm - 4:00 pm EDT

The three-hour live training will be led by a pathologist experienced in CPS scoring. It will consist of an introductory lecture on scoring followed by an interactive live-cases walkthrough. The course will include a self-assessment and final test. The objective of the session is to demystify and simplify the CPS approach so that pathologists can be confident in their assay assessment.

Limited seats available.

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Trusted Answers

The answer to the ultimate question – how to prevent and recover from burnout

The other day, an image – uncredited and unsourced – crossed my social media dashboard, asking me a simple question: "How much rest is adequate?" It also offered an answer: "Science says: 42 percent."

A quick search revealed that the claim is from a book by health scientist Emily Nagoski and music professor Amelia Nagoski (1) and is often accompanied by a pie chart that allocates 14 hours of one's day to "work and kids and stuff," leaving 10 hours (or approximately 42 percent) for sleep, recreation, and connecting with others. It also explains that the 42 percent rule is not a choice – you can ignore it for short periods but, in the long term, you disregard it at your peril.

Do you get your 42 percent(ish)? I know I often deprioritize rest and recreation in favor of other things – sometimes to the point where even things I should enjoy begin to seem like chores. Burnout is real and the pressures of the world (from pandemic problems to encroaching wars) aren't making mental health, wellness, and stability easy for anyone.

But who has time to rest? Nagoski continues, "We're not saying you should take 42 percent of your time to rest; we're saying if you don't take the 42 percent, the 42 percent will take you." Perhaps the problem lies in the fact that many of us still view rest as optional. We have work. We have families. We have responsibilities. We assume that those will take as much time as they need – and rest can have whatever is left over.

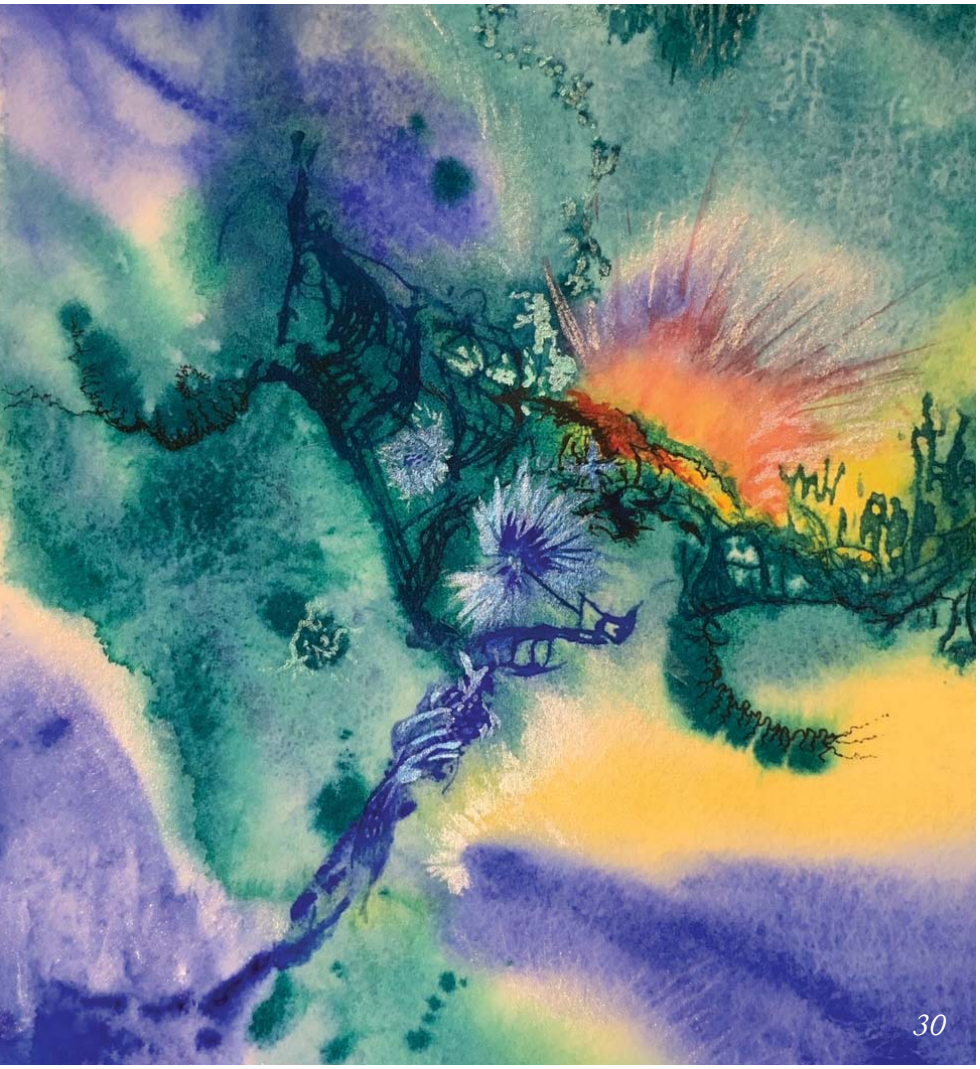
If you're beginning to feel burned out, inventory your days. Are you achieving a balance between rest and responsibility? Could you carve out some extra time for recreation or block off a day on your calendar to focus on things that tend to be overlooked during busier times? That may not always be possible, but it's always worth keeping in mind. Many doctors want their patients to rest and recover – but forgo the same privileges themselves. In a discipline where 35 percent of practitioners report burnout (2), it's vital to focus on staying afloat.

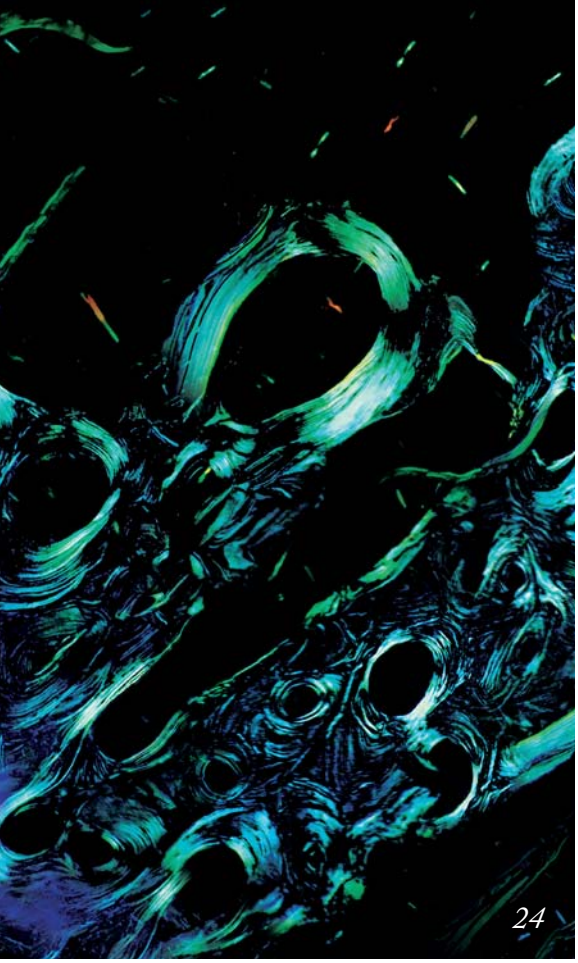
Michael Schubert
Editor

References

1. *E Nagoski, A Nagoski, Burnout: The Secret to Unlocking the Stress Cycle. Ballantine Books: 2019.*
2. *SM Baggett, KL Martin, "Medscape Pathologist Lifestyle, Happiness & Burnout Report 2022" (2022). Available at: https://wb.md/3JBhoWC.*

Contents





Foundations

Profession

Reports

Sitting Down With

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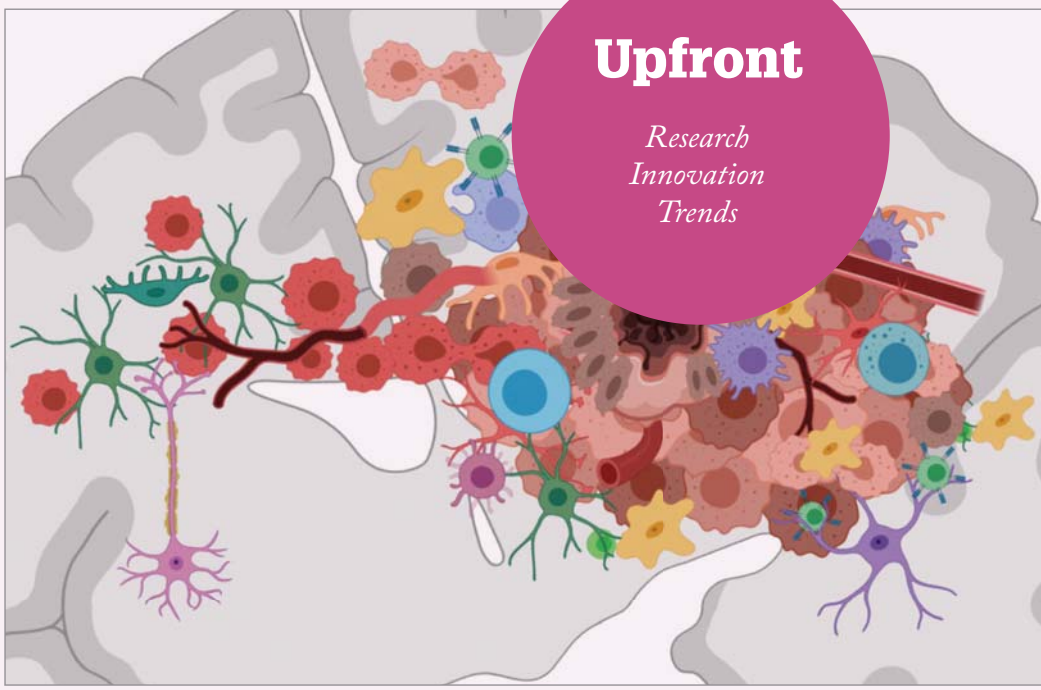
Upfront

Research
Innovation
Trends

The Shapeshifting Cancer

Understanding the heterogeneity and plasticity of glioblastoma



Credit: YA Yabo et al.

Glioblastoma is an aggressive cancer that can form in the brain or spinal cord, with an average survival outlook of 12 to 18 months – even with the wide range of treatments available. Where does the disconnect lie between relentless treatment and survival? It's near impossible to prevent glioblastoma recurrence, meaning that patients face therapy-resistant relapses with a bleak outlook.

Researchers from the NORLUX Neuro-Oncology Laboratory at the Luxembourg Institute of Health (LIH) decided that we can do better. By reviewing recent literature on glioblastoma plasticity and its role in creating heterogeneous cells, they uncovered several reasons these cancers are so good at coming back (1). Some glioblastoma cells carry stem cell properties, allowing the establishment of heterogeneity that can be difficult to overcome. To make matters worse, glioblastoma cells can also change the way they look and function in response to their environment. This plasticity, combined with the recurring nature of the tumors, makes glioblastoma an even deadlier enemy.

"Cellular states interact dynamically with each other and with the surrounding brain to shape a flexible tumor ecosystem, which enables swift adaptation to external pressure, including treatment," explained lead author Yahaya Yabo (2). Therefore, the aim of the literature review was to identify insights into potential new treatments that could target the cancer's plasticity.

The review highlighted the need for a shift in how glioblastoma and other aggressive tumors are treated, but left the door open for exactly which therapies could be effective. "[Glioblastoma] eradication will require targeting the dynamic states rather than single entities," said Simone Niclou, director of the Department of Cancer Research at LIH (2). "Further studies are needed to reveal the drivers of plasticity and treatment escape. These should address which of the changes are fast and reversible, and which are retained in tumors long after treatment."

References

1. *YA Yabo et al., Neuro Oncol, [Online ahead of print] (2021). PMID: 34932099.*
2. *Luxembourg Institute of Health (2022).*

INFOGRAPHIC

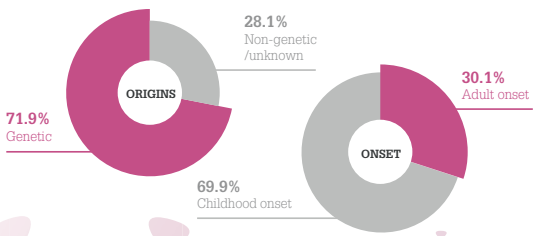
Rare Disease Rundown

A breakdown of the facts in a wide and varied field

1 in **15** people worldwide will be affected by a **RARE DISEASE** (1)

50% of those affected are **CHILDREN** (1)

ORIGINS and **ONSET** of rare diseases (2)



BITESIZE BREAKTHROUGHS

The latest news and research in pathology and laboratory medicine

Benchmarking Exercise

To improve genome sequencing information for diagnosing and treating disease, researchers have used the Genome in a Bottle Consortium's variant benchmark sets to characterize challenging autosomal genes (1). They found that false duplications in GRCh37 or GRCh38 may lead to missed variants for short- and long-read technologies in relevant genes.

Algorithmic Assistance

Researchers have developed a new tool to predict liver cancer risk in hepatitis C patients using only a single test (2). The team used simple algorithms that incorporate post-treatment liver stiffness, albumin levels, and age to accurately identify at-risk patients. The algorithm can also take into account alpha-fetoprotein levels and alcohol consumption.

Vive la Résistance

Like other multicellular organisms, *Trichoplax adhaerens* should be vulnerable to cancer – but no cases have yet been reported. Researchers have investigated the organism's resistance to cancer and found they are able to withstand high levels of radiation damage (3), potentially due to the overexpression of genes involved in DNA repair and apoptosis.

Credit: Oliver Voigt CC BY-SA 3.0

Breaking the Cycle

About 20 percent of patients with human papillomavirus (HPV)-driven oropharyngeal squamous cell carcinoma (OPSCC) experience recurrence within five years of treatment. New research into a circulating cell-free tumor tissue modified HPV DNA test has demonstrated its clinical validity and utility in predicting and identifying recurrent HPV-driven OPSCC (4).

Anticipating Resistance

Researchers have built machine learning models to predict individuals' risk of developing resistance to specific antibiotics (5). By combining data from 140,349 urinary tract infections and 7,365 wound infections with whole-genome sequencing of 1,113 pre- and post-treatment bacterial isolates, they identified alternative susceptibility-matched antibiotics with lower predicted resistance risk.

See references online at: tp.txp.to/bitesz-reasch

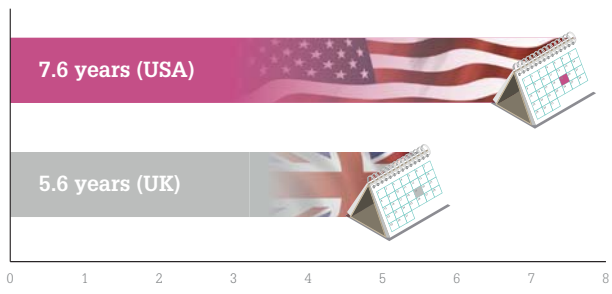
RNA Boost for Childhood Cancer Care

Improving diagnosis and treatment selection for pediatric patients

Mutation analysis in oncology is a fast-growing field, but some mutations – such as gene fusions – are trickier than others. This is not ideal, because gene fusions may play a role in 20 percent of all human cancers (1), and many childhood cancers are characterized by their potential for gene fusions.

Researchers at the Princess Máxima Center for Pediatric Oncology are tackling this issue with whole transcriptome RNA sequencing for every patient – increasing identification of relevant tumor characteristics by almost 40 percent (2). The method successfully identified 83 fusions in 244 patients, 24 of which were missed using routine diagnostic techniques and seven of which modified the original diagnosis or treatment. "We have implemented RNA sequencing into standard diagnostics," said study co-author Bastiaan Tops (3). "Our new study shows that this approach is paying off."

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



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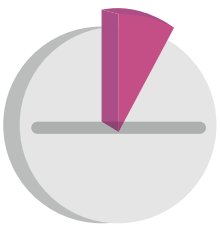
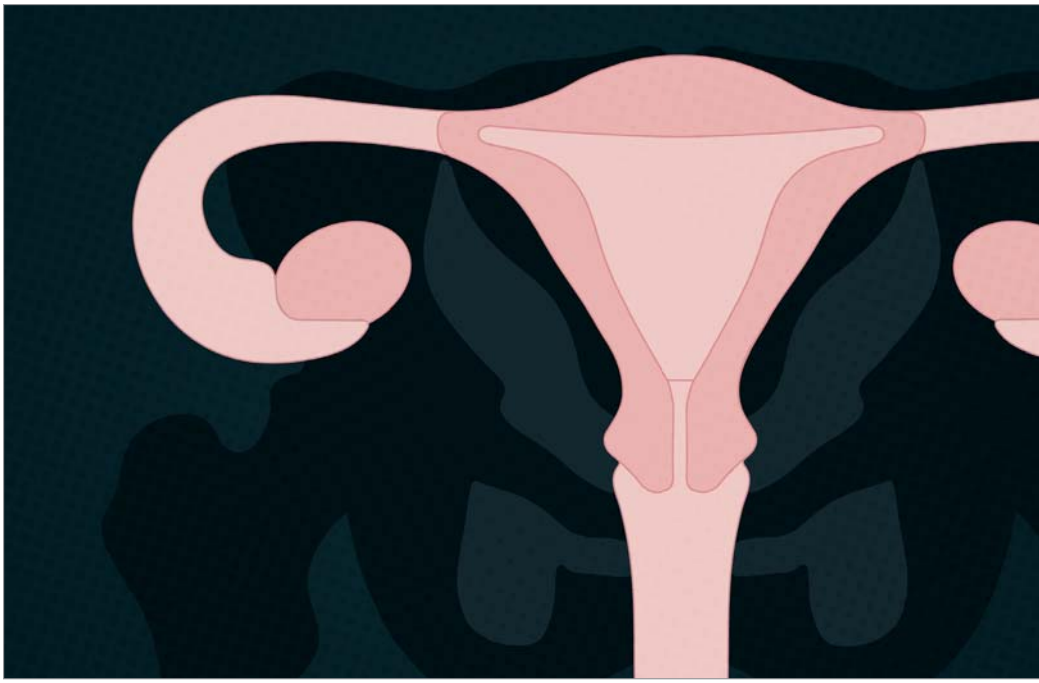


Only **8%** of rare diseases have **APPROVED** or **DESIGNATED TREATMENTS** (4)



Secrets of the Cervical Cells

New indices predict poor prognosis in patients with breast and ovarian cancer

"Cancer development is complex, with both germline genetic and non-genetic influences playing an essential role," says Martin Widschwendter, explaining the inspiration behind two new papers investigating the DNA methylome of cervical cells as a predictor of breast and ovarian cancer prognosis (1,2). "The underlying and principal drive to our work is to develop novel, easy-to-apply primary and secondary cancer preventive measures," he continues. "To achieve this, we need to understand who is at high risk of developing cancer."

In the studies, the researchers developed two indices for predicting risk in breast and ovarian cancer patients. "The Women's Risk Identification for Breast Cancer (WID-BC) and Ovarian Cancer (WID-OC) indices are epigenetic (DNA methylation) signatures in cervical smear samples," explains Widschwendter. "They are based on the combination of DNA methylation levels at several CpG sites. WID indices were derived by comparing DNA methylation in samples from women with and without cancer."

What makes the studies unique is that they selectively included women whose cancers had characteristics already known to be associated with poorer outcomes. "By including women with these types of cancer, we ensured that the WID indices were designed to predict cancers with the worst prognoses," says Widschwendter. "We know that breast cancer is a heterogeneous disease and that some cancers are overdiagnosed – leading to harms associated with overtreatment. By designing our test to identify cancers with the poorest prognoses, we aim to avoid this type of overdiagnosis."

The WID indices have great potential for supporting pathologists and laboratory medicine professionals working in cancer prognostics, which could positively impact patient outcomes. Widschwendter says, "We are hopeful that, in the not-too-distant future, a WID test result derived from a cervical smear sample will afford women the opportunity to understand not only their risk for cervical cancer, but also their risk for endometrial, ovarian, and breast cancer. This will lead to tailored advice regarding primary and secondary preventive measures, and we will continue to work with pathologists and laboratory medicine professionals to achieve these goals. There is also great promise in the WID-test approach to be utilized and delivered in a self-sampling setting.

See references online at: tp.txp.to/cerv-cells

Need for (Diagnostic) Speed

A new DNA sequencing technique can help diagnose patients at record-breaking speeds

How fast is fast? "Rapid" genome sequencing typically takes a few weeks – but researchers have developed a fast DNA sequencing approach that reduces diagnostic time to just a few hours (1). The team achieved a record-breaking sequencing time of five hours and two minutes, and diagnosed the case within seven hours and 18 minutes.

To achieve these super-fast speeds, collaborators from Oxford Nanopore Technologies built a machine made up of 48 flow cells to sequence all the cells simultaneously. Even so, not everything was smooth sailing. To process the data fast enough, the team had to redirect it to a cloud-based storage system that could provide the required computational power and analyze the data in real time. Each genome was then scanned for disease-causing errors and compared against publicly known disease-causing variants, yielding valuable diagnostic and prognostic information.

See references online at: tp.txp.to/diagn-speed

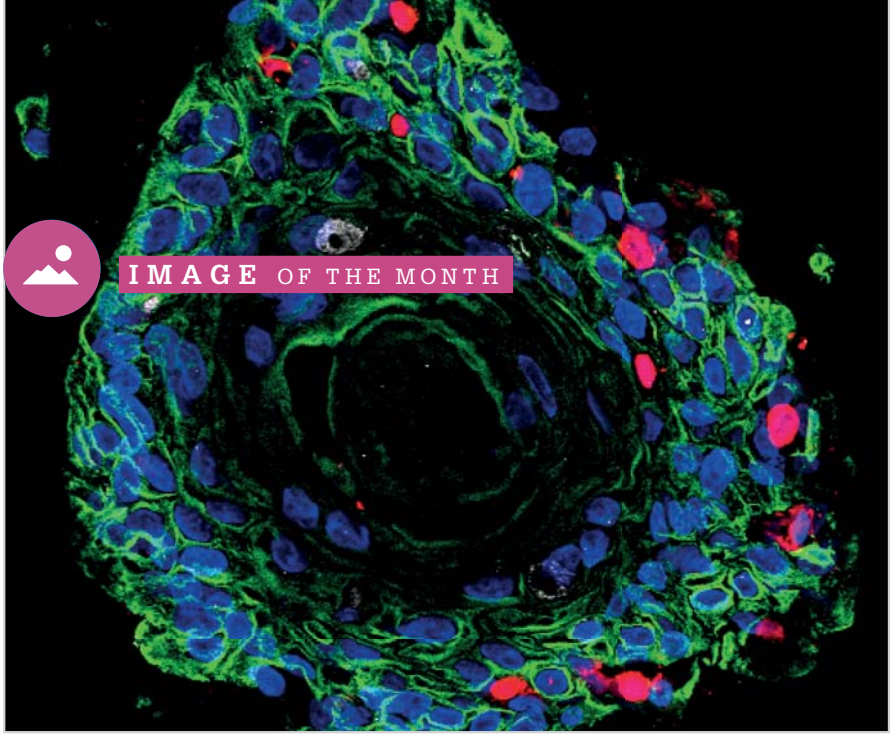


IMAGE OF THE MONTH

Double Trouble

Patients with cervical cancer are often simultaneously infected with human papillomavirus (HPV) and *Chlamydia trachomatis* – a coinfection suspected of adversely affecting the infected cells. Now, researchers have developed 3D organoids to investigate and confirm the coinfection dynamics of HPV16 and chlamydia (1). The image above depicts patient-derived ectocervical stratified squamous organoids (green) infected with *C. trachomatis* (red). Based on their findings, the authors highlight that "co-persistence of HPV and chlamydia in a stem cell could adversely affect cellular and genomic stability and promote neoplastic progression."

Credit: Team Chumduri.

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

QUOTE of the month

"In many European countries, the tradition of teaching pathophysiology as a standalone subject can be traced back to Rudolf Virchow. Elsewhere, it is taught as an integral part of pathology. However it is studied, pathophysiology's central ideas follow Virchow's postulates. In his words, 'The standpoint, which we aim to abide, is a scientific one. Clinical medicine as applied theoretical discipline, theoretical medicine as pathological physiology is the ideal, which we shall strive to realize as far as it is in our power.'"

Zdenko Kovač is Professor of Pathophysiology and Internist at the University of Zagreb School of Medicine, Zagreb, Croatia.

A Better Start to Life

Testing simultaneously screens for three rare genetic disorders in newborns

Infants with Prader-Willi, Angelman, and Dup15q syndromes exhibit varying degrees of behavioral problems, intellectual disability, autism, seizures, and obesity. In Australia, infants are not screened for these rare disorders as part of the standard newborn screening program – leaving many undiagnosed during the first years of life.

Credit: Image from Unsplash.com

To address this need, researchers developed a cost-effective test that can simultaneously screen all three genetic disorders in newborns (1). The test evaluates the methylation levels of the SNRPN gene to distinguish between children with the disorders – who exhibit high methylation levels – and those without. The test yielded high sensitivity, specificity, and positive and negative predictive values for all three disorders – showing that it is possible to use SNRPN methylation analysis to screen for all chromosome 15 imprinting.

Reference

1. *DE Godler et al., JAMA Netw Open, 5, e2141911 (2022). PMID: 34982160.*

CASE OF THE MONTH

Figure 1. A) Initial surgical wound following the first debridement surgery; note the contrast between the injection site and the area of debridement. B,C) Amputated fingertip following subsequent surgical revision; note the dusky necrotic appearance of the fingertip.

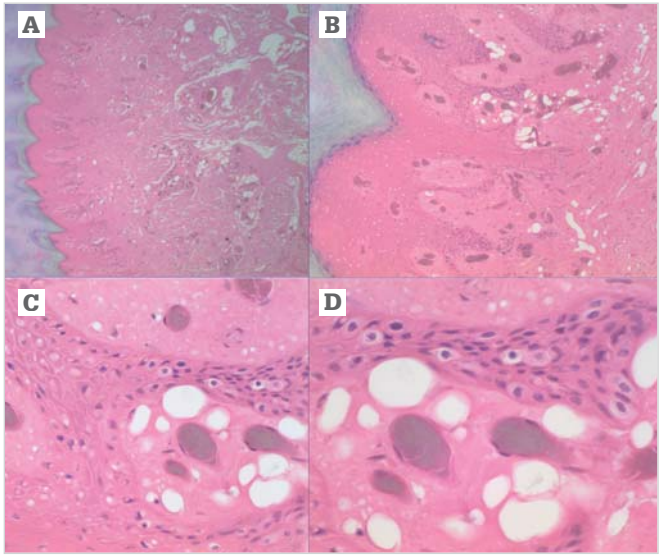


Figure 2. Microscopic images reflecting the extent of injury and the presence of foreign material in the interstitium and intravascular spaces. A) 4x; B) 10x; C) 20x; D) 40x.

A 43-year-old man presented with a puncture injury on the volar surface of the right index fingertip. On examination, there was profuse swelling of the fingertip with dusky skin changes. During operative exploration of the wound, the injury extended down to the flexor tendon sheath (Figure 1A). On further revision, the fingertip was amputated at the distal phalanx (Figure 1B,C). Microscopic examination is shown in in Figure 2.

What is most likely represented in the microscopic images?

a) Ochronotic bodies
b) Tattoo pigmentation
c) Grease
d) Pigment incontinence

Answer to last issue's Case of the Month…

c) Sickle beta-plus thalassemia (Hb Sβ+ thalassemia)

Infants from high-risk ethnic groups are strongly recommended neonatal screening for sickle cell disease because early diagnosis and comprehensive care can markedly reduce morbidity and mortality in early childhood. This newborn's hemoglobin electrophoresis pattern is FSA (in order of relative abundance), indicating the coexistence of sickle cell trait and beta-plus trait and leading to higher production of hemoglobin S than A. Hemoglobin A2 is undetectable or produced at very low levels in newborns, so a lack of elevated Hb A2 is a common finding in beta thalassemia trait. Because of the dominance of hemoglobin F, hemoglobin A can also be insufficient for detection at birth. In other words, sickle beta-plus thalassemia may manifest as FS pattern (as seen in SS, sickle beta-zero thalassemia, or sickle with hereditary persistence of hemoglobin F). If the pattern is FS, it's important to repeat testing in few months or perform molecular studies to make a definitive diagnosis.

Submitted by Ping Sun, Assistant Professor of Pathology, and Daniel Marko, Assistant Professor of Pathology, University of Manitoba, Winnipeg, Manitoba, Canada.

To register your guess, please go to http://tp.txp.to/0422/case-of-the-month
We will reveal the answer in next month's issue!

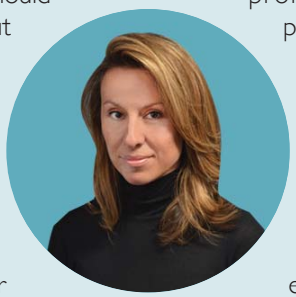
Case of the Month is curated by Anamarija M. Perry, University of Michigan, USA.

In-House Matters

Molecular pathology is complex – and the benefits of keeping it local are extensive

By Nikoletta Sidiropoulos

When it comes to next-generation sequencing (NGS), does it matter whether testing is kept in-house or outsourced to centralized laboratories? You might think not – after all, the results should be the same either way. But genomics is a complex discipline and the discussion is equally nuanced.



At the University of Vermont Health Network's inaugural Genomic Medicine Program and Laboratory, we conduct extensive molecular testing for cancer diagnosis, prognosis, and treatment – and we've found that in-house testing really does make a difference.

The strategic benefits of on-site NGS

Simply put: local practice matters. Healthcare delivery relies on operational models that differ based on location. Incorporating genomic information equitably at the point of care requires a thorough understanding of local practices and systems. A key benefit of investing in an on-site service is having a "champion team" to navigate the local landscape across the laboratory, the clinic, information technology and information services, and leadership. And that's how you build a robust service to support next-generation sequencing (NGS)-based testing.

Additionally, if an organization invests in local NGS with a vision of delivering precision care, it shows forward-thinking leadership, which attracts forward-thinking talent, inspires confidence, and breaks ground with respect to expanding genomic literacy internally and in the regions they serve.

The clinical benefits of on-site NGS

An on-site service, when implemented correctly, provides patients with two key things. First, it gives them a steward of their tissue – an extracorporeal extension of themselves – as it moves through the healthcare system. And second, it builds care pathways that support equitable access to testing when clinically indicated.

Pathology and laboratory medicine professionals are perfectly positioned to establish tissue workflows that optimize successful portfolios of testing on small samples. As a result, on-site genomic professionals who understand the nuances of NGS can educate their healthcare colleagues and champion efforts to establish critical clinical workflows and informatics systems that deliver usable genomic information to the point of care. It's this work that really makes a difference for patients.

The financial benefits of NGS

There is mounting evidence that, when implemented responsibly, genomic information improves healthcare outcomes without increasing the overall cost of care.

There's no denying that insourcing NGS and the professional service it requires is expensive, but classic financial models cannot show the return on investment from such a service – and that's unlikely to change until testing is reimbursed appropriately and reimbursement models account for the value of the service. Nevertheless, it is important to be up-front about resources; the required equipment is an obvious investment, but it's also wise to seek out those with experience to find out what you might not be thinking of. Planning for – and thereby ensuring expertise in – clinical informatics, business planning, project management, test utilization, ancillary interpretation support, and support for longitudinal professional educators is a foundational element often underestimated when insourcing NGS.

Much of the success of genomic testing is measured by i) equitable access to genomically informed care as recommended by professional practice guidelines and ii) return on investment. Controlling healthcare delivery costs rests on the implementation of services – both educational and clinical – supporting NGS-based assays. In my opinion, this is optimally achieved by investing in on-site NGS.

The in-house key

Pathologists and laboratory medicine professionals are uniquely qualified to champion the delivery and service of genomically informed care within a precision medicine ecosystem – especially when they're invested in all of the components of operationalizing in-house NGS. It is incumbent on us to educate about and advocate for the value of the expertise that informs complex assay development and related laboratory workflows. We're also best placed to show that our expertise ultimately anchors and propels healthcare as a whole – and that it's our input that can help build and sustain high-quality services to support NGS assays. In that way, it's the pathologists and laboratory medicine professionals themselves who ultimately drive the undeniable return on investment of in-house NGS.

Nikoletta Sidiropoulos is Associate Professor and Director of Molecular Pathology, Department of Pathology and Laboratory Medicine, University of Vermont Health Network, Burlington, Vermont, USA.

In My View

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

A Light in the Darkness

Spectroscopic liquid biopsy testing – a new route to brain cancer diagnostics

By Matthew J. Baker, Chief Technical Officer and Co-Founder, Dxcover, and Paul Brennan, Reader and Consultant Neurosurgeon, University of Edinburgh, UK

Fast and effective routes to cancer diagnosis have never been more needed. Thanks to COVID-19, hospitals are burdened by a huge backlog of routine procedures. The scale of the impact of the pandemic on hospital care, and in particular on cancer treatment, is now becoming increasingly apparent.

We need innovative strategies to stratify patients' risk of cancer and to prioritize patients for diagnostic investigations – and here's where technologies incorporating high-level artificial intelligence (AI) could play a key role. AI applications in healthcare have progressed rapidly in the past few years and new, innovative ways of implementing AI are starting to make a real difference within diagnostics. These methods are already being used across the world; for example, AI now assists with detecting lung cancer – one of the most common cancers – from CT scans (1).

AI applications also have an important role in supporting the diagnosis of rare cancers, such as brain cancers – a traditionally difficult task. Patients most often present to primary care with nonspecific symptoms indicative of more probable non-cancer diagnoses. Referring every patient for expensive brain scans is neither possible nor cost effective. The best-performing symptom-based referral guidelines for suspected brain tumor only expect to identify a brain tumor approximately 3 percent of the time (2), so developing translatable technology that can be implemented within the clinic to improve triage for brain imaging is a major unmet need. Because smaller tumors are more often and more easily managed surgically, with less harm to the patient, early cancer detection is a key goal for improving patient outcomes.

Spectroscopic liquid biopsy is an innovative strategy for assessing blood samples – and, because it is quick and cost-effective, it could be a major game-changer in the diagnosis of cancer and other diseases. Blood samples are readily available and convenient for patients, so can be ordered earlier than current diagnostic pathways in the investigation of new-onset nonspecific symptoms. The low-cost technology, based on the interaction of infrared light with molecules present in the patient sample, generates a biological signal which can then be classified using an AI algorithm to detect cancer. In the brain tumor population, this allows the detection of disease within a symptomatic population – identifying which patients need urgent imaging and which do not.

Advances in AI have allowed us to maximize the opportunity that computational approaches offer for the detection of cancer and other diseases. If the technology is harnessed appropriately, spectroscopy-based liquid biopsy and AI have the potential to not just triage patients effectively, but ultimately increase survival rates and improve quality of life..

See references online at: tp.txp.to/light-dark

Biospecimen Access for Biotechs

Quality, provenance, and "taking pot luck"

By Robert Hewitt, Founder, Biosample Hub, Carmarthen, UK

The COVID-19 pandemic has demonstrated our reliance on the biotechnology and pharmaceutical industry. Industry R&D has resulted in vaccines and diagnostics that have saved hundreds of thousands of lives. But industry can only do this work if it has access to patient samples; without clinical biospecimens, industry researchers cannot develop new and improved treatments and diagnostics. This principle applies to all human diseases – infectious diseases, cancer, heart disease, stroke, and so on, across the spectrum of human ailments.

Furthermore, these biospecimens must be carefully processed and correctly annotated to yield reliable research results. When we use biospecimens for research, the maxim "garbage in, garbage out" applies (1); samples must be of suitable quality and fit for purpose. For this reason, many hospitals have established professional biobanks or biorepositories. These facilities manage the collection, processing, storage, and distribution of patient samples in a systematic and standardized way – but, because they need significant equipment and dedicated staff, they are expensive to establish and run. And because most of their funding generally comes from allied academic centers, their primary purpose is to support local public sector researchers.

Although industry researchers also need sample access, they have limited access to hospital biobanks. This is a particular problem for biotech companies, which tend to be younger and smaller than other pharmaceutical companies and may not have had time to build networks of hospital contacts for sample supply. Furthermore, unlike pharma companies, they do not run clinical trials and therefore don't have access to the patients and samples that clinical trials provide.

As a result, biotech companies get most of their samples from commercial brokers who work on a commercial basis and need to make a profit to pay shareholders. The main scientific disadvantage of using a broker is that sample traceability, or provenance, is often lacking (2). This is because brokers tend not to reveal their sources for business reasons – but lack of sample provenance results in uncertainty about sample quality and brings into question the reliability of the resulting research.

Biotech companies play a crucial role in the advancement of modern medicine by translating promising ideas into potential therapies, vaccines, and diagnostics. Biotechs are risk-takers and innovators and, increasingly, big pharma depends on them for new opportunities. It seems clear that biotechs should have access to the very best biobanks and biospecimens – but, instead, circumstances often force them to take "pot luck." They may have no option but to use samples without adequate provenance information. This situation is unacceptable – so what can we do to improve it? How can biotech companies access clinical samples with adequate provenance information?

One answer is regulation. The new EU law governing the manufacture of in vitro diagnostic devices provides an example. This regulation is the IVDR, and it requires the makers of IVDs to use acceptable samples to validate their devices (3). For biosamples to be acceptable, they must come from biobanks that meet defined quality standards. Consequently, the IVDR will pressure commercial brokers to change their business practices and reveal the origin of their samples. One-way brokers sometimes do this is by including non-circumvention agreements in their contracts.

Another answer is government funding (4). For example, the award of biobank grants could be conditional on service to industry. It could also be dependent on the availability of sample access policies and annual reports on sample distribution. Furthermore, industry representatives could be a requirement for sample access committees. Patient representatives are well accepted, so why not industry representatives?

Another possible answer is a change in attitude. Might this be one positive consequence of the pandemic? The pandemic has demonstrated our reliance on the biotechnology and pharmaceutical industry. It has also shown that their products can be lifesaving. Will this influence the decisions of policymakers and grant agencies when it comes to determining hospital biobank access? We can only hope so.

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2. *P Hofman et al., "Point of View: Traceability and Transparency Should be Mandatory for All Human Biospecimens" (2017). Available at: https://bit.ly/3BLMmX2.*
3. *G Dagher et al., "Pre-analytical processes in medical diagnostics: New regulatory requirements and standards," N Biotechnol, 52, 121 (2019). PMID: 31102798.*
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Harnessing the Diagnostic Data Revolution

Rethinking our approaches to diagnosis and information management in the 21st century

By David Wells, Chief Executive of the Institute of Biomedical Science and Scientific Lead for Pathology – London Region at NHS England, London, UK

Accurate and timely diagnosis sits at the heart of patient care. And yet, despite myriad advances in our medical knowledge and systems, the perennial problem with diagnoses is the same as it ever was – human nature. We put off calling our doctors for as long as we can, producing every excuse under the sun. Put bluntly, humans are the first point of failure in our health system.

But this need no longer be true. Pathologists can lead a data-driven revolution that will bring health systems firmly into the 21st century, transforming patient outcomes globally via world-class interoperable diagnostics and data workflows. Using data-rich laboratory information management systems (LIMS), pathologists can reshape healthcare with patients firmly at the center of models of care.

Briefly consider these questions:

- What if our diagnostic and clinical systems were entirely flipped?
- What if your primary care provider developed a data-driven preventative care plan to keep you healthy and active before illness struck?
- What if your clinician identified your personalized risk profile based on your integrated pathology and fitness app history?
- And what if we ride the coattails of COVID-19's lightning-fast innovation momentum to deliver all of this within the next three years?

As pathologists, we are uniquely positioned to lead this dramatic change. LIMS are at the forefront of large-scale improvements to patient flow across disparate disciplines and vast geographies. Innovative diagnosticians are already collaborating with clinicians across the traditional organizational silos throughout labs, hospitals, and trusts to deliver a higher quality of care that is increasingly integrated and multidisciplinary.

Mature pathology and radiology networks are successfully incorporating the fast-growing plethora of clinical AI apps, giving trusts access to more predictive analytics and putting more personalized care within reach.

Recently, NHS England announced new requirements to share results across previously rigid healthcare settings and organizational boundaries. To ensure future-proofed interoperability across their countrywide pathology network, NHS Wales scoured the globe before selecting a LIMS that has, over three decades, proven extraordinarily successful at aggregating diagnostic services and delivering equitable patient access over vast geographies in Australia. But to truly move diagnostics forward, we need to close the feedback loop and show clinicians the longer-term effectiveness of their recommendations on patient outcomes. We must accelerate the adoption of scalable data and interoperability standards, continually evolving virtual lab management to orchestrate data across patient journey settings.

So how do we drive the necessary pace of change? The pandemic proved that, where there is a will, there is a way. Specifically, it proved that high-quality healthcare system change can be rapidly delivered. The UK has exponentially grown its molecular diagnostic capability – from processing 300,000 molecular microbiology tests per year in England to performing more than that number in just one day for SARS-CoV-2.

In the early years of my career, we brought in troponin as a protein marker for heart attacks. This transformative blood test saves lives and is now the de facto diagnostic, but it took 14 years to become universally available because the NHS did not plan holistically or act collectively with urgency. But the decisions back then were driven by money and departmental budgeting, rather than by patient need. In contrast, when it came time to roll out the COVID-19 antibody test countrywide, we did so in just two weeks. Harnessing this can-do attitude and maintaining this appetite for collaboration across organizations, disciplines, and trusts could swiftly transform diagnostic networks on a national scale. There is already enough diagnostic patient data across radiology and pathology systems to provide life-saving patient insight. Unlocking the potential of this data and better integrating the information at our fingertips could prioritize patients appropriately, connecting them with the best clinicians for their needs.

Going further, plugging a clinical AI into this process could identify correlations of concern between image

reporting and test results, helping clinicians optimize treatment plans based on similar patient cohorts.

By supporting clinicians with patient insight drawn from historical and real-time data, we can accelerate diagnosis, reduce the need for intervention, and keep more people healthy in the long run. For example, lung cancer is often only identified in a patient after they present in the middle of the night with shortness of breath. Clinicians will send the patient for tests, leading to consultant visits and hospital treatment with varying degrees of success. Yet proactive blood tests for at-risk patients could identify lung cancer before the disease has spread, vastly improving the prospects of a positive outcome.

More accurate and integrated diagnostics could serve as an early alarm for future pandemics or help uncover previously unknown genetic links to chronic conditions. Interconnecting wearable technology, mobile apps, or home cameras could even help predict mental health issues or the potential for falls based upon movement, gait analysis, or other indicators. The richness of data collected and analyzed from laboratory, radiology, and therapeutic systems, alongside the wealth of personal device data, would mean any change in patient pathways could be quickly identified and the most appropriate treatments and actions implemented.

One setting where this could be particularly useful is among our aging population. We can extend our diagnostic capability beyond healthcare – particularly into social and aged care, where slips, trips, and falls are the primary reason older people are brought to emergency rooms, shortening their lives and costing the NHS England £435 million every year.

The possibilities of better health data sharing are endless, as is the potential for better patient outcomes and a more sustainable, proactive healthcare system. Yes, we'll need a new approach to determining who can access patients' health data. But if you'd like better outcomes with more personalized treatment pathways, lowered healthcare costs, and better clinical teams, you can simply call the challenges the price of admission.

So what's next? It's time to build a coalition of the willing, rallying those armed with the revolutionary potential of a fully integrated LIMS and eager to be at the vanguard of change to embrace a proactive diagnostic system worthy of a 21st-century healthcare system and all those who rely upon it.

Diversity, Equity, and Inclusion in the Laboratory

The lab is in the spotlight – but it's our job to use that attention for good

By E. Blair Holladay

Fostering an environment that accepts individual differences – whether gender, race, age, ethnicity, or religion – is essential to building a laboratory workforce that is not only sustainable, but truly able to deliver the high-quality care all patients deserve.

Diversity, equity, and inclusion efforts have been rising over the past two years. Never have these three words been so important in healthcare. Now that deep inequities have been exposed, patients are demanding – and deserve – equal access and care. For the American Society for Clinical Pathology, an ethos of diversity, equity, and inclusion has been part of our core tenets for many years and continues to drive how we advocate on behalf of pathology and laboratory medicine, as well as the resources we develop to ensure that patients are receiving the best possible care.

Although the work we do to help develop and sustain a diverse pathology and laboratory workforce is critical, it's important to understand the "why" behind this drive. ASCP doesn't pursue diversity, equity, and inclusion efforts simply to check a box. To do so would be doing pathology and laboratory medicine a grave disservice. Diversity, equity, and inclusion are central to our identity because we recognize that the patients we serve represent every demographic of the population – and the laboratory touches each and every patient who receives care. We can provide better healthcare outcomes when our workforce looks like the communities and populations it serves.

We also recognize that there is strength in diversity. A diverse workforce provides a sense of belonging and acceptance. It allows people to share ideas and innovate, which can increase employee retention and morale and create a stronger team. When pathologists and medical laboratory scientists feel seen and accepted by their employers, that translates to better patient care. A lack of diversity, however, can be detrimental to relationships with not only patients, but also other members of the healthcare team.

Conversations around diversity, equity, and inclusion are only just getting started – and there is still much work to be done. These are challenging conversations, but not ones from which the pathology and laboratory medicine can shy away. As the cornerstone of healthcare, it is up to us to lead by example and to foster relationships with underserved and underrepresented communities. It is up to us to leverage these relationships to strengthen our pipeline and develop the workforce we need – now and in the future.

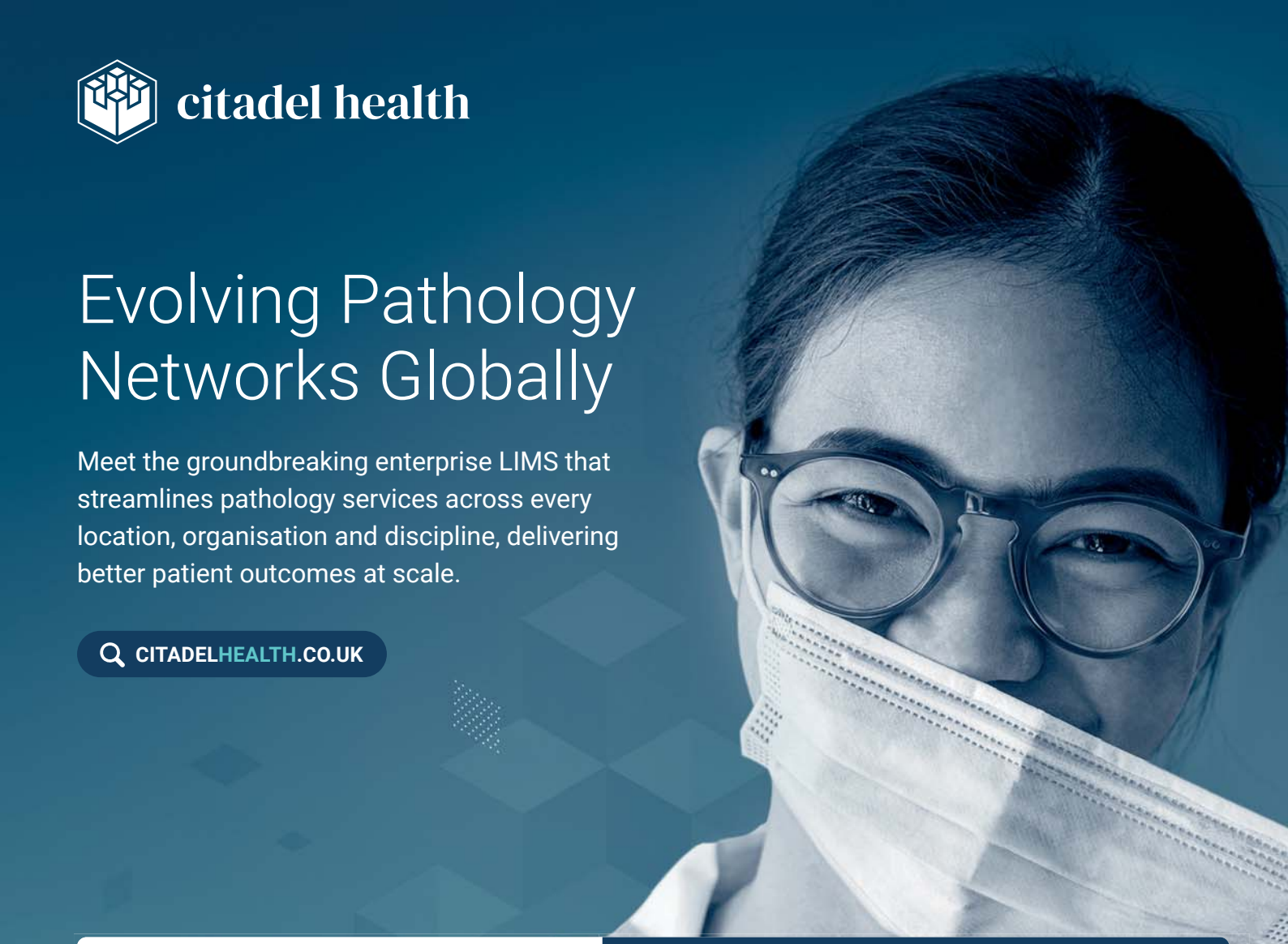
Embracing our differences, rather than letting them divide us; leveraging the knowledge we have; and putting diversity, equity, and inclusion into action will further the laboratory as a leader in healthcare. When we do this, we do better not only for our profession, but also for our patients.

citadel health

Evolving Pathology Networks Globally

Meet the groundbreaking enterprise LIMS that streamlines pathology services across every location, organisation and discipline, delivering better patient outcomes at scale.

CITADELHEALTH.CO.UK



Enterprise LIMS

Evolution vLab

Gain a single view of pathology workflows to transform decisions, lab operations and quality at scale.

Feature sets:

- Innovative multi-site pathology workflows
- Intelligent analytics & clinical reporting
- Highly secure, single database solution
- Configurable features to adapt faster

A Connected Clinical Suite Advantage

Our clinical software suite gives every clinician the tools they need to connect, collaborate and improve patient pathways, wherever they work best.

Comprehensive Genomic Profiling – A New Look

In an ideal world, all cancer patients would benefit from personalized therapy – and all personalized therapy matching would be guided by comprehensive, reimbursed, genomic profiling tests. How close are we to this ideal?

Increased understanding of the molecular drivers of disease allows us to offer targeted therapy to patients with disease-associated molecular variants. But for personalized cancer care to reach its full potential – in terms of both global reach and individual patient impact – we need genomic profiling technology that can detect key variants and improve outcomes by directing management. It's this need that underlies Illumina's CE-marked IVD TruSight™ Oncology Comprehensive (TSO Comprehensive) test for solid tumor profiling. We spoke with Phil Febbo, Chief Medical Officer at Illumina, about how this unique technology will maximize information for pathologists – and help drive better patient outcomes.

Advantages of CGP over iterative single-biomarker and small panel tests

Laboratories:
- Reduces turnaround time
- Spares biopsy material
- Improves operational efficiency
- Provides more actionable information to guide therapy

Patients:
- More likely to receive genomically matched or targeted therapy
- Potential improvement in outcomes

Optimal clinical content

The advantages of the comprehensive genomic profiling (CGP) approach (Sidebar 1) are clear. First, pathologists no longer need to constantly update gene panels or collate results from various individual gene tests – simplifying planning and saving time. Second, CGP generates a comprehensive profile from a single specimen, using less tissue than alternative options that require more tissue for each sequential assay or panel (1,2). "Almost 30 percent of advanced lung cancer patients lack sufficient tissue for serial molecular tests," says Febbo, emphasizing the importance of tissue preservation. Furthermore, the CGP approach improves efficiency, because laboratory personnel and validation procedures focus on a single platform. Finally, comprehensive biomarker coverage for both DNA and RNA variants increases the probability of generating actionable findings (3,4). These attributes clearly optimize disease management.

Informing therapeutic choices

Patients often do best when their therapy targets genetic variants matched with their individual tumor. That's why it's critical to employ CGP technology that can detect relevant variants – not just tumor-specific markers, but also tumor-agnostic markers such as microsatellite instability (MSI), tumor mutational burden (TMB), and *NTRK* fusions (5,6).

TSO Comprehensive has been designed with these requirements in mind. This future-proofed, sample-to-answer CGP solution covers predictive markers specified by NCCN guidelines. Using Illumina's highly sensitive hybrid capture-based technology, it can interrogate both DNA and RNA variants associated with over 500 genes, detecting insertions, deletions, single nucleotide variants, amplifications, fusions, and splice variants. "This helps maximize detection of actionable alterations, including low-prevalence variants that are peripheral to or outside protein coding regions," says Febbo. Importantly, TSO Comprehensive allows detection of TMB and MSI – important pan-cancer biomarkers for immunotherapy so patients who might benefit from these transformative therapies can be identified. In addition, its RNA capabilities allow TSO Comprehensive to identify more fusions than methods that interrogate only DNA. Febbo adds, "Given the impressive responses seen when we target *NTRK* and similar fusions, I would demand a technology that can reliably detect these variants. Just as we do not want to miss any patient who can benefit from immunotherapy, we cannot miss any patient who has a targetable fusion such as *NTRK*, given the remarkable outcomes experienced." To ensure that more and more patients can potentially benefit from these promising therapies, the knowledge base for TSO Comprehensive is continuously updated as new biomarkers are identified, assuring pathologists of continued state-of-the-art coverage.

Finally, the TSO Comprehensive roadmap begins to address economic challenges associated with CGP: namely, larger test panels are not fully reimbursed and healthcare institutions consequently have to subsidize genomic analysis for the good of their patients. By working with pharmaceutical partners to validate TSO Comprehensive for the addition of future companion diagnostic claims to the test, Illumina is establishing broad clinical utility for the technology. "This de-risks reimbursement," says Febbo.

illumina

On-site testing delivers more advantages than just speed

TSO Comprehensive is a kit-based IVD test and thus permits in-house implementation of CGP, so the test can be performed closer to the clinicians who will make therapy decisions. Tissue samples don't need to leave the pathology department, reducing turnaround times (7) and facilitating follow-on assays. This, in turn, enables rapid development of treatment recommendations – essential for late-stage patients.

But the benefits of this approach are not limited to speed. First, in addition to a final clinical report, all other data files containing variant and genomic information about the sample, are made available to the hospital, supporting additional studies and empowering generation of databases that can be used to help inform the care of other patients. Similarly, performing CGP on-site enables stronger stewardship of patient samples, which enables efficient case triage and compliance with requests for additional tissue. Finally, in-house CGP fosters strong links between pathologists and clinicians. "Increasingly, molecular pathologists are part of the care team in cancer," Febbo reports. "When that happens, more patients who have a targetable variant identified get a genomically matched therapy." Indeed, hospitals now commonly form multidisciplinary tumor boards in which oncologists, pathologists, and staff collaborate to discuss treatment options for each patient. Here, oncologists learn about the impact of gene mutations on prognosis or therapy and pathologists become more involved in disease management.

Overall, in-house CGP brings testing closer to the patient, encourages closer integration between molecular pathologists and oncologists (Sidebar 2), and uses genomic profiling results to inform therapy choice. In this way, solutions such as TSO Comprehensive contribute to the ongoing major transformation in oncology: the broad adoption of genomic tests – exemplified by the incorporation of molecular markers into the American Joint Committee on Cancer classification system.

Looking ahead

Illumina believes that genomic profiling tests will become increasingly integral to patient healthcare. TSO Comprehensive is a key component of this vision because it permits in-house testing of a broad range of cancer-relevant markers and genomic signatures to inform treatment decisions in patient care, which may lead to better clinical outcomes. The comprehensive biomarker content of the test has also attracted interest from multiple pharma companies, such as Bayer AG and Eli Lilly that offer groundbreaking cancer therapies. Illumina has established partnerships to add Companion Diagnostic claims to the test over time.

The impact of cancer genomics is not limited to guiding treatment. "It will contribute to a massive shift of clinical focus towards early-stage disease," Febbo asserts. "Multi cancer early detection (MCED) tests, based on cell-free DNA, can identify patients in the first stages of cancer; when detected, detailed assessment of tumor genomics will suggest optimal disease management strategies." Finally, post-treatment monitoring for minimal residual disease or recurrence is already leveraging genomics and the number of cancers for which these tests improve management will increase dramatically over the next few years. "It is our hope that blood-based tests detecting residual disease or progressing disease will be ordered in conjunction with radiology in this setting. Instead of a paradigm of 'scan, then use a genomic test,' the paradigm will be 'test, then scan.'"

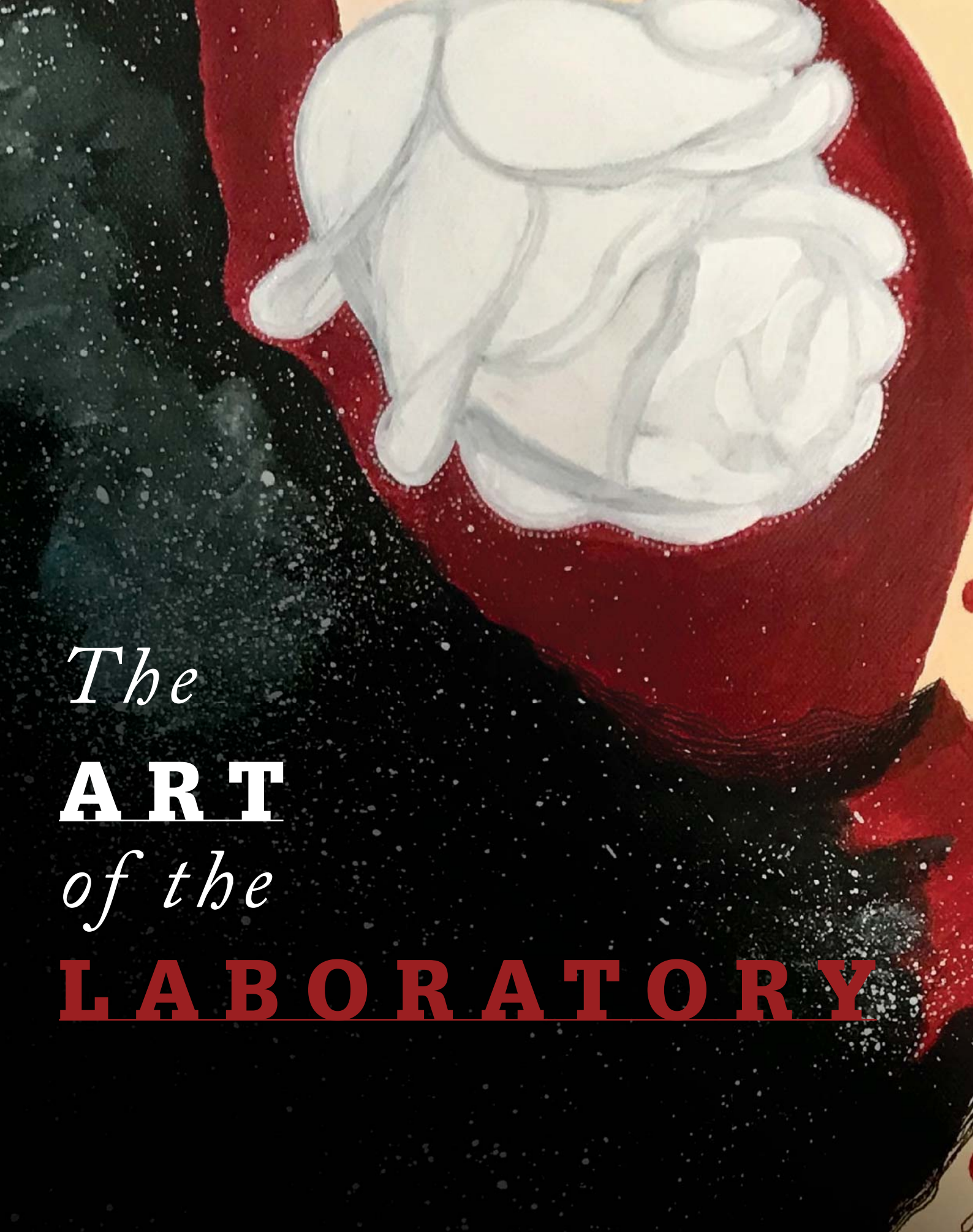
Performing CGP will allow realization of the promise of personalized cancer care. Adopting TSO Comprehensive in routine diagnostic workflows will allow pathologists to rapidly generate more complete, actionable results that can help improve patient outcomes. The approach is part of a larger organizational shift that will see molecular pathologists becoming increasingly essential to the care team. This will benefit all team members – with the patients being the biggest winners.

How TSO Comprehensive supports pathologists

- Provides insights to help inform therapy decisions according to clinical guidelines
- Detects full spectrum of genomic variant types in a single test, avoiding delays associated with serial testing, to accelerate clinical decisions
- Consolidates the pathology workflow into a single, comprehensive test and single report
- Brings CGP on site, giving pathologists control over the entire workflow from sample receipt to report delivery
- Enables pathologists to become more involved in patient care and treatment decisions

For in vitro diagnostic use. Not available in all Countries or Geographies.

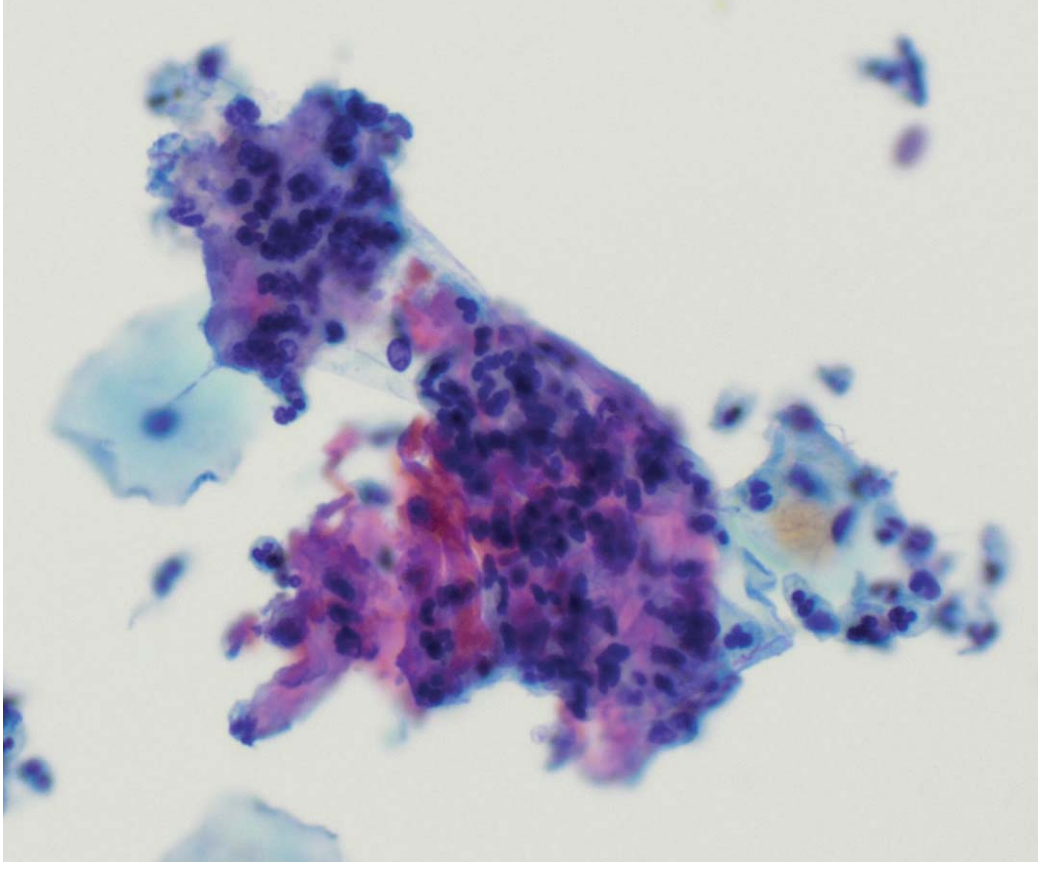
See references online at tp.txp.to/Comp_Genom


The
ART
of the
LABORATORY

The Bond of Love

This art was a recent commission for a kidney pathologist as a present from his cardiologist wife.

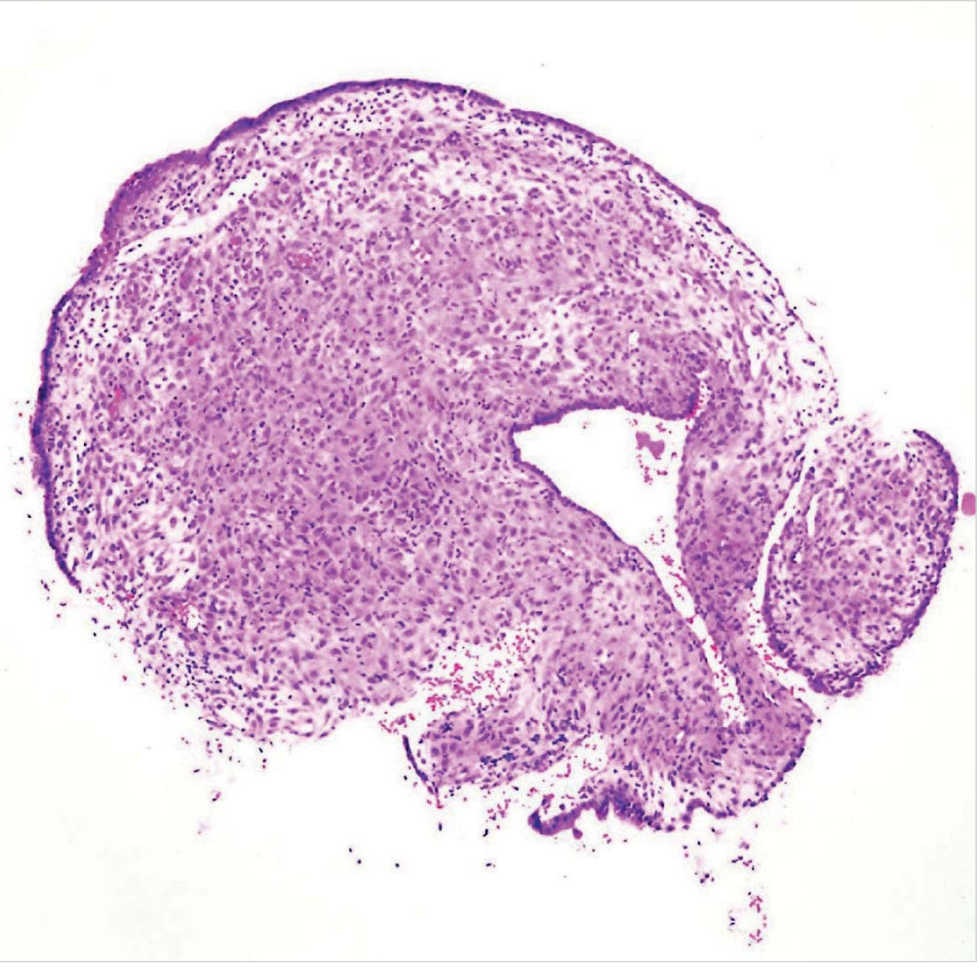
Maaia Jentus, Medical University of Vienna, Austria

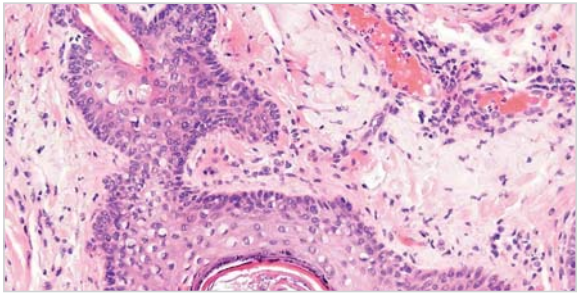


Lazy Goat

Right: When you're trying to screen slides, but pareidolia takes over...

Mercia Locke, Cytotechnologist, Southern Arizona VA Health Care System, Tucson, Arizona, USA





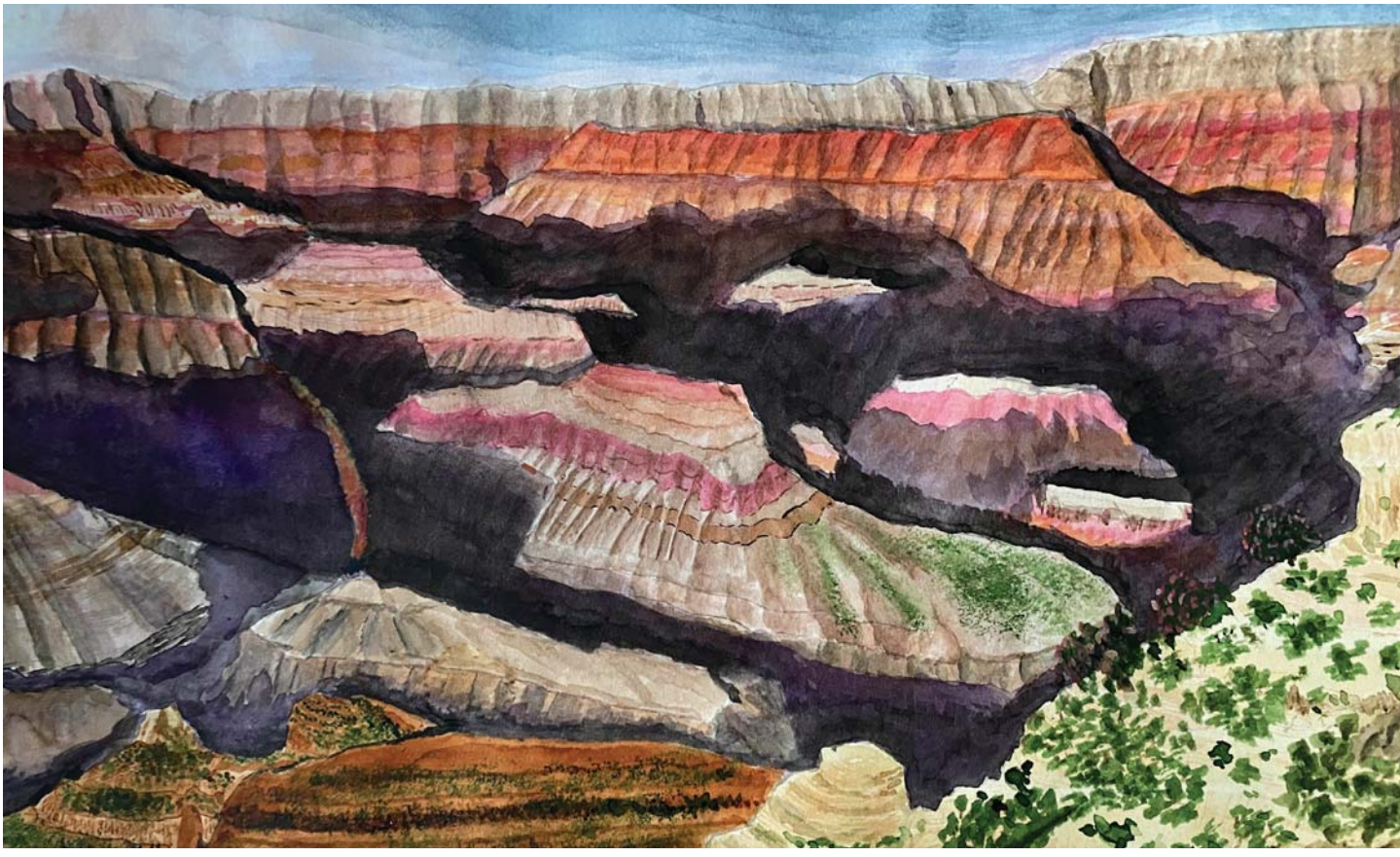
Barking Dogs Seldom Bite

Above: A hair follicle in the histologic section of a skin biopsy specimen Looks like a barking dog

O Lord, Grant Us Your Peace

Left: A histologic section of a small piece of decidual tissue in an endometrial curettage specimen looks like a lady praying in a prostrate position.

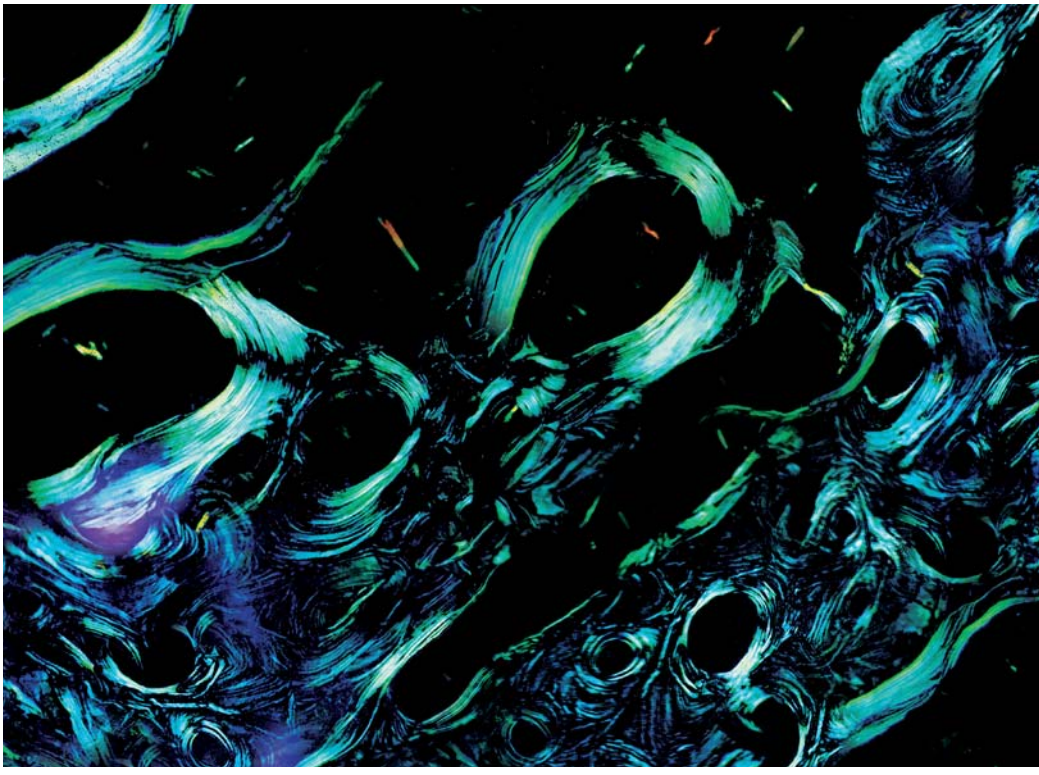
Jagmohan S. Sidhu, Medical Director and Chairman, Department of Pathology and Laboratory Medicine, United Health Services Hospitals-Wilson Medical Center/ Binghamton General Hospital, Johnson City/Binghamton, New York, USA



Pandemic Paintings

At the Hospital for Special Surgery, we were lucky enough to be able to use whole-slide imager (with FDA approval) to do at least some of our signout work from home. Nonetheless, the pandemic definitely increased my reading time and my bread-baking skills. For me, however, a return to painting watercolors after a 40-year break has been a good distraction. I am not too good at artwork, but I have learned enough to know that, when interpersonal contact comes back and I'm less paranoid about getting a breakthrough case, I'm going to invest in lessons from someone who knows how to paint a bit better than I do!

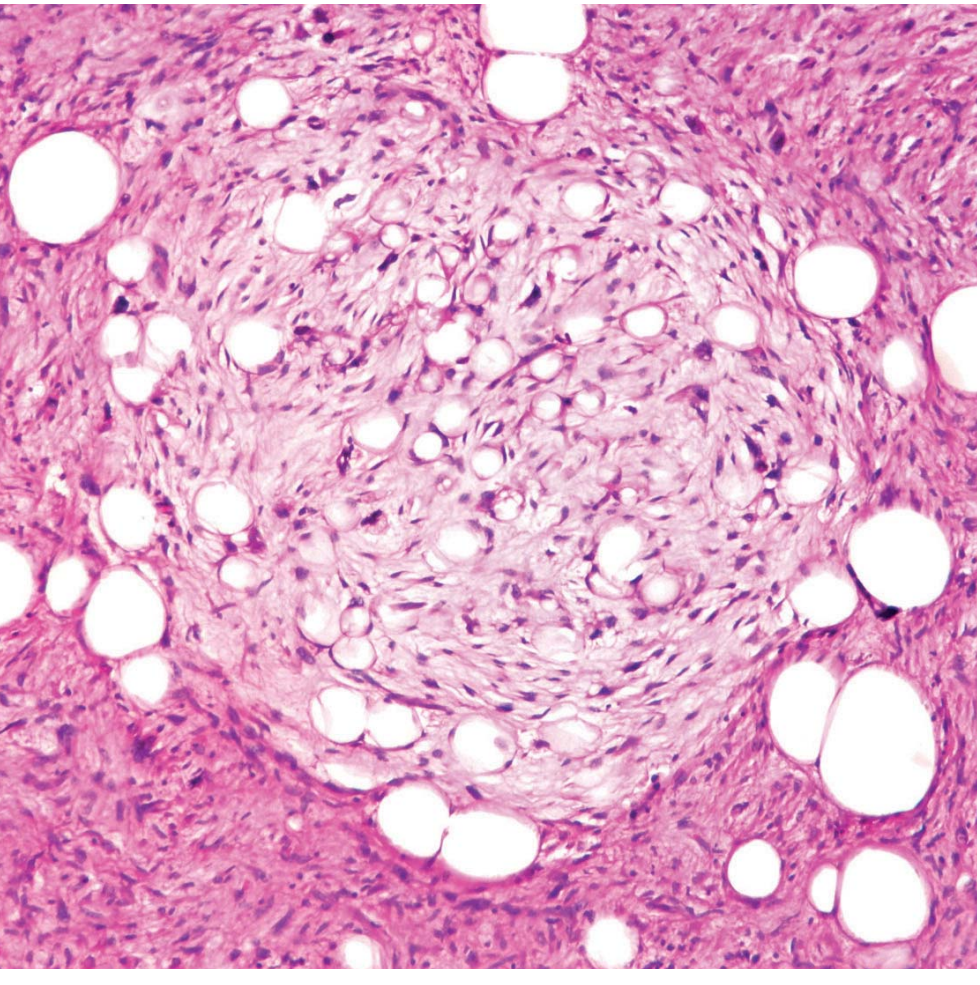
Michael J. Klein, Professor of Pathology and Laboratory Medicine at Weill-Cornell College of Medicine and Pathologist in Chief Emeritus at the Hospital for Special Surgery, New York, USA

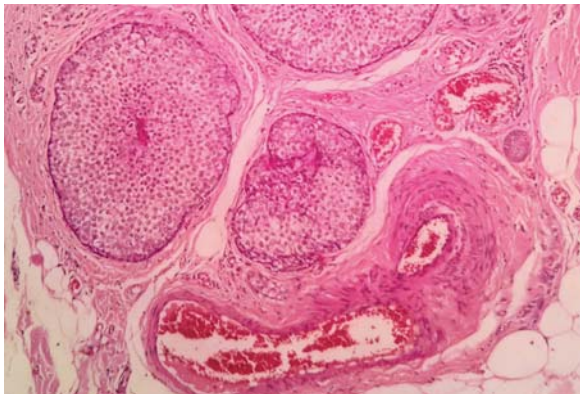


Another World

Right: Digital manipulation of amyloid deposits visualized by polarized light microscopy.

Dana Razzano, Yale School of Medicine, New Haven, Connecticut, USA





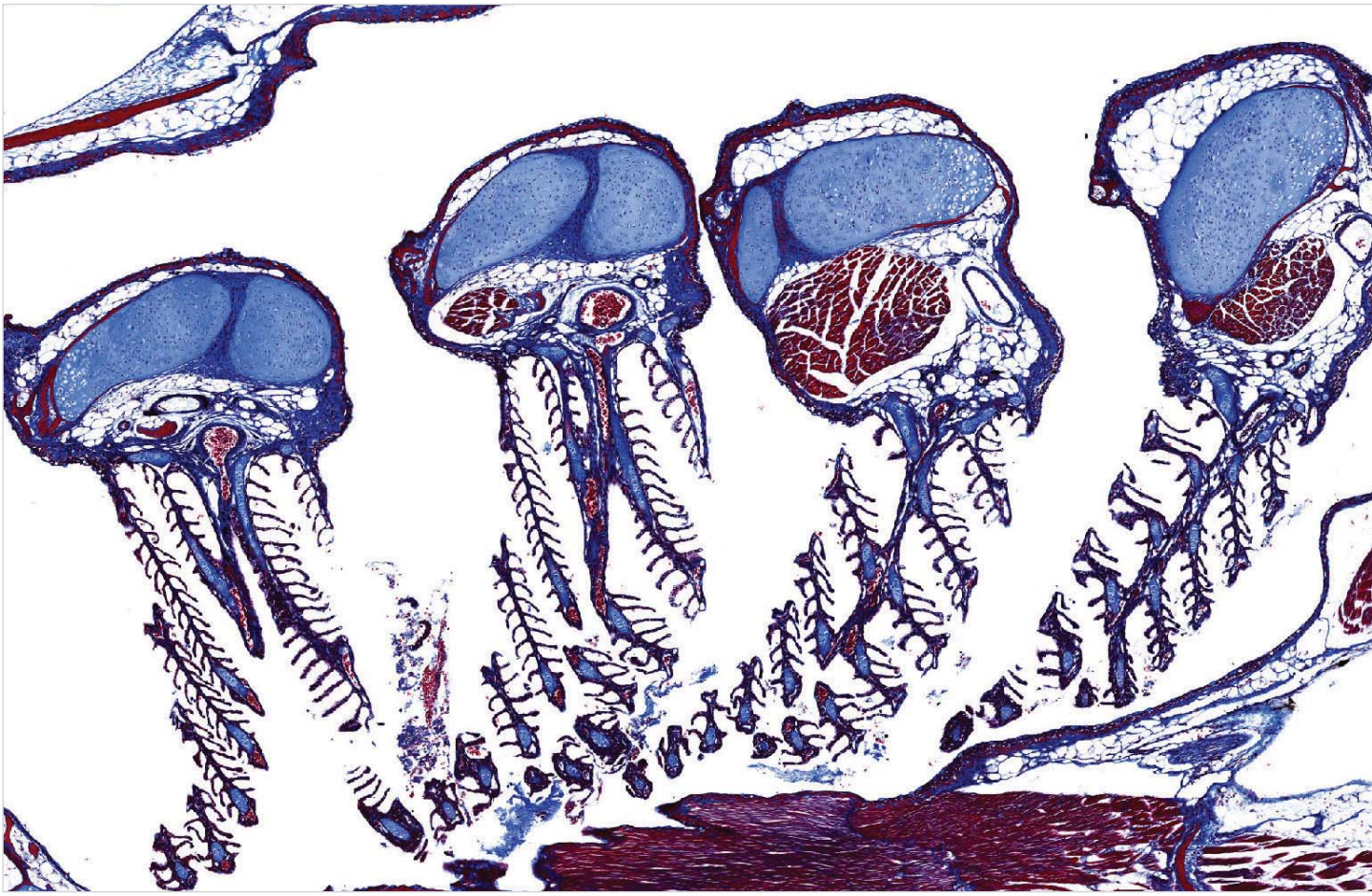
Malevolent Clown

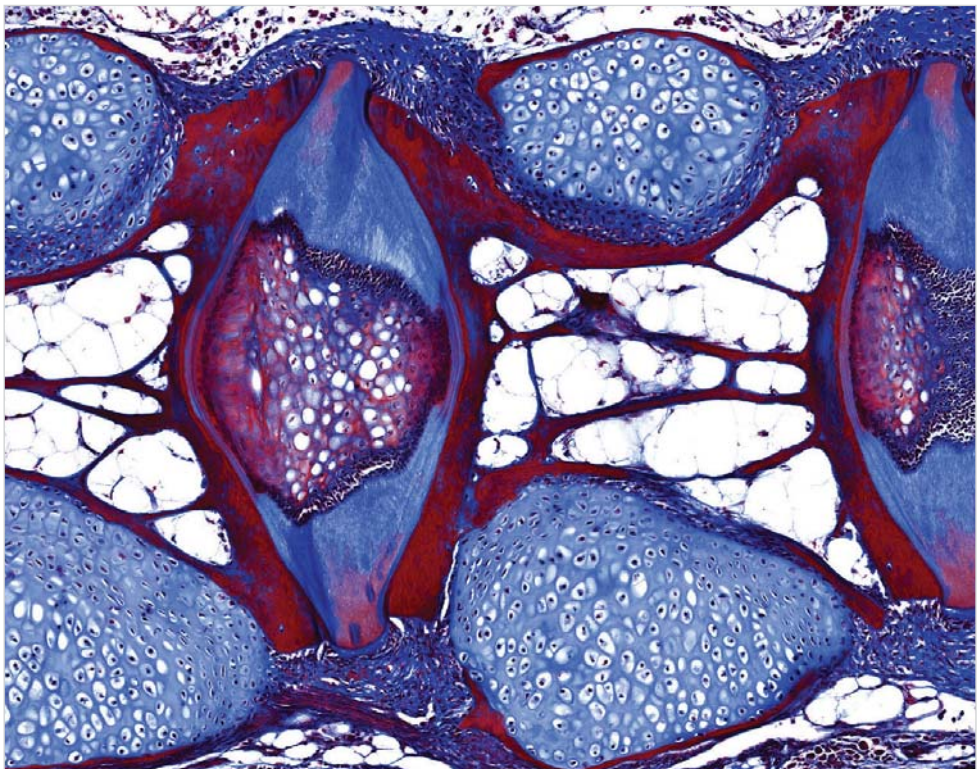
Above: Picture from a surgical piece with breast ductal carcinoma. (Histology technicians: G. Arteaga and P. Arteaga.)

Supernova

Left: Picture from a chest tumor: pleomorphic liposarcoma. (Histology technicians: G. Arteaga and P. Arteaga.)

Gabriel Arismendi-Morillo, Pathologist, Professor, and Researcher, Electron Microscopy Laboratory, Biological Researches Institute, Faculty of Medicine, University of Zulia, Maracaibo, Venezuela





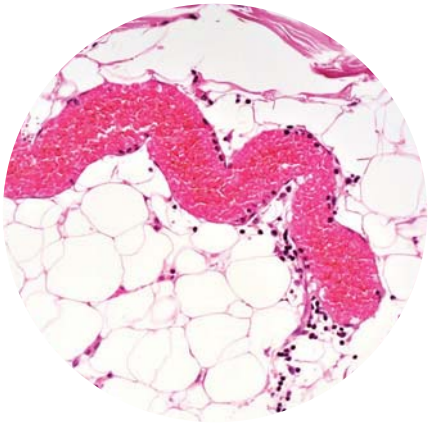
Medusa Fish Gills

Top: Fish gills look like jellyfish during the medusa phase; stained using Masson's trichrome protocol. By Frazer Bell, Lynn Stevenson, Lynn Oxford, and Jan Duncan.

Stained Glass Fish Spine

Bottom: A magnified look into the spine of a fish – almost like a stained glass window. By Frazer Bell, Lynn Stevenson, Lynn Oxford, and Jan Duncan.

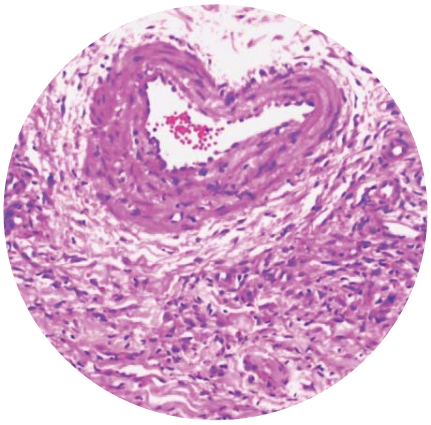
Frazer Bell, Histopathology Technician, Veterinary Diagnostic Services, University of Glasgow, Scotland, UK



Snake Vessel

Adipose tissue and a snake-shaped blood vessel.

Alicia Rumayor Piña, Dentistry School, Autonomous University of Coahuila, Saltillo, Coahuila, Mexico



Message from the Heart

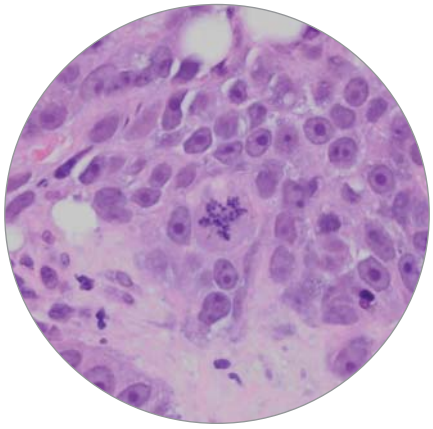
An incidental finding from an affectionate specimen. Taken using the InfinityCapture system.

Inny Busmanis, Senior Consultant Pathologist, Singapore General Hospital, Singapore

Flying Bird

An image taken from ThinPrep preparation of a fine needle aspiration biopsy of a thyroid nodule.

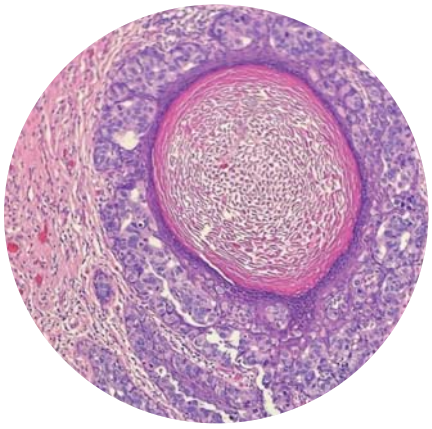
Nusaiba Alrefae, Cytopathology Unit, Sabah Hospital, Kuwait



Star Mit, Star Bright

A uniquely shaped mitosis in a triple-negative breast cancer.

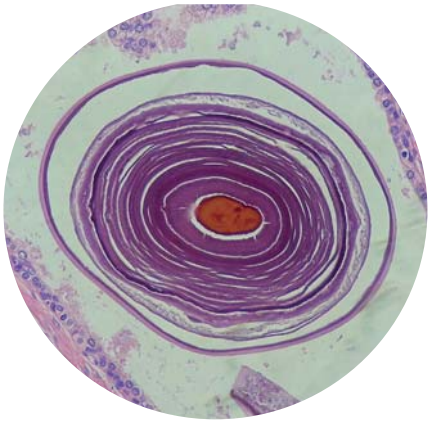
Nika Gloyeske, Clinical Assistant Professor, Pathology and Laboratory Medicine, The University of Kansas Health System, Kansas City, Kansas, USA



Breast Disease

Lactiferous duct with DCIS and florid secondary Paget's disease in the breast.

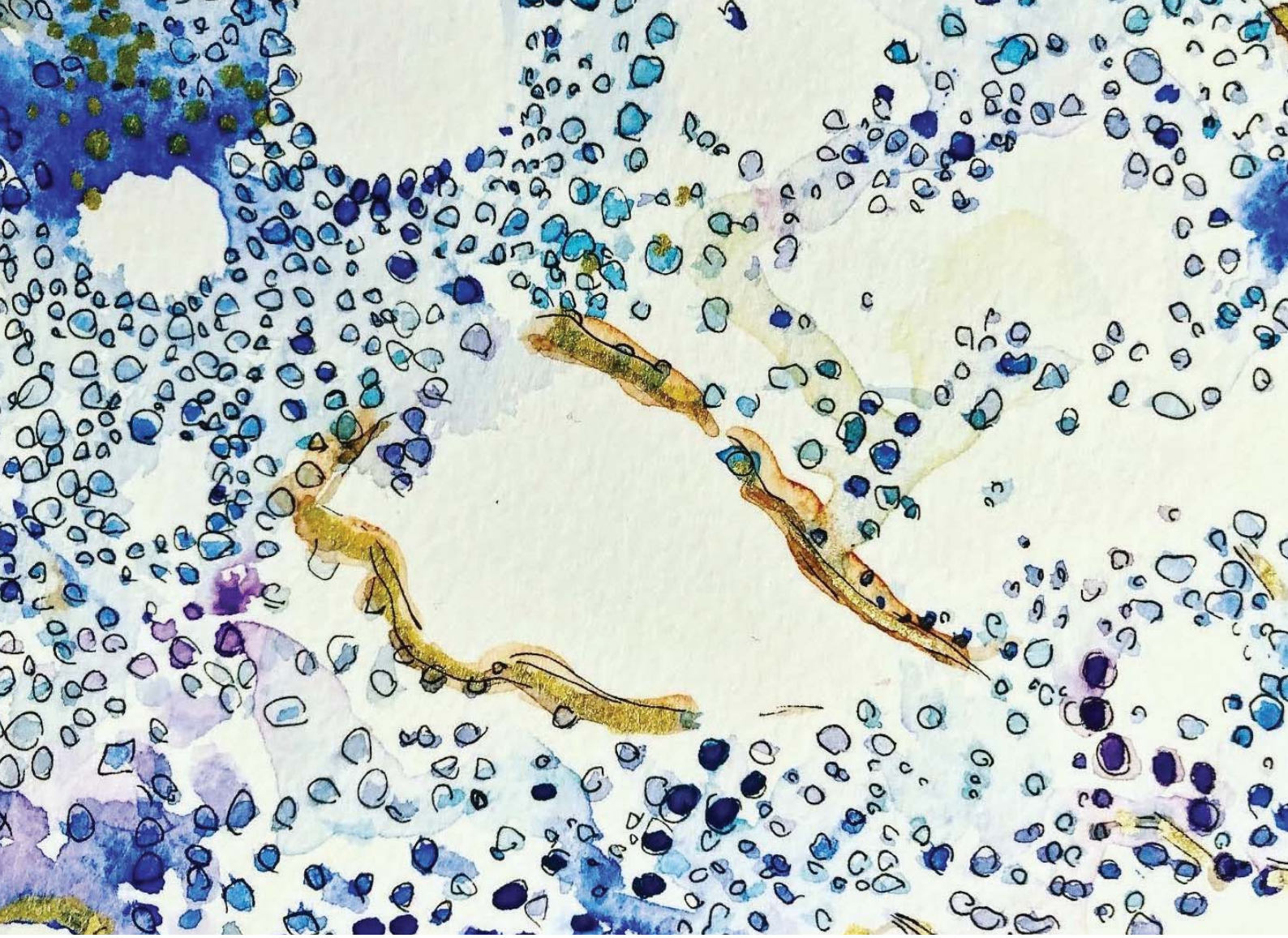
Sameer Al Diffalha, The University of Alabama at Birmingham, Alabama, USA

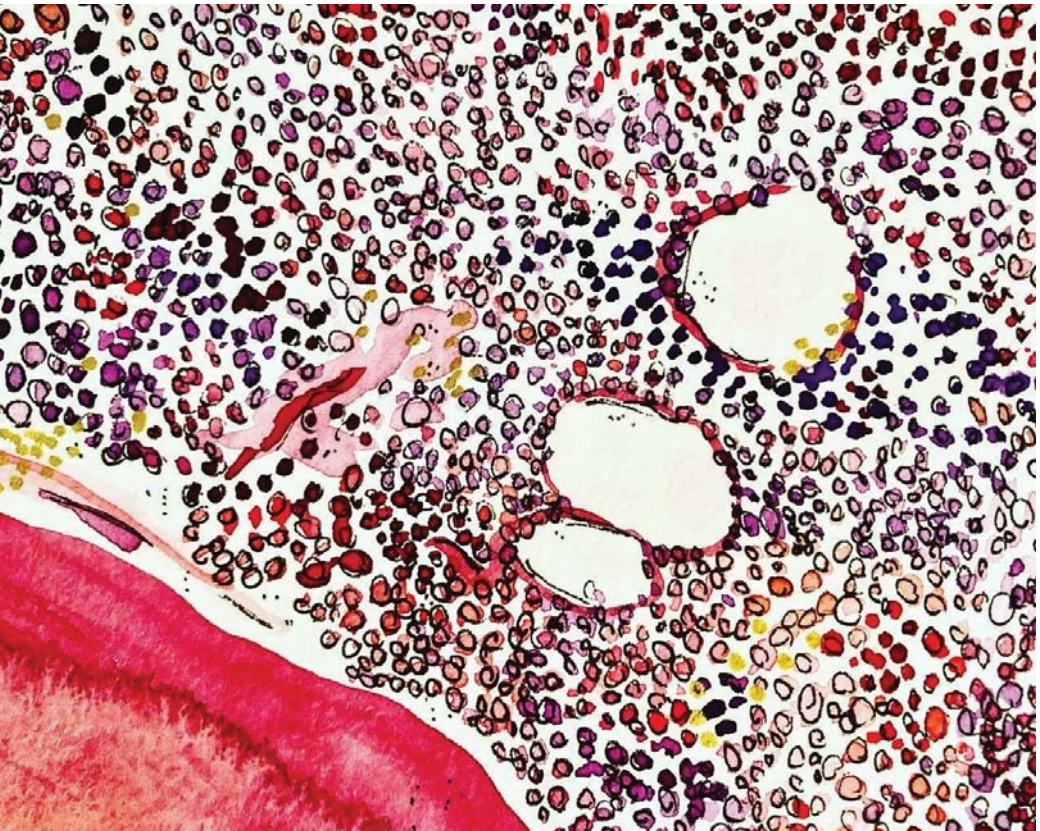


Corporae

Gorgeous concentric circles in a corpus amylaceous. In reality, this would be a sphere; let your imagination run wild to this artistry in life.

Mayah Hijazi, Resident, Department of Pathology, LAC+USC Medical Center, Los Angeles, California, USA





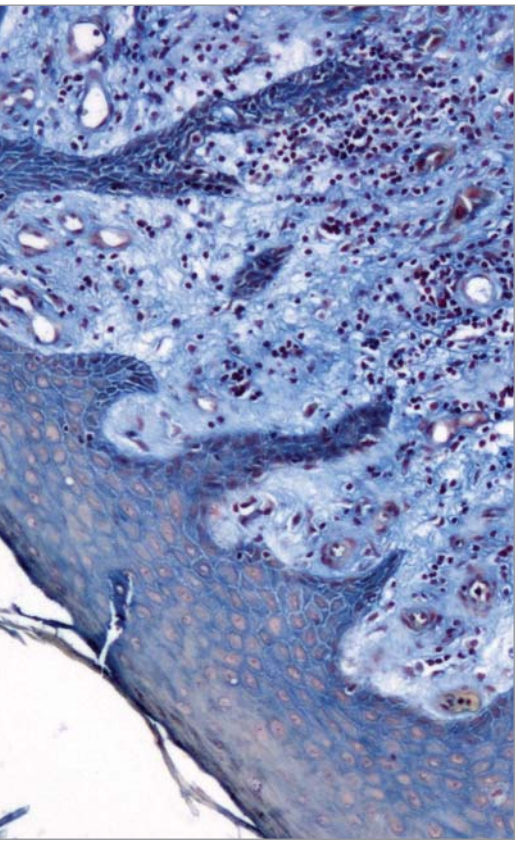
BM CD34

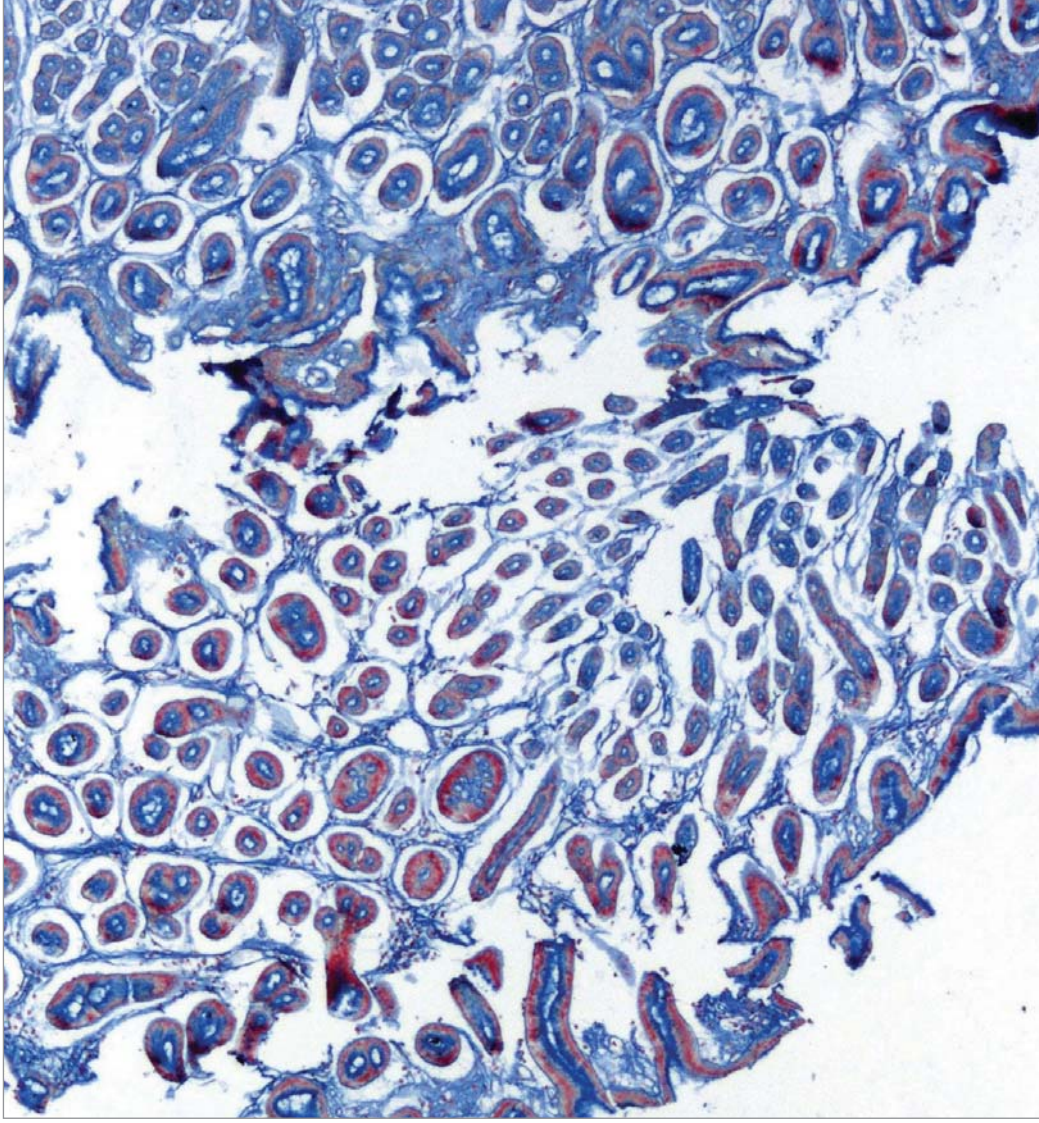
BM H&E

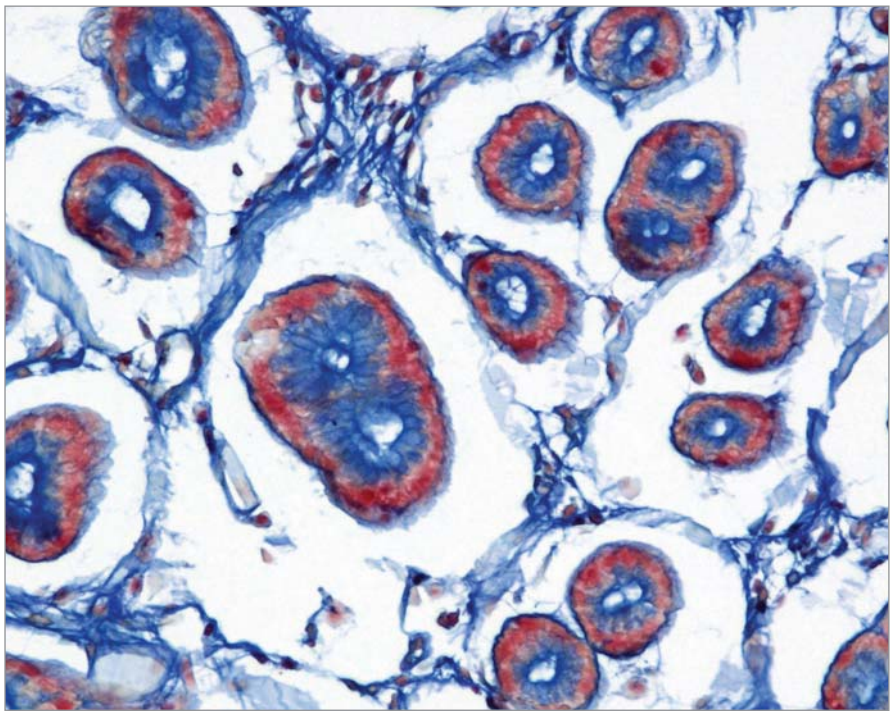
Top: BM CD34
Bottom: BM H&E

These pieces were created for a mentor of mine who is a pathologist. They are inspired by CD34 and H&E stains of bone marrow; the medium is watercolor, metallic paints, and ink.

Yeonsoo Sara Lee, Medical Student, Mayo Clinic Alix School of Medicine, Rochester, Minnesota, USA



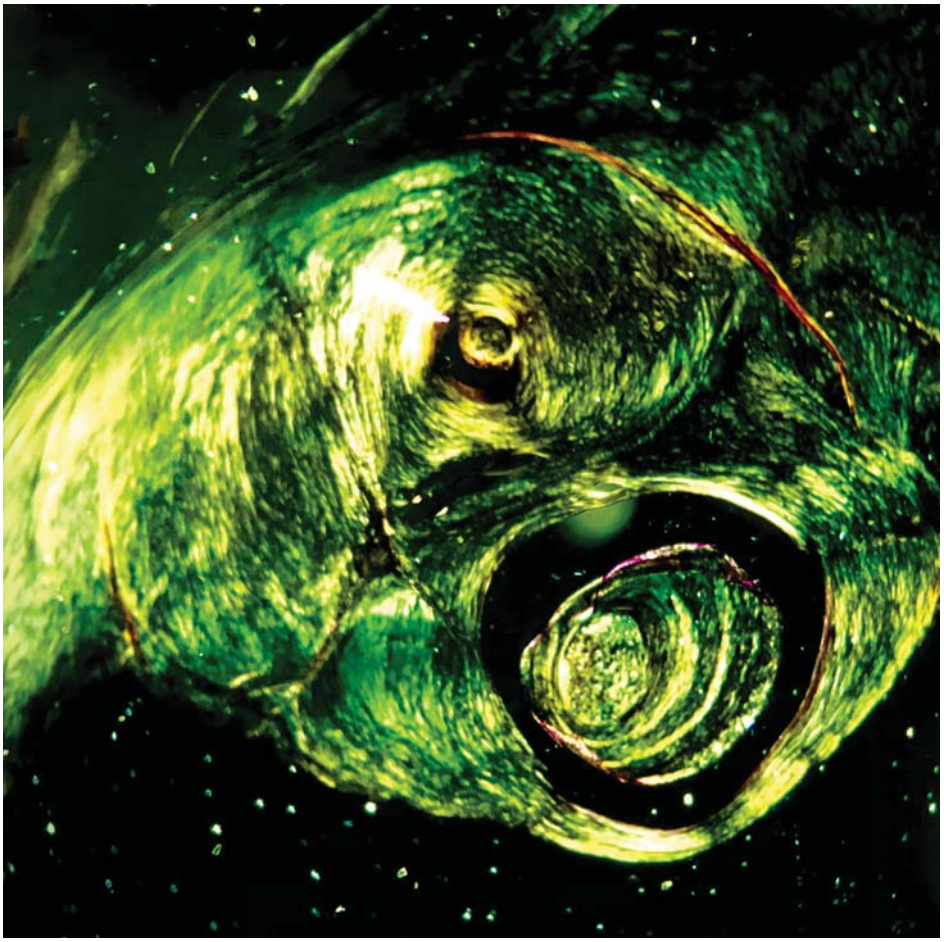




A Novel Stain

This is a stain of my own invention, based on picroanyline, Ziehl's fuchsine, and acetic acid. The stain is useful in dermatopathology; it is good for differentiating squamous epithelium keratinization (yellow/brown) and lymphocytes (dark red). It is also useful for differentiating metaplastic glands in gastric biopsies.

Dmitry Zinovkin, Department of Pathology, Gomel State Medical University, Gomel, Belarus



The Invasion Begins

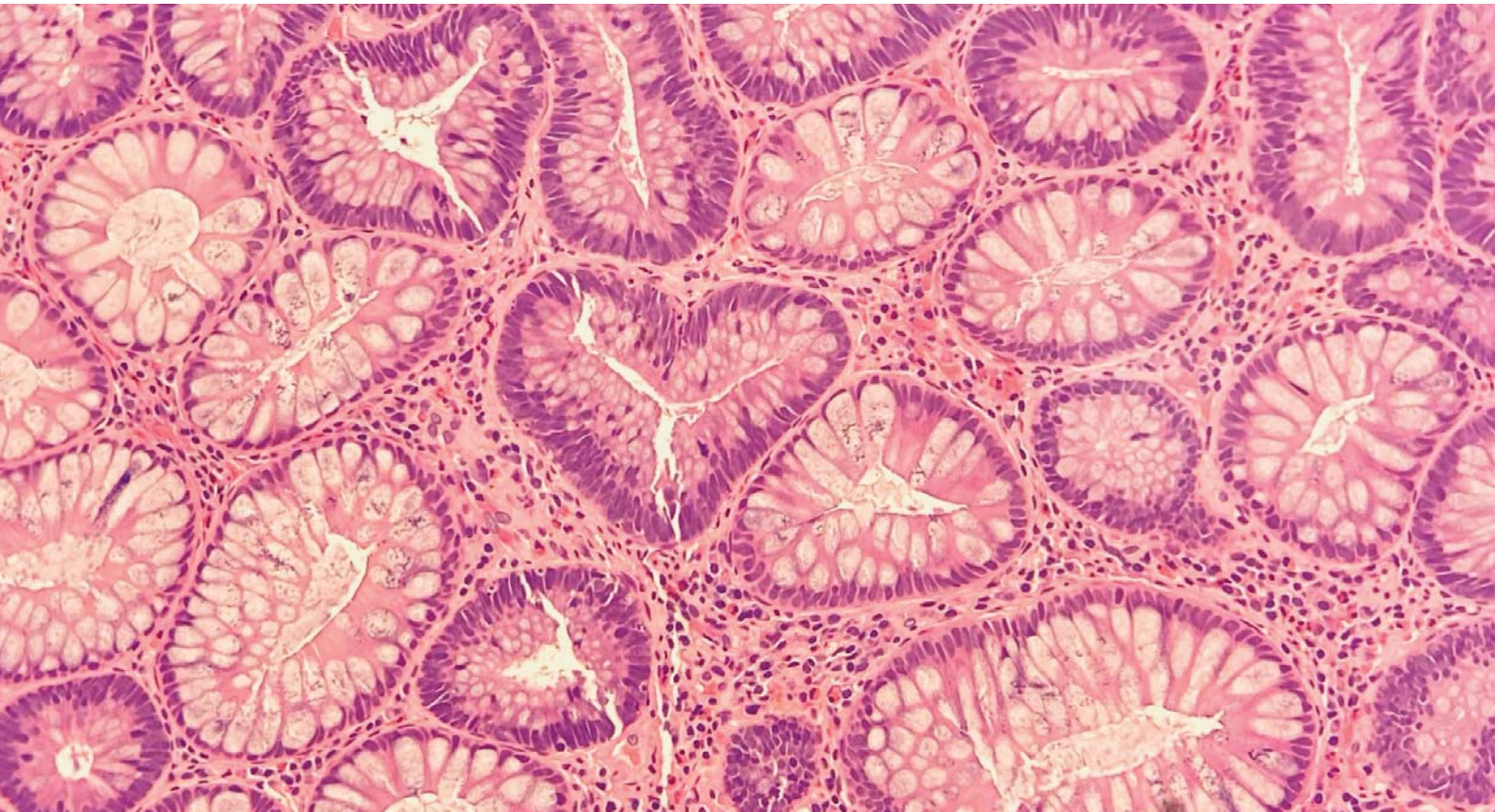
Left: A long time ago in a galaxy far, far away... a galactic strike ship from an unknown planet is ready to invade and conquer the universe. This photomicrograph is a mitral valve from a patient with rheumatic heart disease with amyloid accumulation, stained with Congo red to show the characteristic apple-green birefringence on a polarizing microscope.

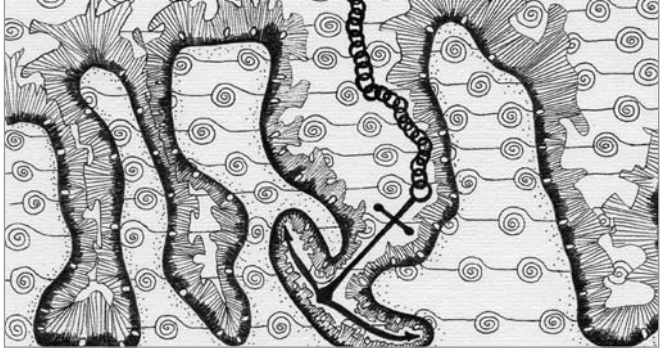
Franz Jobert L. Sebastian, Philippine Heart Center, Quezon City, Philippines

XOXO Biopsy

Bottom: A tubular adenoma from a GI biopsy.

Caroline Stanek, PGY-1, Department of Pathology, Heersink School of Medicine, The University of Alabama at Birmingham, Alabama, USA





Fasciola Hepatica Tree

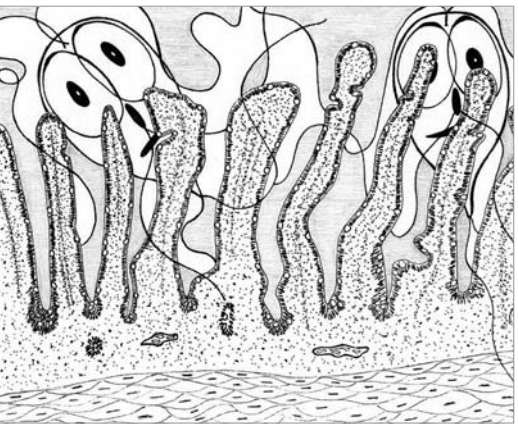
Sessile Serrated Adenoma Ocean

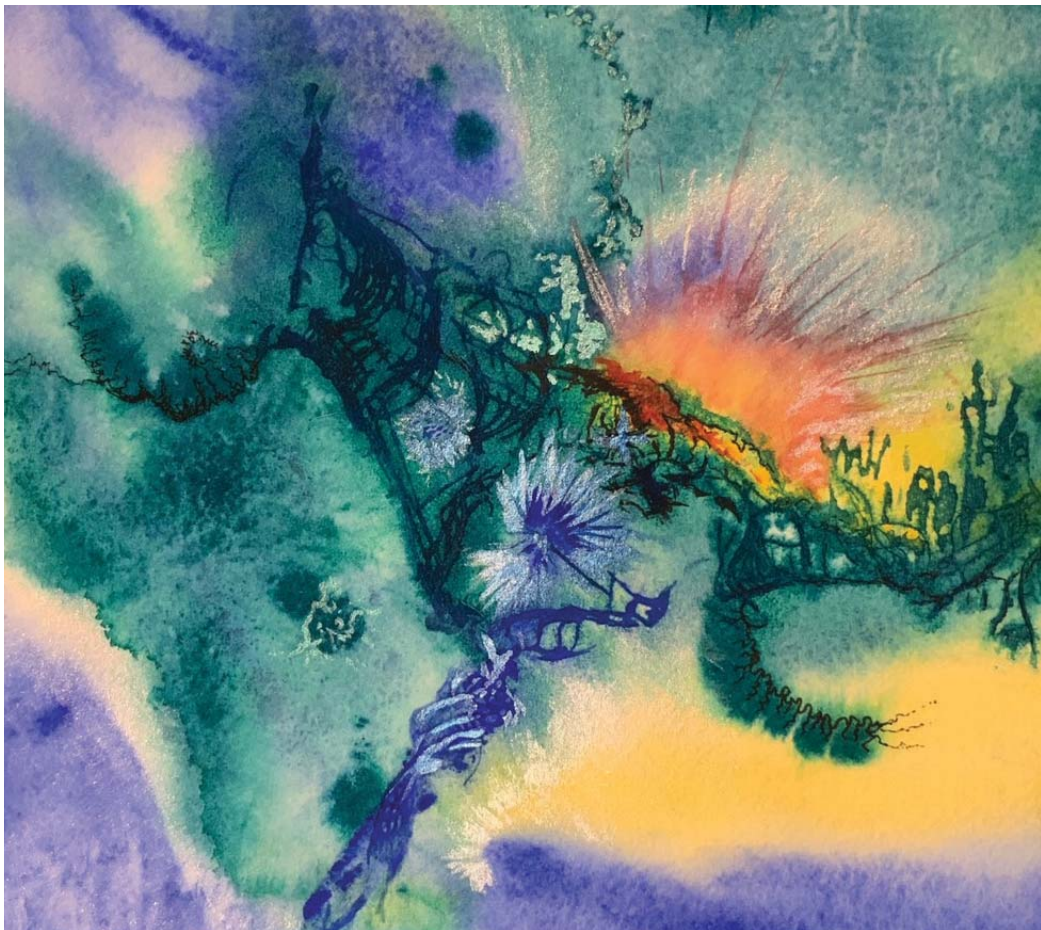
Curious Giardia

Top left: Fasciola Hepatica Tree
Top right: Sessile Serrated Adenoma Ocean
Bottom left: Curious Giardia

Pathology images are often reminiscent of real-life objects, animals, and many other things we frequently find in our daily surroundings. I am inspired by what I see under the microscope to create a connection between these two worlds.

Emanuela Veras, Highlands Pathology, Bristol, Tennessee, USA





Invasive

Watercolor and ink.

Sheryl Lammers, Retired Medical Technologist, Metropolitan Medical Laboratory, Moline, Illinois, USA

Gouty Rain

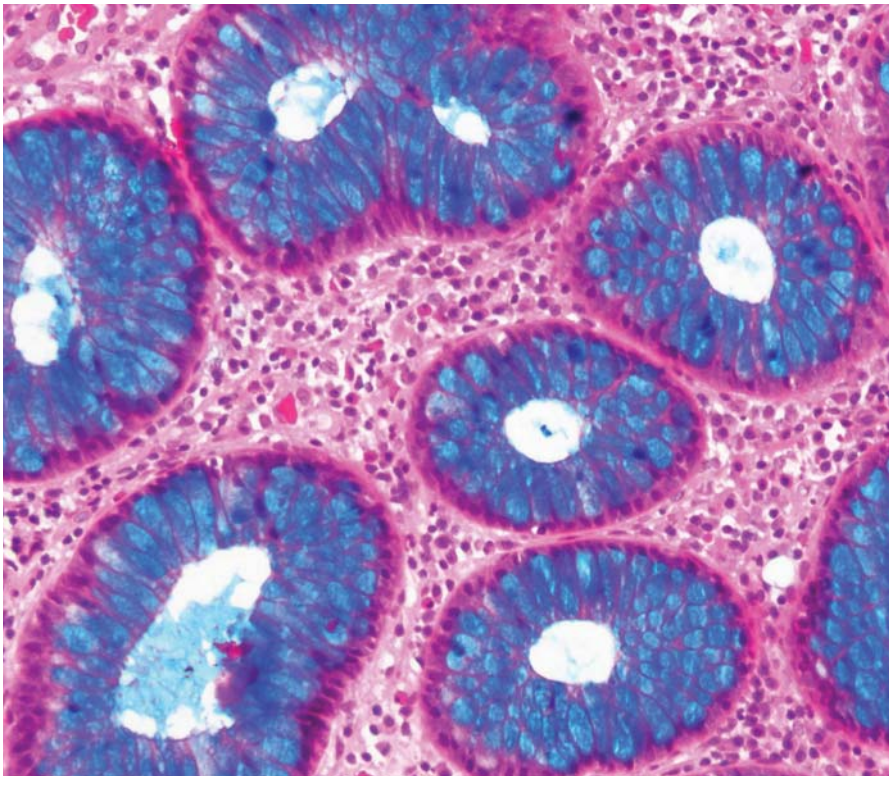
Top: A needle-shape negative birefringent image of gout.

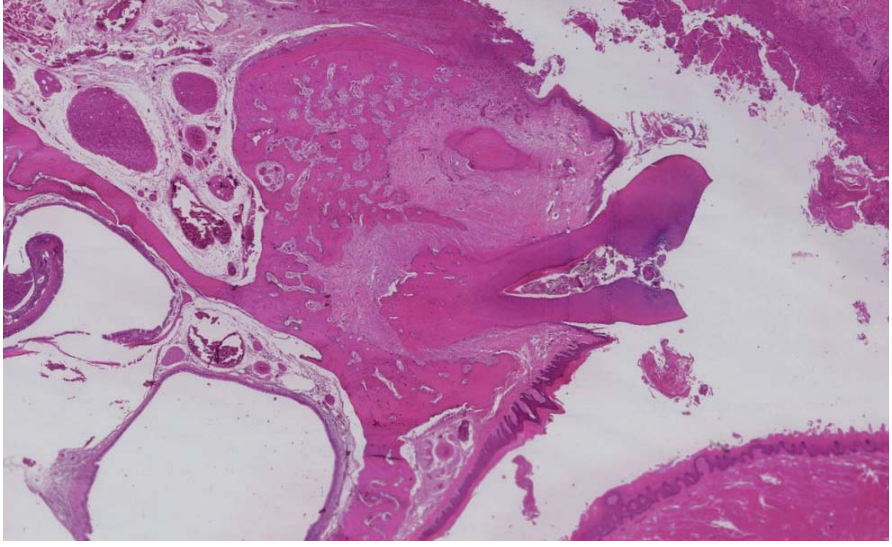
Dalila Villalobos, PGY-5 Anatomical Pathology, Queen's University, Kingston, Ontario, Canada

Colon Flowers

Right: Kreyberg stain of a colon biopsy.

Ana I. Hernandez Caballero, Department of Pathology and Laboratory Medicine, University of Rochester Medical Center, Rochester, New York, USA

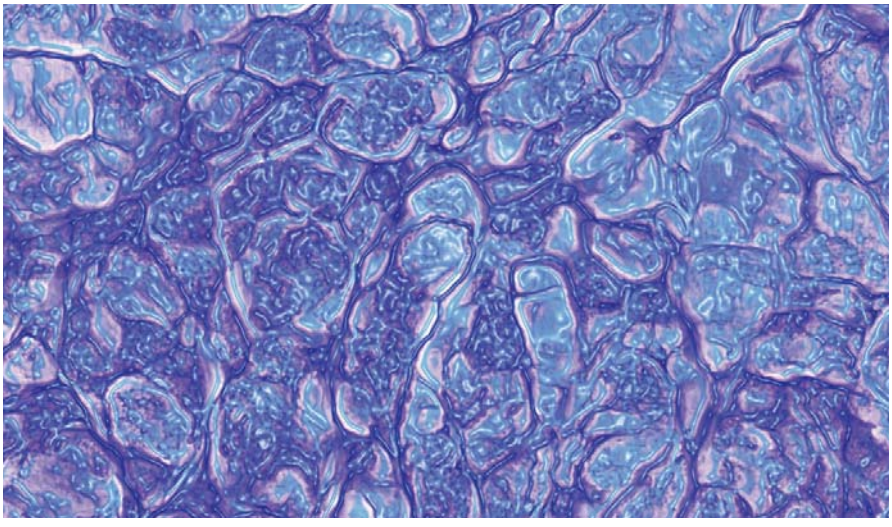




Phoenix

Top: Rat oral cancer.

Christine Carreira, Research Assistant, WHO/IARC Classification of Tumours Group, International Agency for Research on Cancer, World Health Organization, Lyon, France



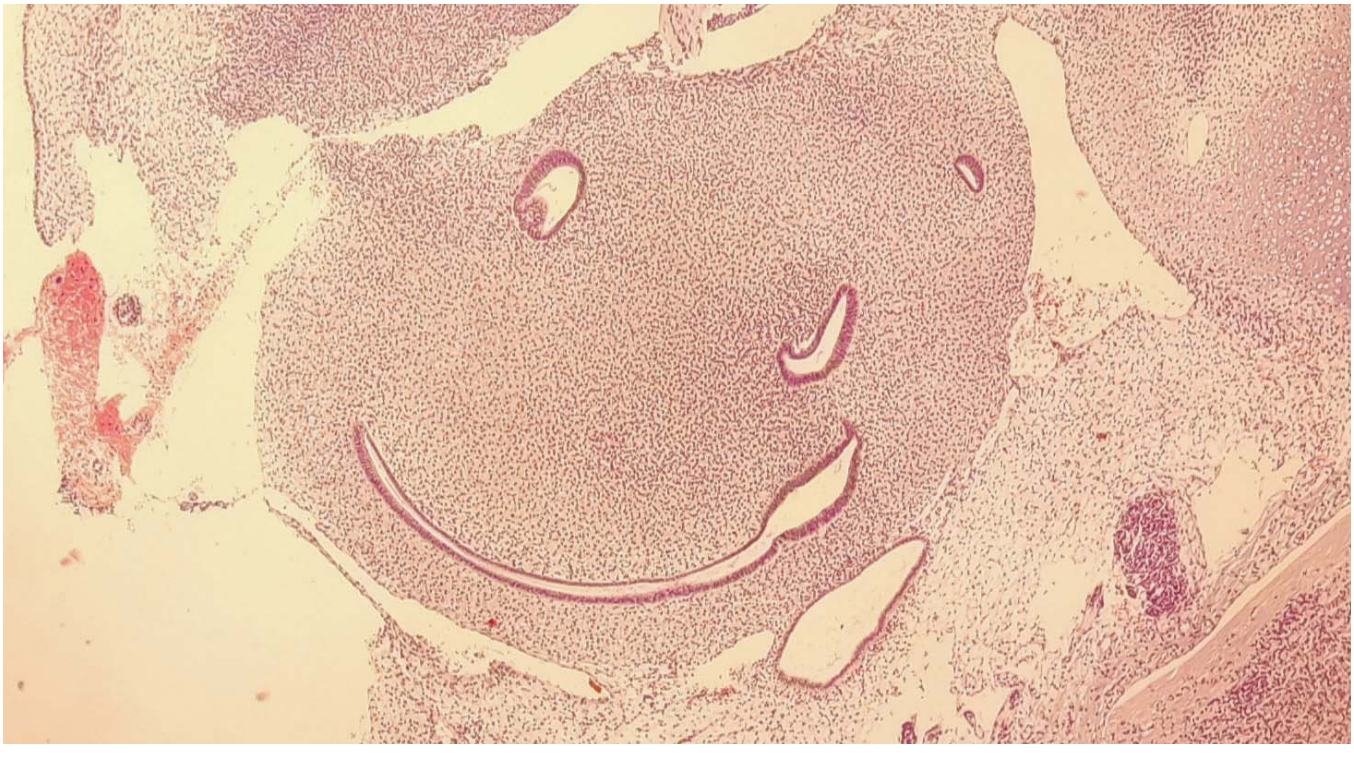
Mucineon

Middle: A stylized example of histopathology from a mucinous cholangiocarcinoma.

Alan Rampy, Associate Professor of Diagnostic Medicine and Medical Education and Distinguished Teaching Professor, The University of Texas at Austin, Texas, USA

Goofy Smile

Bottom: Fetal tissue.
Georgios Kitsakis, Histopathology Resident, General Hospital of Volos, Greece



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"Doing more with less" is a phrase every lab knows well – and is likely experiencing right now. Studies show that pathologists' workload has increased by 23 to 41 percent over the last decade, even before COVID-19 (1,2). Additionally, the Protect Access to Medicare Act (PAMA) has cut deep into labs' revenue streams and is expected to continue slashing reimbursements by 35 percent over the next three years (3,4). Labs and pathologists must either drive efficiency and cost-effectiveness through digital optimization or risk losing revenue – or even the entire business.

Over 70 percent of labs use workflows without full digital integration, resulting in lost time, efficiency, and revenue. Even with a laboratory information management system (LIMS), the laboratory workflow may need optimization to bolster these areas while maintaining quality patient care and regulatory compliance.

For pathologists, a workflow-optimized LIMS solution with a user interface designed for efficiency can significantly increase diagnostic capacity.

Organizing incoming work

Ensure that incoming requisition and patient demographics are digitally presented in the LIMS and specimens are barcoded throughout the process. The LIMS should organize assigned cases into separate pages – new cases, work in progress, and those awaiting tests – with detailed patient information such as medical ID and collection date.

The LIMS should display the specimen diagnosis workflow page when each barcode is scanned. Digital pathology imaging tools must have a seamless connection between the viewer and the LIMS diagnosis operations – eliminating time spent searching for image files.

The system should also allow pathologists to quickly find patient histories. Users must be able to view patient history within the case itself, rather than having to sort through paperwork. The LIMS should also sort new and in-process cases and prioritize time-critical "stat" cases.

Optimizing the diagnosis

An efficient LIMS can use macros with the diagnosis, microscopic, and comment text values that are auto-filled in the specimen diagnosis selection. Moving to the next specimen should take one keypress or button click. A default benign diagnosis macro assigned as the first selection increases efficiency. Ordering additional tests and recuts should take minimal effort during diagnosis.

A programmable scheduled release for diagnostic reports gives pathologists additional time to contemplate and the ability to recall cases and rework or re-diagnose. The system should also provide a full report preview before case completion, allowing pathologists to view exactly what the physician and patient will see.

Streamlining downstream information

Additional LIMS-aided efficiencies can include automatic calculations of billing CPT and ICD codes prior to sign-out while still allowing pathologists complete control of any applied codes. Here again, automation is essential for workflow productivity. If any codes need to be added, changed, or removed, automation eliminates wasted time and potentially costly billing errors.

These methods are proven to increase daily workflow efficiency for pathologists in the lab. Small, incremental optimizations add up to significantly alleviate each pathologist's workload, time, and effort – so make sure to evaluate your workflow and LIMS to determine whether you can implement these productivity boosts.

For a free demo of LABdivus for Anatomic Pathology labs, contact us at www.cerebrumcorp.com

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OLYMPUS

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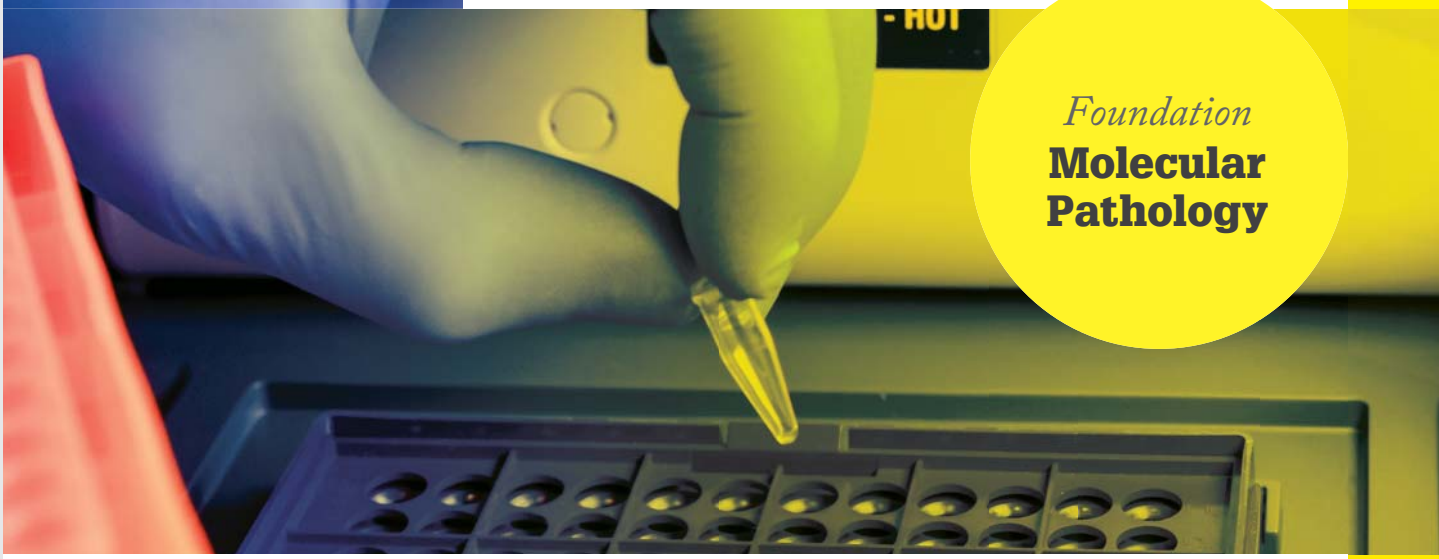

Foundation
Molecular Pathology

Remission Revamp. Childhood cancer remission rates are high – but, for relapsed patients, treatment is limited. To solve this, a recent study examined the effect of precision medicine on outcomes for pediatric patients with recurrent or refractory cancers (1). The researchers successfully sequenced tissues from 632 patients, identifying targeted treatment options for 436. Of these, 107 received one or more targeted therapies, leading to a 17 percent objective response rate – and more than double this rate in patients with alterations considered "ready for routine use."

Peeling Back Parkinson's. Most transcriptomic studies focus on gene or exon annotations, with fewer investigating intronic alterations. But introns, too, have their uses – for instance, to allow us to detect nascent transcription. A new study takes advantage of intronic RNA sequencing to uncover disease-specific nascent transcription in Parkinson's disease patients over time (2). Patients were sequenced at the time of diagnosis and three years later, at which point they exhibited changes in the intron expression of 4,873 genes – many associated with neurodegenerative diseases.

IVF Investigations. Preimplantation genetic testing can prevent rare diseases during in vitro fertilization. However, susceptibility testing for common conditions, such as heart disease or cancer, is not available – even though many can be detected before implantation with up to 99 percent accuracy (3). The findings are based on predictions made for 110 embryos across 10 couples by combining molecular and statistical approaches to infer inherited genome sequences. The genotype predictions showed 97.2–99.1 percent accuracy in day three embryos, increasing to 99.0–99.4 percent accuracy by day five.

Joining Forces. Single-cell RNA sequencing doesn't preserve spatial information – and spatial transcriptomics currently lacks single-cell resolution. A new study combines the two approaches for a more detailed profile (4). The novel computational approach showed the capacity to distinguish between topological patterns in different mouse cell types and states, and identify distinct tumor subclones in samples of human ductal carcinoma in situ and specific T cell states in surrounding tissue.

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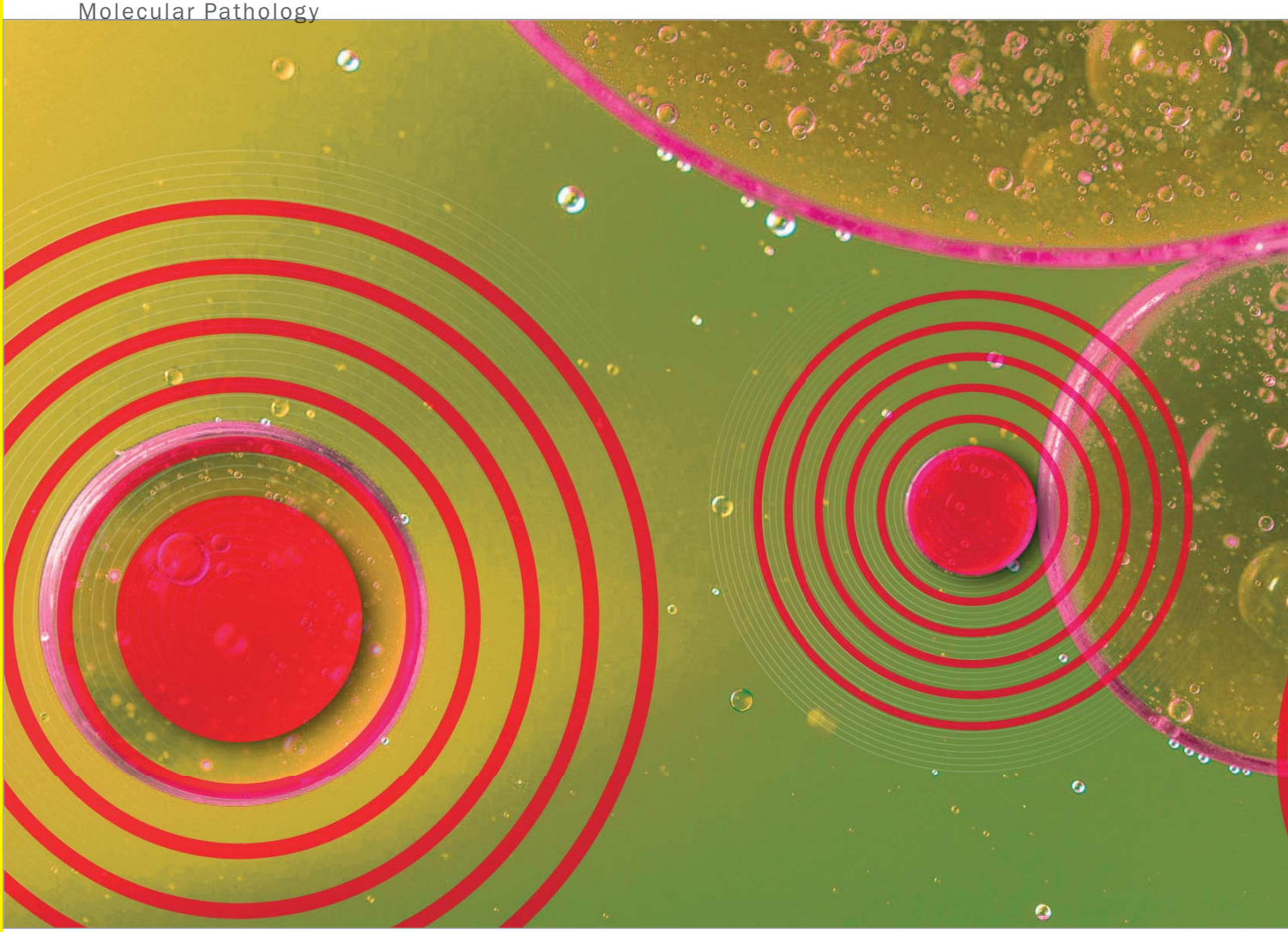
IN OTHER NEWS

A decade of checkpoint blockade. *Review examines immune checkpoint inhibitor therapy for advanced melanoma and calls for new, rational combinations to increase efficacy (5).*

Tumor immunity insight. *Combined Imaging and spatial transcriptomic determine extracellular "environmental control" functions of tumor genes uncovered by CRISPR screening (6).*

Protein phosphorylation progress. *New brain protein phosphorylation database – detailing sites, signaling strategies, phosphoproteins involved, and participant kinases – opens up new neuropathology research opportunities (7).*

COVID-19 in circulation. *Mendelian randomization shows causal link between five blood proteins – GCNT4, CD207, RAB14, C1GALT1C1, and ABO – and risk of COVID-19 hospitalization, respiratory support, or death. Endocannabinoid enzymes may also increase risk (8).*



A Spatial Biology Startup Guide – Part 2

Top concerns for establishing multiplex image analysis

By Michael S. Nelson, Shawn Jensen, Lau Mai Chan, Michael Surace, Trevor McKee, Joe Yeong, and Colt Egelston

As a result of quickly advancing technologies for multiplex tissue assessment, researchers are faced with ever more complex image datasets to analyze and interpret. Here, we discuss common questions researchers may have prior to setting up a multiplex immunofluorescence/immunohistochemistry (mIF/IHC) or other multi-channel image analysis workflow in the lab. We provide general guidance that will help enable efficient, productive, and reproducible mIF/IHC research results. These considerations apply largely to mIF/IHC data acquired from relatively low-plex (up to eight markers) staining of 3–5 µm formalin-fixed tissue sections.

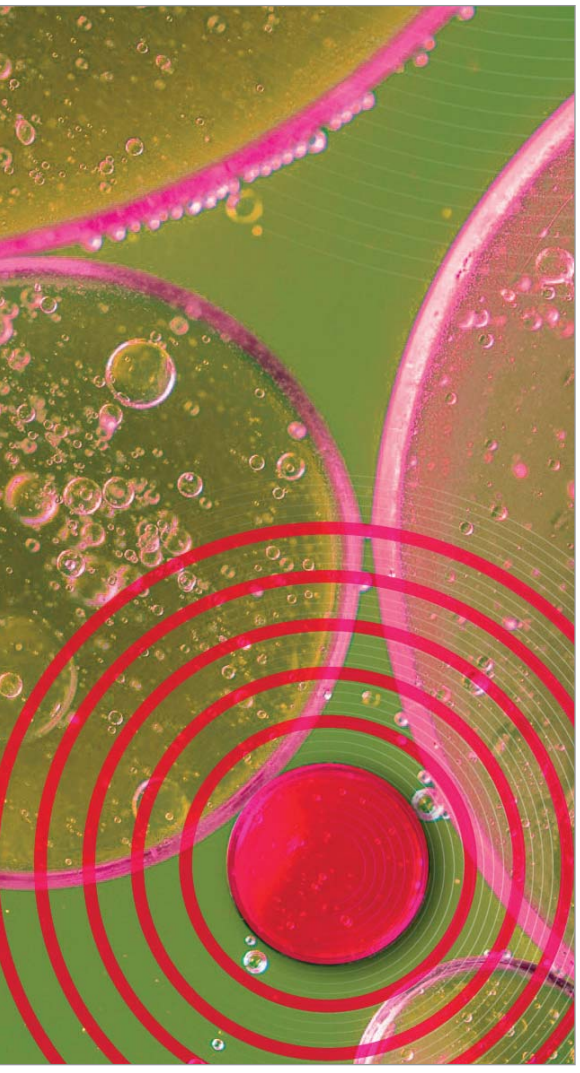
A successful mIF/IHC analysis workflow strategy must meet each research group's unique needs – and every implementation will benefit from input given by a collaborative group of experts in immuno-oncology, pathology, microscopy, and image analysis. A carefully designed image analysis workflow will reward users with a wealth of tissue-based biological information.

What are the basic steps for multiplex image analysis?

Analysis of multiplex images is generally divided into four key steps:

- Tissue identification and segmentation
- Cell segmentation
- Cell classification and validation of any classifier
- Measurement exportation and data interpretation

Sometimes additional steps, such



as tissue type segmentation, may be needed; in other cases, certain steps (such as cell segmentation for pixel-based approaches) may be unnecessary.

What are some common metrics produced by image analysis?

The most common metrics are cell density within segmented tissues (e.g., CD3+ T cells per cancer nest or per mm2), percentages of cells (e.g., percentage of CD3+ T cells that are also CD8+), and nearest-neighbor measurements (e.g., how many microns on average from a CD3+ cell to the nearest cancer cell).

My lab does not have a bioinformatician. Will this limit our ability to analyze mIF/IHC data?

Not at all! Many software choices are user-friendly and yield datasets that can be handled in simple spreadsheets. Although scripting and complex data processing may benefit from a bioinformatician's input in the long run, one is not needed to establish mIF/IHC capabilities. The Image.sc forum is also an excellent place to ask questions about starting a pipeline – but make sure to provide enough information about the problem to ensure an adequate response.

How should I quality check my image analysis?

Quality control (QC) for mIF/IHC imaging is critical to ensure that reported data are accurate. Multiplex IF/IHC QC should address technical aspects of histology, preanalytical phase, staining, and imaging, as well as pathology and immunology considerations. Some facets of QC can be conducted with image analysis software, whereas others require human observation. Briefly, folds, tears, dried areas of tissue, and gross fixation artifacts should be annotated and excluded from analysis (either manually or using a pixel classifier). Saturation (due to staining or imaging), out-of-focus areas, obvious blocking of one marker with a colocalized marker, spectral bleed, and clear staining gradients should be ameliorated by reimaging or excluded. Finally, unexpected staining patterns, marker localization, and multimarker phenotypes (markers that should not colocalize in the same cell) can disqualify individual slides or entire batches.

Negative controls should contain only autofluorescence or nonspecific signal in each of the channels of interest. Positive controls, which should be run consistently with each batch, should be compared with the same positive control from preceding batches to establish that the peak, mean, and minimum intensities observed in each channel are comparable.

What hardware do I need to perform image analysis?

Hardware needs depend on the number and size of images you routinely analyze and your preferred software. However, mIF/IHC analysis software often can run on standard desktop or laptop setups. 16 GB of RAM is usually sufficient for simple whole-slide analysis, whereas 32 GB or more might be required for complex analyses, especially if running multiple threads or programs simultaneously. RAM limitations can be a bottleneck for certain software processes because pixel classifiers and more complex analyses can require significant overhead.

See an extended version of this article and references online at: tp.txp.to/spat-bio-pt-2

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*Lau Mai Chan is Senior Research Fellow at the Institute of Molecular and Cell Biology, A*STAR, Singapore.*
Michael Surace is Associate Director of Translational Medicine Oncology at AstraZeneca, Gaithersburg, Maryland, USA.
Trevor McKee is Director of Image Analysis at HistoWiz, Brooklyn, New York, USA.
*Joe Yeong is Group Leader at the Institute of Molecular and Cell Biology, A*STAR, Singapore.*
Colt Egelston is Assistant Research Professor in the Beckman Research Institute at City of Hope National Medical Center, Duarte, California, USA.
With thanks to JEDI – the Council for Multiplex IHC/IF Global Standardization.

Hunting the Unknown

When it comes to human health, we cannot ignore unknown molecules simply because they present analytical challenges

By Aaron M. Robitaille, Senior Product Marketing Manager, Thermo Fisher Scientific, Seattle, Washington, USA

The human body is teeming with amino acids, carbohydrates, and other small molecules. Collectively referred to as metabolites, these molecules are the intermediates and end products of cellular processes. Analyzing metabolites and lipids is a critical step in human health and disease research – from studying how tumors grow to predicting the severity of COVID-19.

Mass spectrometry (MS)-based methods are the industry standard for measuring metabolites and lipids in biological samples. Over the last few decades, advances in MS have led to the emergence of large-scale approaches to study these molecules: metabolomics and lipidomics – but sample complexity and the limitations of current technologies lead to challenges in identifying and elucidating the structure of unknown metabolites and lipids.

In each cell or tissue sample, thousands of different molecules may be present – challenging enough, but there is yet more complexity. Some molecules are far more abundant than others, pushing the limits of dynamic range; the levels of others may vary by several orders of magnitude in time and space; and, finally, some compound classes – particularly lipids – may include many molecules with similar structures. In short, finding unknown metabolites and lipids in biological samples and identifying their molecular structures is a task akin to searching for needles in haystacks.

So how can MS help? First, a little background for those less familiar with the technology. In simple terms, MS ionizes compounds and separates them by charge-to-mass (m/z) ratio, generating plots of ion signal against m/z – known as spectra – which researchers can use to identify compounds. To tackle the complexity of determining metabolites and lipids in biological samples, researchers use tandem (MS^2) or sequential (MS^n) mass spectrometry. In these techniques, a first MS step ionizes and separates all the compounds so that users can select ions of a specific m/z to be broken into fragment ions; subsequent MS steps separate and detect fragment ions by m/z until structures can be assigned to all molecules present.

The challenge of identifying unknown molecules using MS is further complicated by the presence of irrelevant (from the chemical background) or redundant (from adducts, isotopes and in-source fragment ions) spectra. Existing instruments do not have sufficiently high-resolution to consistently prevent these spectra from interfering with detection of the compounds of interest, making MS data less reliable. Furthermore, low-resolution MS technologies cannot unambiguously identify elements within molecules, making it difficult to spot isotopologues (molecules that have identical molecular structures except that one or more atoms has a different number of neutrons).

In summary, the complex nature of biological samples and the limitations of current technologies prevent researchers from effectively annotating acquired spectra in many cases; sometimes only known metabolites and lipids can be identified.

But things are no less important for being difficult to find – particularly in the context of human health. To that end, new technologies are emerging to allow researchers to embrace the unknown. One such example is real-time spectral library matching, which uses spectra from known molecules to refine MS^n workflows in the search of unknown (but closely related) molecules, including metabolites of a drug. It

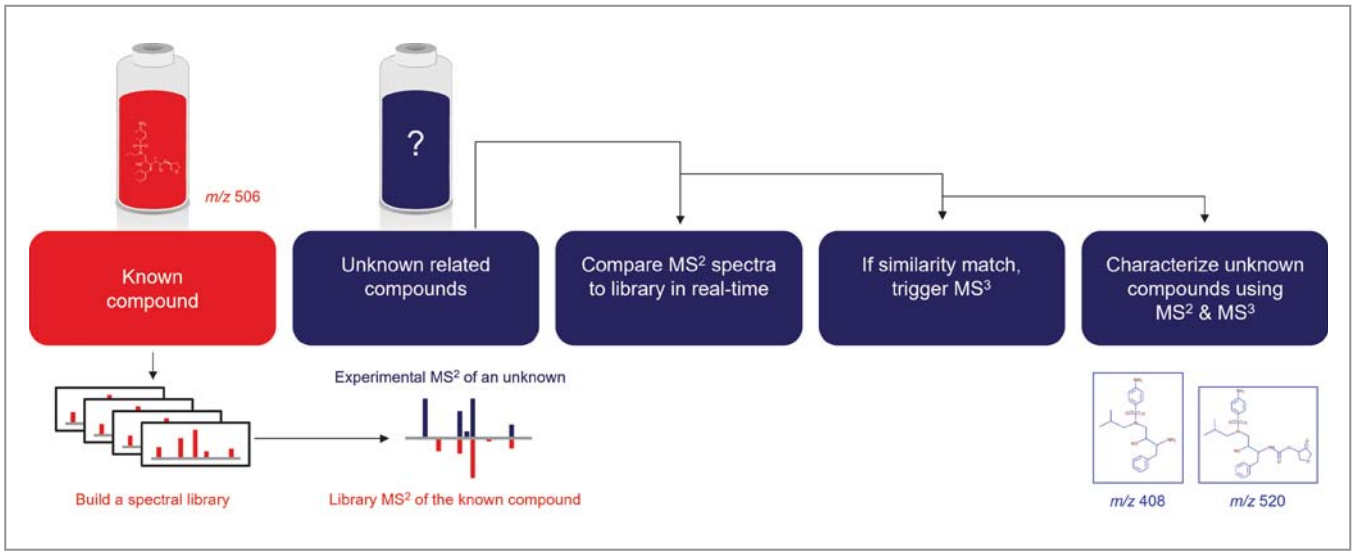

Figure 1: Real-time library searching for small-molecule mass spectrometry.

can simplify data analysis and speed up identification because it only triggers MS^3 scans on spectra similar to the compound(s) of interest, focusing those scans on fragments unique to the unknown molecules. It also increases the effective MS^2 scan rate, allowing the sampling of more MS precursors, and it can be combined with other workflows for automated background exclusion. As a result, real-time spectral library matching enables researchers to discover more unknown molecules related to compounds of interest. For example, a recent study of the drug amprenavir – a treatment for HIV – in human liver microsomes found 17 metabolites using real-time spectral library matching, only 11 of which emerged using a conventional MS^3 approach (1).

Real-time spectral library matching can also help identify lipids and other molecules that produce fewer fragment ions. For example, by refining the search criteria to use a narrow mass tolerance and only advancing fragment ions with high match scores, researchers at the University of Wisconsin-Madison were able to adapt the real-time library search workflow to identify molecular structures of lipids, including the acyl chain composition of phosphatidylinositol (2).

Other new technologies are also helping to elucidate molecular structures by providing additional fragmentation pathways for ions not amenable to traditional collision-induced dissociation (CID). Ultraviolet photodissociation (UVPD), for example, uses high-energy photons to break apart the ions. An angiotensin II receptor blocker called telmisartan – commonly used to treat high blood pressure and heart failure – produces few fragment ions when exposed to CID. Researchers recently demonstrated that using UVPD on telmisartan produced more fragment ions than a traditional CID approach (1). Furthermore, the fragment ions produced using UVPD were of different sizes, allowing researchers to identify the drug in the sample with more confidence.

Finally, some researchers use a technique called stable isotope labeling to track small molecules and their metabolites through downstream biochemical pathways, but these traditional approaches are only suitable for tracking known compounds and their metabolites because they require prior knowledge of the compounds' molecular structures. However, the introduction of ultra-high resolution accurate mass MS systems – coupled with new software solutions – give researchers the opportunity to use stable isotope labeling as a discovery tool for unknown metabolites.

Here, I've provided a few examples of advanced MS technologies that help researchers identify unknown metabolites and lipids, but there are others – and this exciting field is constantly evolving. Untargeted methods based on modern MS technology can produce more reliable data than ever before, enabling researchers to discover unknown compounds, elucidate their molecular structures, and understand their fate in the body. With this knowledge, we can dig even deeper into the details of disease and better understand the impact of treatment – allowing us to provide better care now and in the future.

See references online at: tp.txp.to/hunt-unkno

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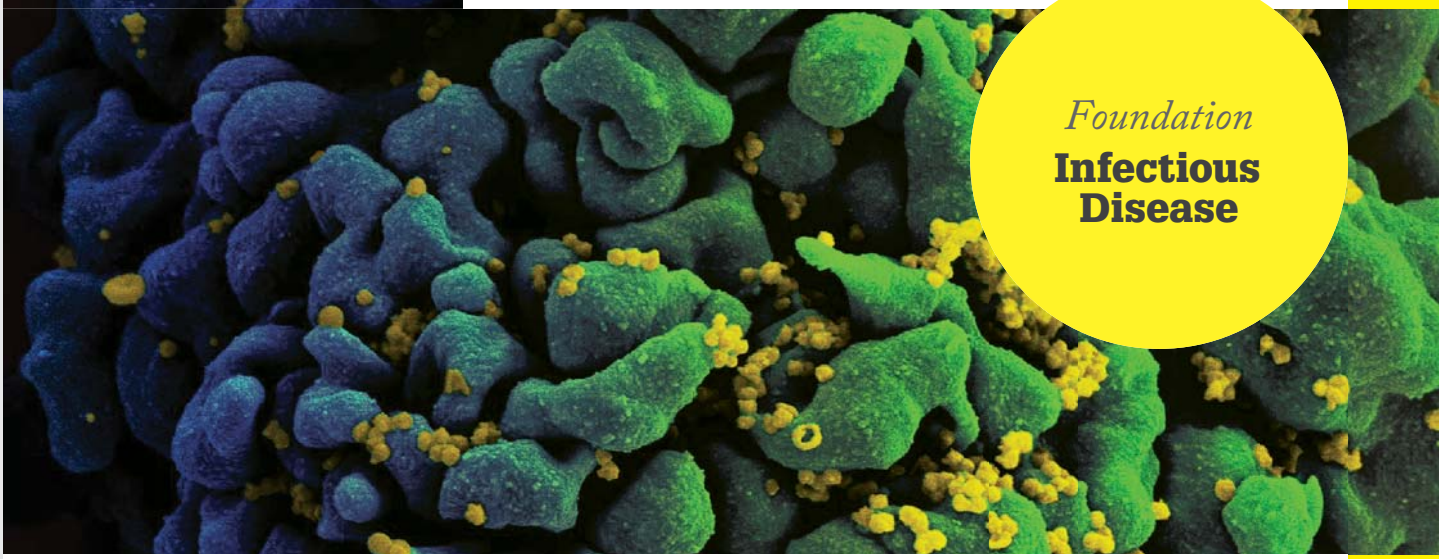

Foundation
Infectious Disease

HIV/AIDS: A Shifting Epidemic

HIV diagnoses in heterosexual people in the UK have overtaken those in gay and bisexual men

June 1981 – the first recorded case of a disease that would go on to kill an estimated 36.3 million people worldwide. Over the past 41 years, HIV/AIDS has typically been viewed as a problem most prevalent in gay and bisexual men; however, for the first time in a decade, heterosexual HIV diagnoses in the UK have overtaken those in LGBTQ+ groups (1).

Relative to population size, gay and bisexual men are still impacted more by HIV than heterosexuals – but the fall in diagnostic rates over the past eight years makes it clear that targeted interventions have been hugely successful. At the Terrence Higgins Trust, testing is a crucial component of HIV prevention. "Testing access has expanded with the introduction of online testing (self-sampling and self-testing) and, in turn, the number of people with undiagnosed HIV has gradually been decreasing," says Marianne Holt, the sexual health charity's Media Manager. "Testing is the only way to know your status. The sooner you know it, the sooner you can get treatment and avoid passing the virus on to anyone else."

Reducing viral load is crucial to halting HIV transmission. "People with undetectable virus levels cannot pass HIV on. This is known as U=U (undetectable=untransmissible)," says Kate Folkard, Interim Deputy Director of Blood Safety, Hepatitis, STIs and HIV Division, UK Health Security Agency.

"Test, test, test" has always been an underlying message of prevention campaigns but, in the era of social media, dating apps, and the metaverse, the approach to outreach and advocacy has changed. At the Terrence Higgins Trust, teams use social targeting to tailor posts to specific audiences who need to engage with the message most. "This is particularly helpful for health promotion or campaigning for policy change," says Holt. "When we launched 'Their Story, Your Choice,' a series of interactive films that targeted men who have sex with men from Black African and Asian communities, we were able to promote the films to individuals from these groups."

She continues, "The rise of influencer culture has also affected how we promote HIV testing. Influencer work is integral to HIV Testing Week – a campaign coordinated by HIV Prevention England to promote regular testing to groups most affected by HIV in the UK. During the campaign, we work with individuals whose audience consists of at-risk groups and send them self-testing kits to educate their followers and encourage them to get tested."

"The rise of influencer culture has affected how we promote HIV testing."

To replicate the reduction in diagnostic rate seen in gay and bisexual men, targeted interventions that lead to increased testing for other groups are needed. "HIV can affect anyone – regardless of sexuality, gender, ethnicity, or age – and everyone needs to know how to protect themselves," says Holt. "We need to see an increase in regular testing in at-risk groups to prevent anyone from living with undiagnosed HIV for a long time. This is important for their own health as well as for efforts to stop HIV transmission, given that the vast majority of people get HIV from someone who is unaware they have it."

Reference

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On the Sanctity of SARS-CoV-2 Sequencing

Could the adoption of antigen testing put the US farther behind in SARS-CoV-2 sequencing and variant tracking?

By Tian Yu

As of March 10, 2022, the US has reported over 81 million COVID-19 cases. As the disease continues to spread, it is increasingly essential to obtain up-to-date sequencing data to trace emerging variants. Viruses are always evolving – and SARS-CoV-2 is no different. These changes occur over time, bringing with them new variants such as Delta and Omicron – both of which are currently considered variants of concern in the US. And who knows what evolutionary adaptations may arise next?

The ability to detect and monitor various SARS-CoV-2 strains quickly and accurately can provide crucial data on early signals of new variants, as well as variant-specific information on symptoms, hospitalization rates, death rates, age distribution of positive cases, and disease spread. For example, the Washington State Department of Health recently released a comprehensive study on SARS-CoV-2 sequencing and variants (1). Public health officials could use this information to determine disease patterns and track occurrences – helping scientists to swiftly identify epidemics and limit the spread of illness.

Tian Yu

In the US, COVID-19 testing, sequencing, and reporting are largely regulated by state and local public health departments. Due to differences in state health law and public health programs, the average percentage of positive cases that have been sequenced per state since January 2020 varies from 19 percent in Wyoming to less than one percent in Oklahoma. According to the Centers for Disease Control and Prevention, which runs a

the Pathologist

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National Open Genomics Consortium called SPHERES (Sequencing for Public Health Emergency Response, Epidemiology, and Surveillance), the United States sequenced approximately 80,000 virus samples every week in December 2021.

Surveillance via genomic sequencing may be time-consuming and patchy – complicating the picture of how and where mutations spread. COVID-19 PCR testing has long been the gold standard for detecting and diagnosing the virus; the patient's swab sample is usually kept in a vial with transport media that stabilizes the viral genomic material for later PCR testing, after which a small number of positive sample vials are sent to sequencing labs for variant analysis. Premium transport media containing chemicals that inactivate live viruses and stabilize RNA at room temperature should be used to preserve and protect DNA during sequencing, which can take weeks following sample collection. However, it is worth mentioning that new sequencing blind spots are created when we embrace rapid antigen testing as an alternative to PCR molecular testing. This creates a risk of undersampling and underreporting for monitoring and early detection of new, potentially severe SARS-CoV-2 variants.

The rate of positive COVID-19 samples sequencing in the US has increased significantly since 2020, in large part due to the rise of the Delta and Omicron variants. However, based on data from the global science initiative GISAID, as of March 14, 2022, the average proportion of cases sequenced over 30 days in the US has fallen to three percent, compared to 13 percent in the UK (2). Without sufficient sequencing, we will no longer be able to detect potentially dangerous SARS-CoV-2 strains when they appear.

Currently, viral transport media containing fetal bovine serum (FBS) and saline buffers are recommended for antigen tests because of their lack of chemicals that interfere with SARS-CoV-2 protein structure and the lateral flow detection mechanism. However, samples collected in these media require refrigeration; viral RNA is unstable at ambient temperatures. In underserved areas, collecting samples under favorable conditions is difficult. According to Northwestern University, a group of scientists in Nigeria had to make four separate journeys that each took hours with terrible road conditions just to collect dry ice, pack samples, and drive them to a sequencing lab (3). Due to large testing volumes, many samples collected for antigen testing in FBS transport media and saline buffer will not be viable for RNA-based assays such as PCR confirmation and viral RNA sequencing. This is an urgent issue that must be addressed as antigen testing becomes an integral part of infectious disease control and monitoring. Specifically, we must ensure that sample integrity is maintained during storage and transportation without the use of refrigeration – and that confirmatory testing and variant sequencing remain a viable part of our disease control toolkit.

A lab technician demonstrating use of a COVID-19 antigen test.

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The Digital Revolution

Fujifilm providing end-to-end solutions for digital pathology customers

Tell us about Fujifilm's digital pathology solutions…

Fujifilm distributes the *Dynamyx* digital pathology solution. The *Dynamyx* software was originally designed by and for pathologists and laboratory teams, keeping the workflow, case management, case history, image evaluation, and management system all in one highly functional package. *Dynamyx* links to many scanners using either the original image file formats or Dicom. This enables Fujifilm to support any customer, whether they have legacy scanning devices or not. This openness extends to LIMS connectivity and AI. If a customer prefers a particular scanner, AI solution, or reporting tool, Fujifilm will provide the entire end-to-end solution.

How has Fujifilm's transition to digital pathology changed its service?

Histopathology services are facing a "perfect storm" – a yearly 5–7 percent increase in demand, often with increasingly complex cases, alongside a reduction in the number of Consultant Histopathologists. Pathology services are finding it difficult to recruit in a competitive employment market because, as young professionals make their career choices in scientific medicine, the "Xbox generation" of modern medical students are looking for IT-oriented opportunities that take advantage of AI. By transitioning its customers into digital pathology, Fujifilm is helping make histopathology more attractive. In addition to the user benefits, digital solutions offer significant logistical and operational benefits, enabling hospitals to achieve higher levels of productivity. Because the move to digital pathology is a natural extension of Fujifilm's already extensive history in digital imaging, Fujifilm is excited to be a part of the digital revolution in histopathology.

What kind of service support and training does Fujifilm provide?

Fujifilm understands that not everyone finds digitization easy and therefore provides a full support and implementation service that ensures program success. Fujifilm manages the entire process, allocating a dedicated project manager and application specialists. Particularly during the training phase, our experience has shown that it is preferable to engage one-on-one with the pathologists throughout the process. We tailor the project and address their personal views, such as acceptance of digital pathology, worries or concerns about the technology, and change reticence. Our engineering teams also implement the IT and technical infrastructure for the customer. Fujifilm's partner scanner companies operate similarly, teaching lab teams how the technology works. After training is complete, we allocate a Customer Relationship Manager to maintain regular contact in case users have any further needs or questions. Our CRM is backed up by the Clinical Application team if any further assistance is required.

What challenges did Fujifilm face when transitioning to digital pathology?

Convincing the pathology community that digital pathology is a viable alternative to microscopy has been a long journey. Five years ago, some pathologists were reluctant to discuss moving to digital. For a few, losing their microscope was described as "losing their right arm!" We rarely hear those concerns today because the histopathology community understands the role of digital pathology in the patient pathway.

The challenge for us is to help pathology management as they seek to convince their leadership that digital pathology generates significant return on investment.

How does Fujifilm's focus on digital pathology benefit both pathologists and patients?

Healthcare providers are regularly required to reduce diagnostic wait times. However, with fewer pathologists and more complex cases, the targets that are being set can be difficult to achieve. In support of healthcare providers, Fujifilm offers *Dynamyx* with digital tools that pathologists can use to speed up the measurements, diagnosis, and quantification of disease. The *Dynamyx* Open Platform facilitates the use of AI to give these initiatives greater impetus.

Combining AI with digitization can facilitate faster, more accurate, and more consistent clinical diagnosis. AI makes use of objective, quantitative data to give a true representation of disease. Everyone involved in the process can benefit from using AI, because it offers pathology services higher throughput with more consistency than a decreasing consultant workforce would otherwise allow.

In addition to all of this, Fujifilm can also deploy a Vendor Neutral Archive as part of its Cloud First strategy. This enables customers to adopt sophisticated rules that govern image data management, lifecycle management, data dissemination, recall, and enterprise access.

Finally, there are additional benefits. Consultants have told us that digital pathology "liberates them from the lab," allowing them to choose their own working environment.

One immediate benefit has been that pathology tasks that are repetitive and time-consuming, such as analyzing immunohistochemistry samples in breast pathology, can be supported by image analysis. These new tools support pathologists, freeing up time for them to focus on the complex cases in which their experience and expertise is most valuable.

Tim Wing is Head of Digital Pathology at Fujifilm Europe. Its UK subsidiary, FUJIFILM UK Limited, is based in Bedford, UK.

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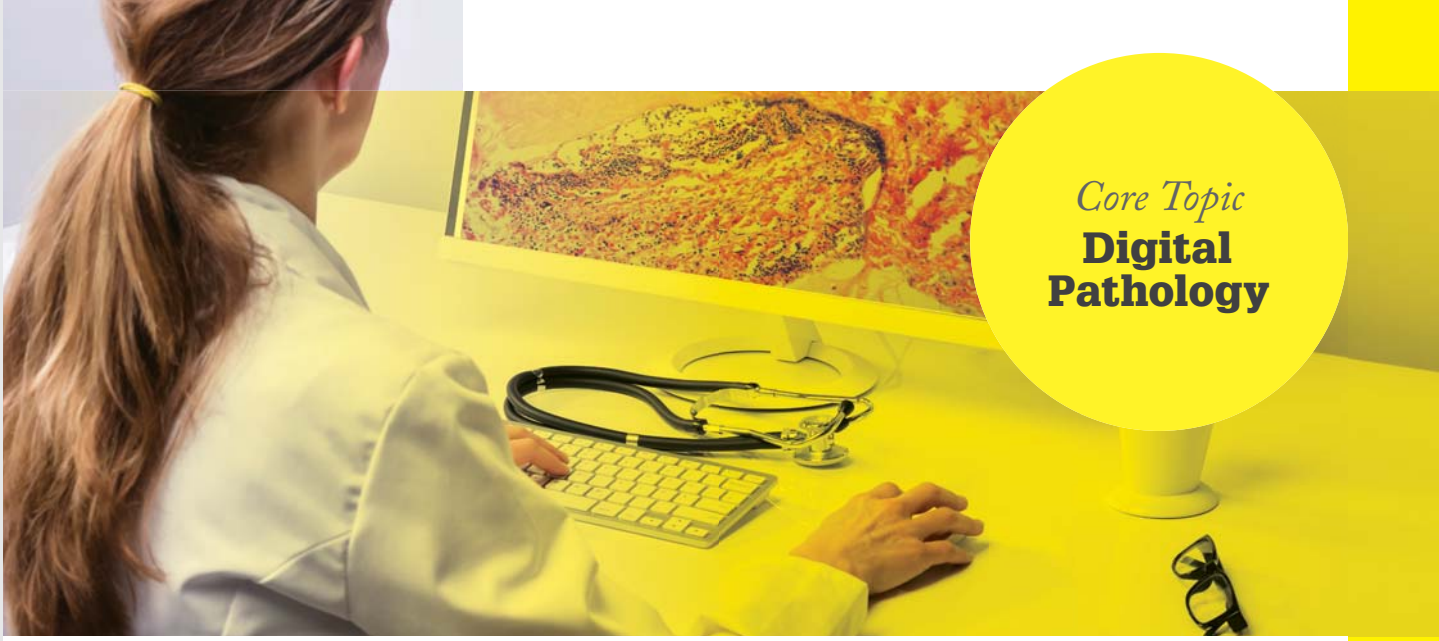

Core Topic
Digital Pathology

Superpixel Perfect. Colorectal cancer (CRC) is the most common gastrointestinal malignancy – but its stroma and tumor microenvironment are biologically complex and poorly understood. A new machine learning-based superpixel approach has linked low proportionated stromal area, high immature stromal percentage, and high myxoid stromal ratio with worse CRC prognoses (1). This could lead to a more effective and less invasive profiling approach.

Gut Feeling. The human gut plays host to many potential beneficial antimicrobial peptides (AMPs), but these molecules' tiny size makes computational prediction difficult. New research has shown that combining multiple natural language processing neural network models can help identify AMPs from human gut data (2). Of the study's 216 synthesized AMPs, 181 (over 83 percent) showed antimicrobial activity – and the 11 most potent showed significant efficacy against even antibiotic-resistant Gram-negative pathogens. This suggests that machine learning can bolster mining for promising antimicrobial peptides.

Private Pathology. Much of digital pathology implementation literature is focused on public health facilities, with little on private practice. A new report explores the challenges and opportunities of implementing digital pathology in private lab settings, with guidance on issues such as software integration, workflow adjustments, and change management (3). The authors conclude that digital pathology will ultimately benefit the private sector and lay a suitable foundation for future adoption of artificial intelligence.

Slide Away. A single whole-slide image is rarely enough – but matching and overlaying dissimilar scans sourced from different tech presents a challenge. To overcome it, researchers developed algorithms with adaptive smoothing, modified scale-invariant feature transform, and more to account for variations in images and streamline feature matching (4) – leading to even greater efficiency than current gold-standard methods.

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IN OTHER NEWS

AI ethics. *A new study explores the ethical issues that AI-led digital pathology poses for privacy, choice, equity, and trust (5).*

Blockchain pathology. *Avoiding the pitfalls of privacy legislation, researchers demonstrate how a decentralized, peer-to-peer approach to medical data could lead to rapid, reliable illness detection (6).*

Beating brain tumors. *Glioma outcomes vary widely, so accurate tumor subtype identification is key. New research highlights a multimodal MRI decision fusion-based network approach with high classification accuracy (7).*

Digital growth. *A new program is helping digitize pathology across the UK. The multi-million-pound initiative already covers six trusts and anticipates significant expansion in the near future (8).*

Dispelling the Myths

Realizing the promise of artificial intelligence today

By Nathan Buchbinder, Co-Founder and Chief Product Officer at Proscia, Philadelphia, Pennsylvania, USA

The era of computational pathology is upon us. Driven by a growing base of evidence on the economic and clinical benefits of adoption, leading laboratories are increasingly deploying AI in routine practice to optimize operations and improve patient care. Detection solutions are now helping pathologists improve quality by identifying cancer foci and providing a second set of eyes, and workflow solutions are triaging and sorting cases to drive critical efficiency gains.

This accelerating momentum is creating a newfound sense of enthusiasm, inspiring some laboratories while increasing the pressure on others to keep up. It's also fueling the hype around AI – and, sometimes, proliferating misconceptions that may make adoption seem overwhelming, especially for the organizations most at risk of falling behind.

AI is poised to make the biggest impact on pathology since the introduction of the light microscope over a century ago, so it's time to dispel these myths. The right understanding can empower all laboratories to chart their path in computational pathology, setting everyone up to realize its potential today and in the future.

Nathan Buchbinder

Myth: Without a clear vision, my laboratory isn't ready to adopt AI.

It's easy to understand why this misconception exists. After all, you know your laboratory's needs better than anyone, so you might assume that you're responsible for framing up your adoption plan – but you may not have a clear vision in mind. Perhaps you're even wondering how you're supposed to know all the answers when dealing with such a novel technology – and you're not alone.

The reality is that you only need to come to the table with an interest in adopting AI. The right AI provider will jump at this enthusiasm and leverage their experience to educate and guide you toward unlocking new value with AI in a way that works for your organization. Importantly, this includes much more than just helping you select and deploy technology. As with all digital transformation, the shift to computational pathology also requires adapting your processes and empowering your team. You should count on your AI provider to serve as a guide throughout all stages of this journey, working with you to establish a business case, build internal support, identify use cases, and configure your workflows at the very least.

Myth: Deploying AI is too hard for my laboratory.

This misconception stems from a somewhat outdated truth. Implementing computational applications into the day-to-day workflow has historically been a challenge, especially when you consider that these solutions add the most value when incorporated into routine operations. As we've already noted, though, leading laboratories are increasingly running AI as part of their regular practice, and we can look to their approach to dispel this myth.

We know that computational applications can only be applied to whole-slide images, not glass microscope slides. It follows that any laboratory implementing AI in routine operations has already made the shift to digital pathology. Just as these laboratories require a digital platform to carry out their day-to-day work at scale, they also rely on it to deploy AI. This platform serves as a launchpad for all of their computational solutions so that they can seamlessly integrate them into daily practice.

"By leveraging an open, interoperable platform, these laboratories – and your laboratory – can easily introduce new AI applications as needs change and technology evolves."

By leveraging an open, interoperable platform, these laboratories – and your laboratory – can easily introduce new AI applications as needs change and technology evolves. You'll gain the freedom to choose other solutions, from laboratory information systems to whole-slide scanners, and incorporate them into routine operations. In doing so, you can create a connected digital ecosystem that will scale with your laboratory and increasingly empower your team.

Myth: Our pathologists don't want to use AI.

This myth probably doesn't need much introduction. Ever since computational applications were nothing more than a pipe dream, pathologists have raised concerns that AI would replace them. More recently, they are also questioning whether AI will disrupt their familiar workflows.

You likely recognize that the growing body of evidence suggests otherwise, making this myth easy to dispel. What can be a bit more challenging, however, is determining how best to approach your pathologists to secure their buy-in and adopt AI in practice.

Keep in mind that your pathologists are the primary users of the computational solutions you're looking to implement. You'll want to put them at the center of the shift to AI, taking the time to hear their voices and educate them on the benefits that lie ahead. Let them weigh in as you determine your use cases and configure your workflows. You should take the same approach if your organization is also in the process of adopting digital pathology, because this, too, is a big transformation for your laboratory professionals. They should be included as primary decision makers when selecting a digital pathology platform. Because this platform powers all your operations, including your AI-powered workflows, it is critical that its users feel it is designed with them in mind.

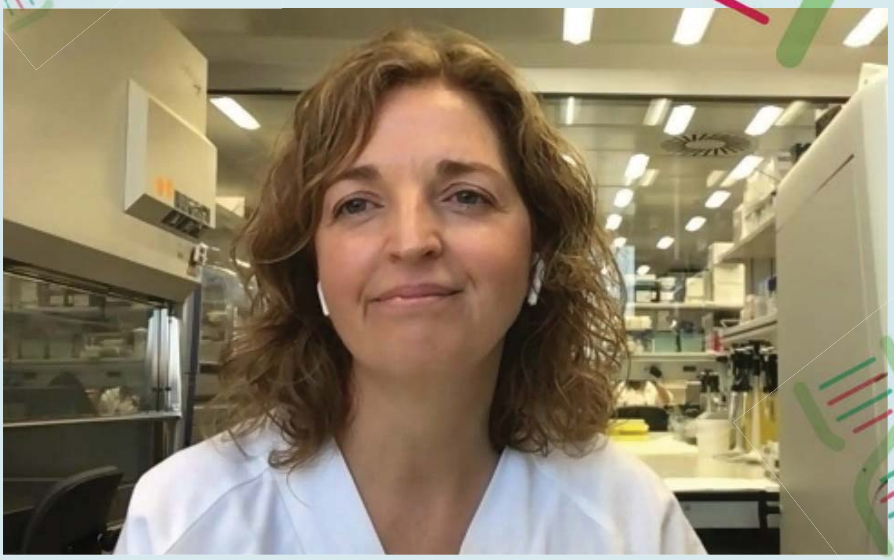
Finally, it's important to remember that you don't have to navigate this journey alone. The right partner will be armed with best practices for winning over your team and provide the insight you need to overcome any objections.

As computational pathology quickly extends beyond academic medical centers and large laboratory networks, it's time for your organization to take advantage of the unprecedented value ahead. With the right understanding, the right partner, and the right technology, you can go beyond the hype to adopt AI in a way that works for your laboratory – and chart your course as a leader in this new wave of diagnostic medicine.

The "Impossibly Easy" NGS

Implementing next-generation sequencing (NGS) for rapid, efficient oncology biomarker testing

An interview with Lara Navarro



Lara Navarro is Head Biologist in the Anatomical Pathology Department of the General University Hospital of Valencia, Spain. Her lab, like many others over last decade, has brought in new approaches to cancer sample testing. Not only do they use conventional methods such as immunohistochemistry and immunofluorescence, but they have also implemented complementary molecular biology techniques for genomic profiling. We sat down over Zoom with Lara to discuss her lab's experience implementing in-house next-generation sequencing (NGS).

Can you tell us about biomarker testing in your lab?

We have 12 to 15 samples each week (so about 50 cases per month), mainly *EGFR, ALK, ROS, RET, MET*, and Her-2. Before we brought in NGS, our biomarker testing was done gene by gene; we mainly used rtPCR, pyrosequencing, and – of course – Sanger sequencing.

Why did you decide to implement NGS – and were there any worries in your mind?

The main reason for the change was that we were increasingly required to test for multiple biomarkers with the smallest amount of sample possible. We needed a new technique that would allow us to conduct many simultaneous tests.

Our main worry was whether the workflow was going to be realistically implementable in our laboratory. Would it be too time-consuming? Would it require too many resources?

We were very surprised (in a positive way!) by the Genexus System. It was so straightforward and so fast that, almost as soon as it was installed, we started using it for routine testing. The workflow is one of the simplest we have here in the laboratory. All the required tasks (such as adding the reagents) are easy to perform and the software checks after the fact to ensure that no errors have been made. The consolidation of the workflow from sample to report, the speed, and the automation all make the system easy to implement and a great fit for our laboratory.

"It takes us a maximum of two working days from getting a sample to returning a report."

How does the Genexus System reduce hands-on time in your laboratory?

The process is practically fully automated and requires only about 20 minutes of hands-on time altogether – from nucleic acid extraction to final result and report. I think techniques such as fluorescence in situ hybridization or immunohistochemistry require the same, or perhaps even less, hands-on time – but analyzing genes using Sanger sequencing requires significantly more hands-on time and can take days to yield a result.

For laboratories like ours, speed and efficiency are vital. We receive samples every day and need to process them fast, so we could not have implemented previous incarnations of NGS that required a lot of hands-on time and took several days to produce a result.

What is your turnaround time for results?

It takes us a maximum of two working days from getting a sample to returning a report. To be more precise, it takes us two working mornings, because we don't work on this type of testing later in the day. If a biomarker test is requested through the department information system on Monday morning, we have the report ready by Wednesday.

What panel do you use – and for what samples?

We use the Oncomine Precision Assay 50-gene panel, which covers all of the biomarkers we need to test. Most of the samples we test are lung cancers, which are notoriously small because most are taken via bronchoscopy. Most of the time, we have only one segment available, which needs to stretch to all of the necessary testing. That is why we value the Oncomine Precision Assay so much; it is an efficient way to use a small sample. We try to use samples with at least 20 percent tumor cells, but we do occasionally have to go as low as 5 percent – and, even when that happens, 98 percent of samples yield a conclusive result.

Although lung cancer constitutes the majority of our samples, we also use the assay for colon cancers, melanomas, gliomas, some breast cancer samples, and some thyroid cancers.

Can you describe the bioinformatics software user experience?

The system employs one user-friendly software interface for the whole workflow, which makes our work very easy. We were also able to create a traceability system so that, at any time, we can see what samples have been sequenced, when they were sequenced, and what else our laboratory did with the sample – not to mention downloading the report.

How would you summarize your experience with NGS so far?

Honestly, based on what we had seen in the past with other platforms, we didn't think it would be possible to implement NGS in our lab. We were pleasantly surprised! With the Genexus System, the level of automation is such that very little hands-on work is needed and our turnaround time is very short. The implementation process went smoothly and, now that we are fully up and running, we no longer experience sample accumulation and work overload. It has changed – very much for the better – the way we test for oncology biomarkers in our lab.

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School's in for Summer

How the Dubrovnik Summer School of Pathophysiology is inspiring the next generation of pathologists

By Zdenko Kovač

Are we ever truly done with school? Personally, I think the answer is "no." School can help young professionals enrich their careers with broader views and visions and spark their enthusiasm for topics that may not have been covered in depth during their training. My own learning inspiration comes from the integration of etiopathogenesis and the understanding of pathophysiology – a lasting fascination that motivated me to create the Dubrovnik Summer School of Pathophysiology.

The summer school was designed to present the inquiring spirits of young biomedical professionals and advanced students with cutting-edge scientific research. In 2021, many overseas students were unable to attend in person – but the class proceeded nonetheless, in a hybrid format that delivered seminars to 45 in-person students and up to 47 online attendees, who actively contributed to the sessions with questions, comments, and added case examples.

Pathophysiology's rightful place

Adopting integrated MET across the care continuum addresses interoperability issues, creates shared quality metrics, addresses communication dndor systems to impact the entire care continuum. Most importantly, MET allows practices and communities to accurately measure performance, identify care delivery and workflow issues, make needed corrections to deliver the highest quality, evidence-based care, and enables the movement to value-based care.

Pathophysiology can be represented in a simple Venn diagram (see Figure 1). Its laws, reactivity patterns, and homeostatic and allostatic steady states are relevant to every branch of research and clinical medicine. Rudolf Virchow, the founding father of pathophysiology, described the discipline as "the stronghold of scientific medicine." This holds true with no exception – interconnecting elements of etiopathogenesis have much in common with even very heterogeneous diseases (see Figure 2).

"The summer school was designed to present the inquiring spirits of young biomedical professionals and advanced students with cutting-edge scientific research."

Overlapping patterns of body responses are considered general pathophysiology, which is often covered as an independent subject at university.

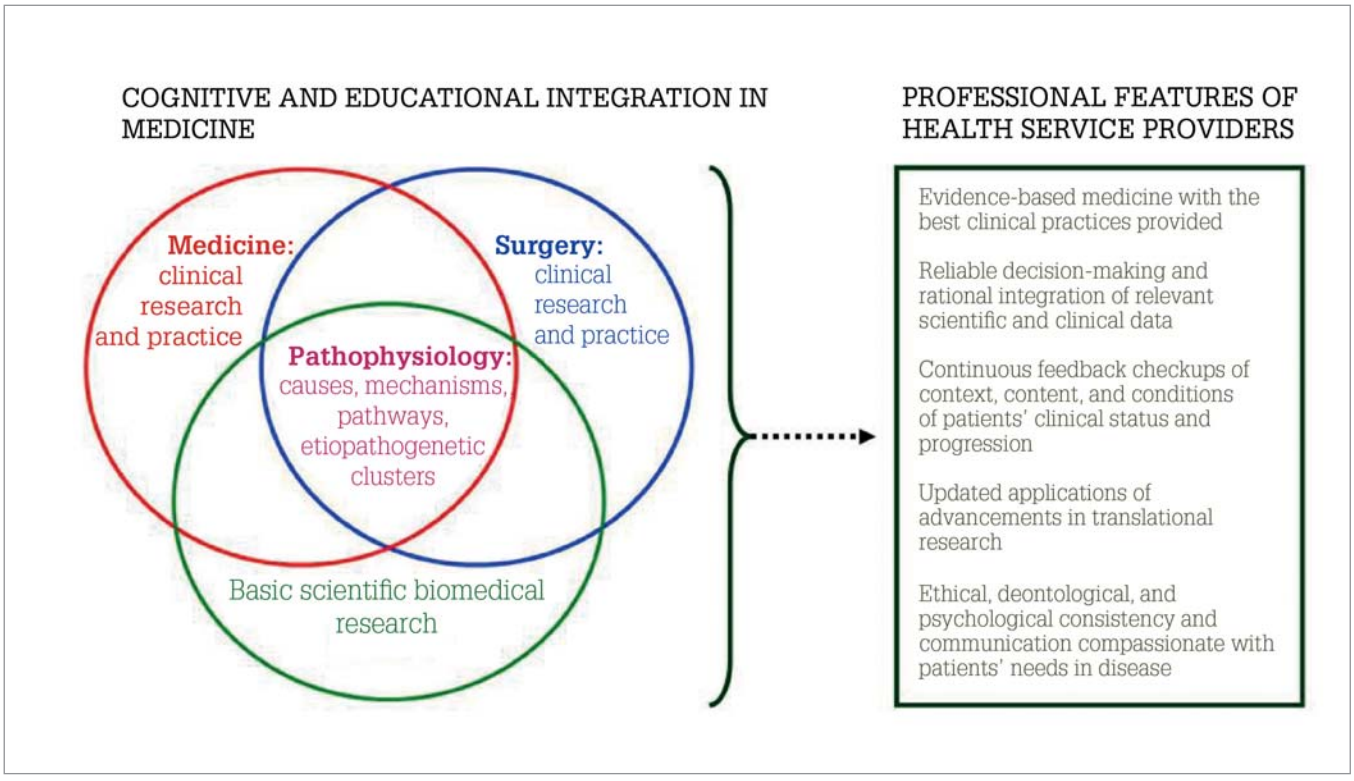


Figure 1. A graphical representation of pathophysiology.

According to the International Society for Pathophysiology, at least 54 countries view general pathophysiology as a separate subject. In other regions, the same etiopathogenetic principles are studied as subdisciplines of clinical physiology, semiology, practical medicine, and general pathology.

Pathophysiology is an important part of medical education – and I intend to keep it that way. Following a century-long tradition of integral pathophysiology in Zagreb, Croatia, my group has developed a four-step method for teaching and learning. It involves the exposition of a problem (reviewing the medical history of a real case), analytical repetitions of related knowledge via multiple-choice questions, designing an etiopathogenetic algorithm from a predetermined set of disease elements, and systematizing with quantitative aspects of the same problem.

Through various activities, students are guided through pathways, regulatory interactions, connections between processes, signs, symptoms, and outcomes. They construct graphic representations of processes and defend their interpretations of relationships between elements of etiopathogenesis. This core intention triggers enthusiasm and fulfills students' expectations – a process known as the "Lego principle of play." Students have praised it for its ability to enable them to navigate a plethora of information, make sense of fragmentary knowledge, and feel like they are opening a treasure chest of biomedical expertise.

After hearing about the foundations and backstory of the summer school, readers may wonder – why host it in Dubrovnik? I was born and raised in the oldest continuously inhabited city (Vinkovci), so my interest in history and material artifacts of human culture naturally influences my way of thinking. Dubrovnik is a pearl of human civilization and cultural creation – it is internationally renowned, with a rich history of tradition and famous figures. Many of our summer school participants have said that they treasured the unique experiences they have had in Dubrovnik – one of my goals already achieved!

Bridging the gap

I view pathophysiology as a bridge between basic biomedical sciences, laboratory medicine, and clinical practice. It can be difficult to build this bridge in medicine, but I kept that concept in mind when designing the summer school curriculum. We tried to highlight the relationship via lectures, problem-oriented seminars, and practical sessions that involved clinical, laboratory, and quantitative exercises –

Participants in the Dubrovnik Summer School of Pathophysiology.

"According to the International Society for Pathophysiology, at least 54 countries view general pathophysiology as a separate subject."

solving algorithms and EPCs highlights the importance of recent scientific discoveries and standard clinical data and showcases the students' ability to integrate both.

At my medical school, the pathophysiology course is taken in the third year and is interposed between preclinical and clinical disciplines – a logical position for bridging the two areas. To stay up to date with new scientific discoveries, concepts, and frameworks, we have continued with *Colloquia pathophysiologica* – weekly seminars held over 1,100 times in the past 25 years. In the sessions, four to five papers are presented, followed by a discussion of their interpretations within the concepts and practices of clinical medicine. In addition, we hold *Seminaria pathophysiologica demonstratorum* (over 150 in the past six years) for advanced students and physicians with similar goals. Each year, teachers actively participate in international experimental biology, clinical, and pathophysiology conferences to update the school's study materials.

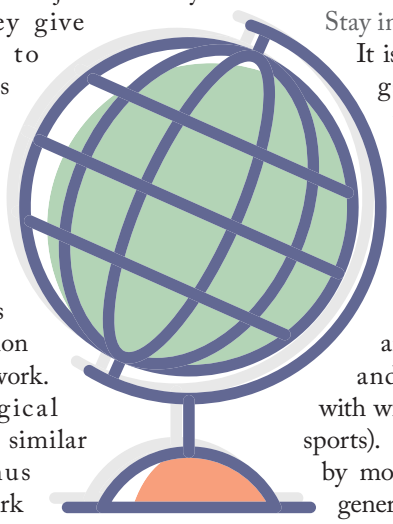
I follow a unique approach to solving clinical problems, which I try to apply throughout my teaching – an analytic-synthetic approach to etiopathogenetic pathways. Algorithmic elaborations have revealed an interesting regularity of the networking of etiopathogenetic pathways. There are integrative "hubs" or nodes where multiple pathways join and others are initiated. We named these hubs "etiopathogenetic clusters" (EPCs). So far, we have identified 91 EPCs that occur in various diseases – heterogenous etiological factors trigger disease pathways that have a natural tendency to form these EPCS. Simply put, human body reactivity is reduced to the networking of those 91 elements – and this simplification is useful because therapeutic intervention in

some of these EPCs can lead to direct clinical improvement. For example, ventricular fibrillation conversion can save lives by preventing cardiogenic shock – one of the 91 EPCs (see Figure 2). Rapidly infusing glucose can correct the hypoglycemia EPC and prevent hypoglycemic coma and shock in diabetic patients with insulin overdose. All EPCs are elements of natural disease pathway networking and, for most of them, these improvements hold true.

This approach has received praise from educators around the world. Leonid Churilov from the University of Saint Petersburg said, "These are around 100 mosaic blocks, interplaying in all nosological forms, like elements of Mendeleyev's table adjoined to any substance, so they give strong impetus to systemic autonomous analysis of clinical pathophysiological problems."

The novelty of this approach lies in the independent disease processes that trigger a common part of the EPC network. Unrelated etiological factors may trigger similar reactions and thus similar EPC network events. From this concept and etiopathogenetic facts, there are clear predictions of disease cross-talks in comorbidities. In the summer school, we present reports of mutual aggravation of two comorbidities and mutual inhibition, prevention, and alleviation of other pairs of diseases.

So far, I have developed over 100 key EPCs for the course and incorporated them into Croatian medical education. Four medical schools in the country have successfully used this system for over 20 years in both teaching and examination; many other universities also use the model and, in Russia, it has been presented in a series of papers in key pathophysiology journals distributed by medical academic communities in Kaliningrad and Vladivostok. So far, 12 sets of algorithms and EPCs with solutions have been published and presented at international conferences and educational symposia (1–4).



Stay in-quiz-itive

It is one thing to bridge the gap between disciplines when students attend the summer school – but how do you encourage active participation? Quizzes are an attractive form of entertainment; they produce emotional, social, and intellectual dynamics, and are quickly resolved with winners and losers (just like sports). Because they're enjoyed by modern students and older generations alike, we included a competition in our program. The quiz consisted of a written test that required thorough understanding of disease physiology, with three top teams (out of nine) selected for the oral competition. Examples of questions included:

"At my medical school, the pathophysiology course is taken in the third year and is interposed between preclinical and clinical disciplines – a logical position for bridging the two areas."

- Name three clinical conditions with hypermetabolic state.
- Explain three direct cellular dysfunctions due to intracellular ATP shortage.

Three team members had 30 seconds to write down their answers; then, the academic judges publicly evaluated the solutions and decided on points to award. The winning team were awarded travel expenses to Kuala Lumpur to participate in the 20th Inter-Medical School Physiology Quiz, which is a large Southeast Asia competition for university quiz teams.

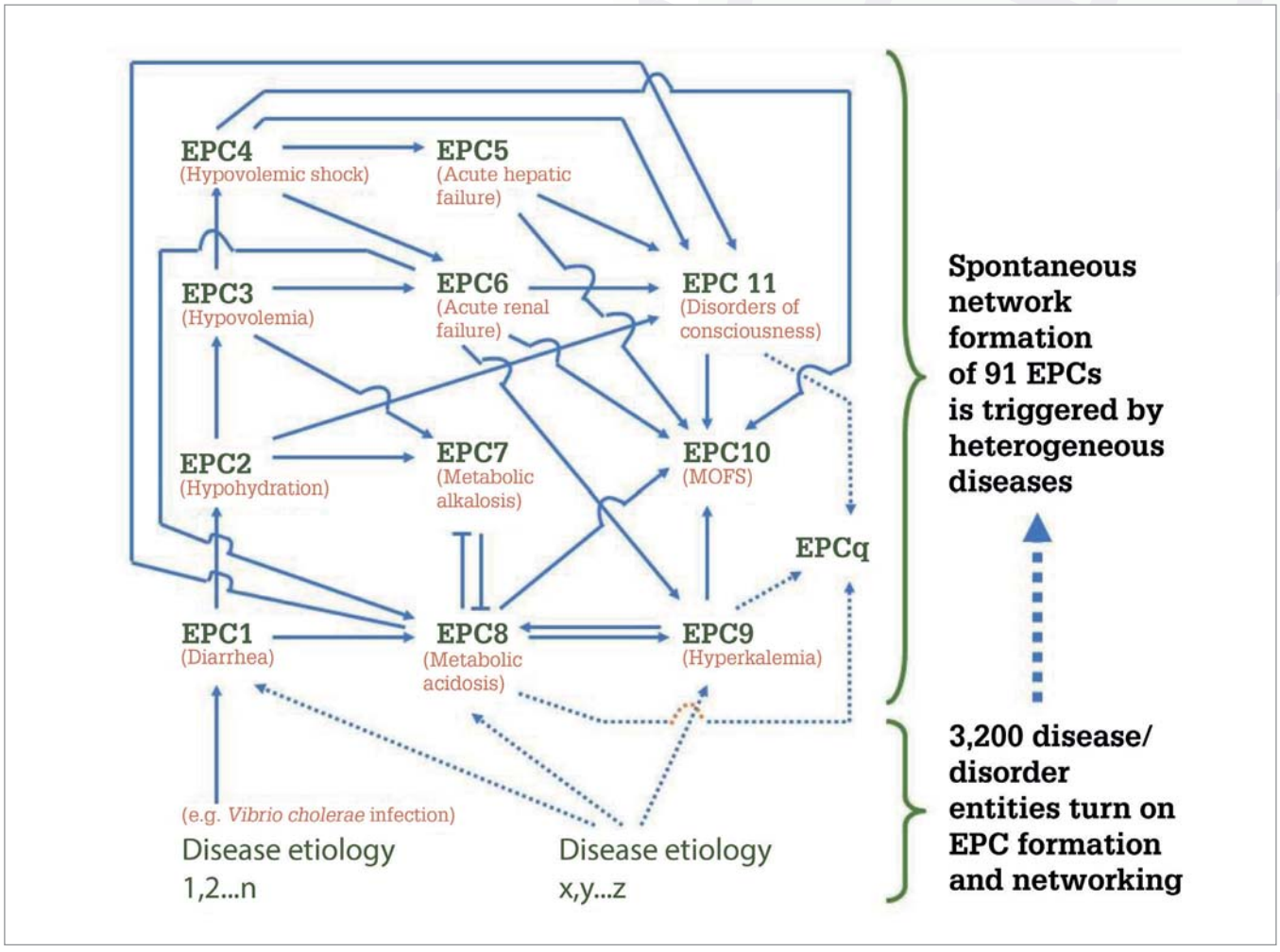


Figure 2. Common interconnecting elements of disease etiopathogenesis.

Proud moments

Since its inception, the summer school has had many significant achievements – but a few of those stand out. Despite the COVID-19 pandemic, we still managed to hold a hybrid version of the summer school, bringing together students and experts from around the world. Across three and a half days, we facilitated active discussions of human physiology via 24 lectures, two audio-visual featured topics, and a competition. Several students also presented case studies and published research throughout the program, helping to build confidence and raise awareness of the great work they're doing.

T-shirts with the school's logo inspired team spirit in the young pathophysiology community. And, of course, both students and teachers enjoyed the beauty and beaches of Lokrum (just 10 minutes by boat from Dubrovnik), where new ideas were brought to life and a new chapter of our academic lives began.

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Drifting From the Norm

Demonstrating the advantages of bead-based normalization for next-generation sequencing

Library normalization is crucial for optimizing clustering and data quality – but what is it? Pedro Echave, Global Leader of NGS Product Experts at PerkinElmer, explains, "Normalization refers to the process by which libraries of different concentrations are diluted to the same final – 'normalized' – concentration before pooling and loading into the sequencer. This step is recommended to obtain best data quality from a run, so most next-generation sequencing (NGS) users do it. To normalize, you must quantify your libraries, do some calculations, and adjust the concentration of each library by pipetting different volumes of buffer (usually manually)."

Though normalization is crucial, the potentially convoluted process places time and cost constraints on labs – particularly those feeling the strain of workforce shortages. That's where PerkinElmer's new, patent-pending, bead-based normalization technique comes in. "Bead-based normalization uses a completely different approach to yield the best data quality," says Echave. "Here, DNA-binding beads are added to all the libraries. A fixed amount of DNA will bind to those beads, which means that, after elution, the libraries will have approximately the same concentration. Therefore, by using bead-based normalization, you eliminate the need to quantify and dilute your samples before pooling."

How, then, can bead-based normalization be applied to NGS? "In theory, bead-based normalization can be used at different points during library preparation workflow, but it is mostly applied at the end – after libraries are finished," says Echave. "The user adds the beads, elutes them, and then pools the samples in a new tube by adding equal volumes of each."

Choosing bead-based normalization for NGS has many benefits for lab medicine professionals – key among them reducing turnaround times and saving costs. "Bead-based normalization is faster and less labor-intensive than traditional normalization methods," says Echave. "Additionally, traditional normalization requires reagents and consumables (such as Qubit reagent, tubes, tips, and microwell plates) that are not needed when using beads."

The method can also help with multiplexing and scale laboratory capacity, which could alleviate shortages in the laboratory workforce. "The main advantages of normalization beads are the savings in reagents and consumables – but, by also reducing the time required to load samples into the sequencer, normalization beads allow laboratories to process more samples," echoes Echave. "With normalization, laboratories can save up to three hours per 96 samples, which increases processing capacity and throughput. If the lab can process a higher number of samples, this will yield a bigger time-saving benefit for them and, in turn, decrease the cost per sample."

A particular application example that comes to Echave's mind is using PerkinElmer's NEXTFLEX® Variant-Seq™ SARS-CoV-2 Kit with normalization beads. "During the pandemic, laboratories were flooded with thousands of SARS-CoV-2 PCR-positive samples to sequence so that they could track the emergence of viral mutations in real time. There was a lot of pressure to deliver results as quickly as possible; however, the yields of libraries from SARS-CoV-2 PCR positive samples are highly variable – a direct consequence of the range of viral loads that appear. That's where normalization beads help. The beads in our NEXTFLEX Variant-Seq SARS-CoV-2 kit v2 successfully normalize libraries with Ct≤32, which saves up to three hours of processing time for every 96 samples – effectively reducing turnaround times for labs at a time when it is sorely needed."

With the advantages of normalization beads clear, how else could labs improve their NGS workflows? Echave suggests, "To be more cost effective and yield rapid, reliable results, labs will need sensitive kits and optimized and automated NGS workflows that are adapted to their throughput and applications. When starting their journey to more effective workflows, pathologists should know that PerkinElmer is happy to support its customers with optimized solutions and application expertise."

Pioneering the Future

Sitting Down With… Alexi Baidoshvili, Clinical Pathologist and Director of Computational Pathology at Laboratorium Pathologie Oost Nederland (LabPON), Hengelo, Netherlands

What led you to pathology – and, from there, to digital pathology?

During my medical studies at the Vrije Universiteit in Amsterdam, I found a side job as a researcher in the pathology department. That allowed me to learn about the pathology department and realize that and a specialization in pathology would suit me well.

My research required me to work with a type of early artificial intelligence (AI) software that could recognize certain structures on photos of glass slides. I found this research very interesting because, alongside my medical studies, computers were a hobby of mine – one that later led to my fascination with digital pathology. After finalizing my training as a pathologist, I was given the opportunity to work for LabPON (Hengelo, The Netherlands), which was looking for a pathologist with an interest in digital technologies. I began digitizing the entire laboratory – a difficult, but instructive and innovative project – and, in 2015, we completed the switch to fully digital diagnostics.

How did you do it?

When we began, nobody had any experience with digital pathology. We visited various laboratories in different countries that used scanners mainly for research and education – but we wanted a suitable scanner and IMS (image management system) software for diagnostic purposes. Unfortunately, there was nothing at the time that met our requirements – so we decided to collaborate with an industry partner to improve scanner technology and develop a diagnostic IMS. Since then, we've worked together on not only an IMS and a scanner, but also diagnostic-quality monitors, an optimal server, and other necessary equipment and software. We tested and validated each new piece of equipment and software and then put it to use in our lab.

Many people at LabPON put huge amounts of effort into this project, which is why it was so successful. After we became the first fully digital lab, there was enormous worldwide interest in our work; visitors came from various countries every week to see our equipment and workflows. Our group – and I personally – learned a lot during not only the digital pathology development process (which has taken many years and inspired products that did not previously exist), but also from our many international visitors.

LabPON has been fully digital for over five years now. What's next?

Our next step is to implement a new IMS – which we're currently working on. Our scanner is also due for replacement; because we want to digitize cytology and solve other challenges in digital diagnostics, we have set higher requirements for a new scanner. And, finally, we are looking for affordable long-term WSI storage so that we can keep our slide images for longer.

One of our most important goals is to integrate AI into diagnostics. We are currently working on determining our vision for the future in connection with AI to plan the next steps properly.

Now that digital pathology has advanced a few years, what are the biggest challenges facing those who want to make the transition?

Not only are there many more scanner choices than when we began, today's scanners can also do much more and the quality of the WSI is much better. It is very important to select the correct scanner when planning a digital transition, because each scanner has its own limitations and the laboratory's needs should guide the choice of equipment.

There are also multiple IMS options. It is important to choose an IMS that can work with the WSIs from different devices so that you are never limited in terms of scanner choice. The IMS must also be easy to use and integrable with not only the laboratory information management system, but also the various image analysis apps used by different companies.

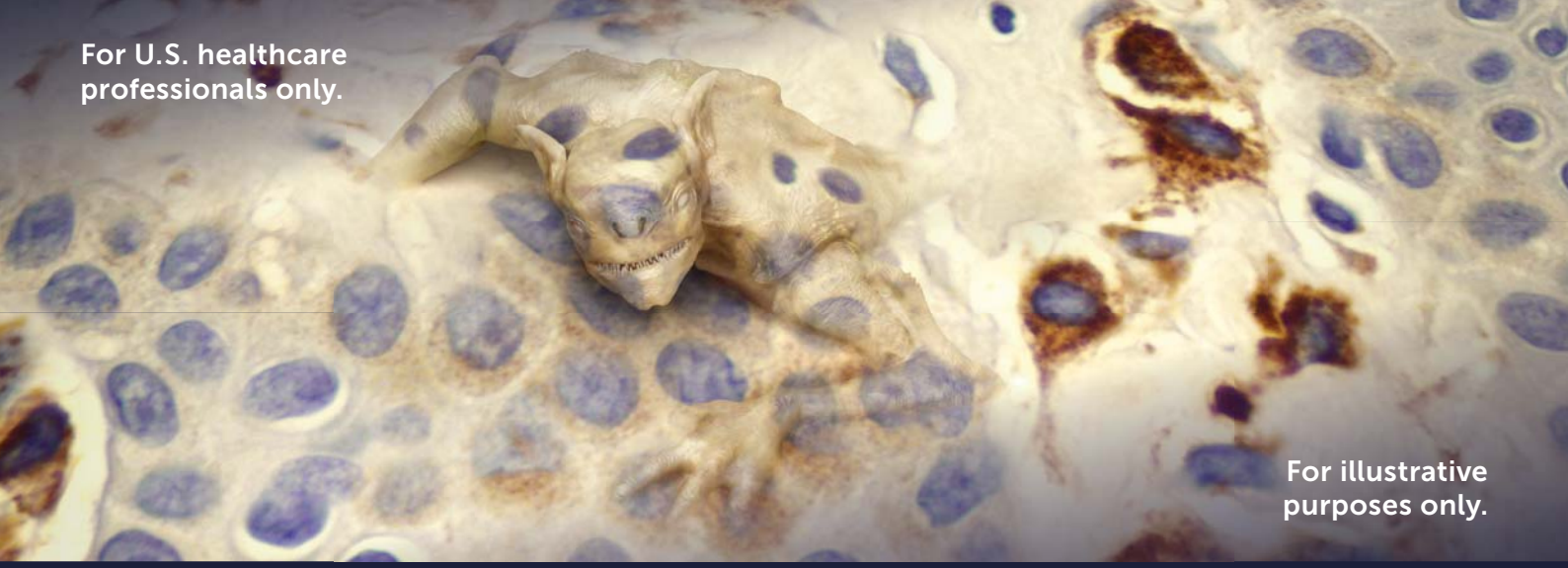
My most important advice is to investigate the laboratory's workflow well before switching to digital diagnostics and to use that information to draw up a phased plan that includes selecting the right scanner and IMS for the laboratory.

Has going digital changed your work-life balance?

Digitization has indeed changed the way we work. Pathologists are no longer dependent on microscopes and therefore on their offices. Thanks to digitization, we now have the liberty to choose our workplaces. We can now work at home, at different locations in hospitals or laboratories, and anywhere else suitable. Of course, it is important to ensure that this advantage is used responsibly on both sides. Don't allow this new freedom of movement to increase pathologists' working hours or tolerance for work in irresponsible circumstances. At LabPON, we have worked remotely for a long time – and we have developed agreements that ensure it's a good situation for everyone.

What is your best career advice for aspiring pathologists and laboratory medicine professionals?

Digitization is the future. Over the next few years, digital diagnostics will replace microscopes and AI will come into its own as a diagnostic methodology. It is important for pathologists to maximize use of new technologies during their studies to gain familiarity. Digitization will lead to changes in tumor grading, immunohistochemical staining assessment, quantitative pathology, and many other areas. Pay good attention to digital pathology while studying and you will be well-prepared for the future of the field.



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