DECEMBER 2019 # 61

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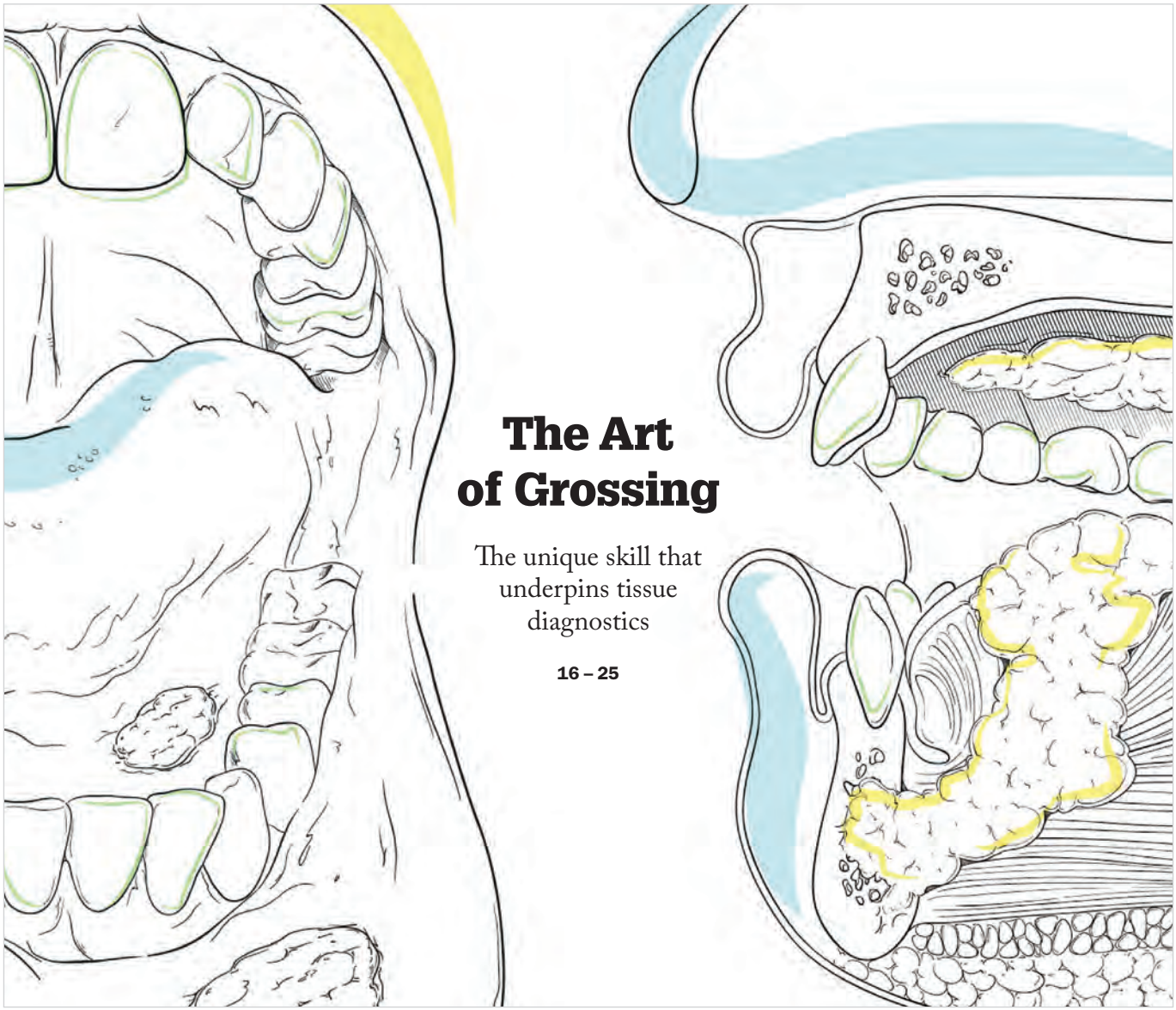

The Art of Grossing

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Case of the Month

A 45-year old female presented with a right parotid mass. The mass was completely excised.

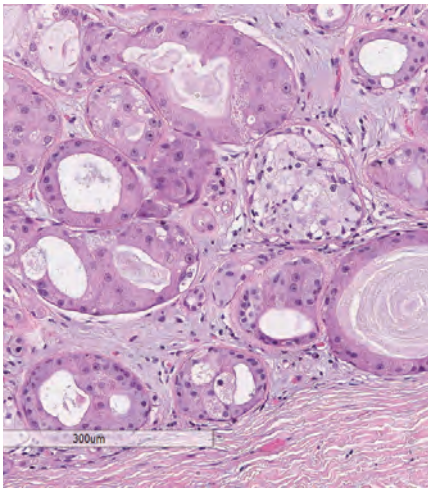
What is the diagnosis?

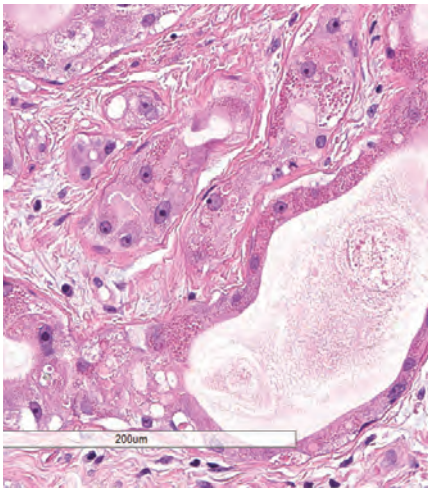
A Pleomorphic adenoma

B Salivary duct carcinoma

C Chronic sclerosing sialadenitis

D Sclerosing polycystic adenosis





Answer to last issue's Case of the Month…

D. Fibroepithelial polyp

Fibroepithelial polyps (FEPs) are rare, benign, mesenchymal lesions, commonly found in the ureters and renal pelvis (1,2). Rarely, FEPs are bilateral. Approximately 70 percent of patients are males. FEPs may occur at any age, but are the most common benign polypoid lesions of the ureters in children (3). Colicky flank pain and hematuria are the most common symptoms. The etiology is uncertain, but the prognosis for patients with these lesions is excellent (4).

Grossly, FEPs consist of single or multiple slender, smooth-surfaced, vermiform polyps that usually arise from a common base. Microscopically, they are cloverleaf-like projections covered by urothelium; can be typical, reactive, or hyperplastic; and may be focally eroded. The core of the polyp comprises an edematous and vascular stroma with few inflammatory cells. Scattered atypical stromal cells may be present (4).

Submitted by José Antonio Navarro Venebra, Hospital Civil de Culiacán, Sinaloa, Mexico.

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To register your guess for this month's case, please go to http://tp.txp.to/1219/case-of-the-month
We will reveal the answer in next month's issue!

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Wise Words

What we've learned this year from pathologists at the leading edge

The old year is drawing to a close. In keeping with the season's tradition of reflection, I've sought out words of wisdom from the leading pathologists and laboratory medicine professionals we've spoken to over the past year to carry with me into the new year – and I thought I would share them with you as well.

"In any field – and especially in science – we achieve very little alone. To become independent, rigorous scientists with the vision to ask and answer important questions, we must be trained and mentored, supported and encouraged." – *Benjamin Garcia*

"If I could go back and give my younger self one piece of advice, I'd say, 'Do it the same way. Follow what you love doing, and the rest somehow works out.'" – *Rick Mitchell*

"One of the things I would tell myself is to be resilient. Resilience is key to being a great leader. I would also say to have fun, and always to focus on the end goal – which, for me, has always been the patient." – *Dame Sue Hill*

"Think carefully about what you really want out of your career, as well as the environments and situations in which you thrive. You are unlikely to find a "perfect" fit with what you want to do, so be prepared to be adaptable." – *Bethany Williams*

"When I speak to young people at the start of their careers, I always give them the same piece of advice: identify the big problems and seek a solution; life is too short to solve small problems." – *Stephen Quake*

"It's important to have confidence in yourself and to speak up, especially when you think everybody already knows what you're going to say. Sometimes they don't; sometimes, your ideas are novel and you engage with people who can offer new opportunities." – *Ann Nelson*

"There's no magic recipe to maintaining a healthy work-life balance – and, sometimes, something has to give!" – *Anant Madabhushi*

"Be bold, confident, and joyful in who you are and don't be afraid of the judgment of others, because you are not being yourself if everyone likes you. The greatest gift you can give society is you!" – *Bennet Omalu*

I hope all of you have a wonderful holiday break and that the new year finds you refreshed and ready for anything!

Michael Schubert
Editor

Upfront

Reporting on research, innovations, policies and personalities that are shaping pathology today.

Do you want to share some interesting research or an issue that will impact pathology?

Email: edit@thepathologist.com

Beating the Biopsy

A new approach to prostate cancer testing could help avoid unnecessary invasive procedures and treatments

Prostate cancer diagnostics have undergone a rollercoaster of opinion over the years. Is the prostate-specific antigen (PSA) test reliable or not? Are patients receiving biopsies that may not be necessary? Are patients being over-treated as a result of false-positive test results?

A new study from Queen Mary University of London aims to reduce false positives and, by doing so, prevent biopsies and treatments that are not only expensive, time-consuming, and painful – but also, in some cases, entirely unnecessary. Instead of proceeding directly from a positive PSA test to prostate biopsy, Yong-Jie Lu and his team measured the levels of circulating tumor cells (CTCs) in patients' blood – a more reliable detector of cancer than the PSA protein, but without the downsides of an invasive procedure. The result? By combining both blood tests, the researchers improved their ability to predict clinically significant prostate cancer – and adding a prognostic 12-gene panel further amplified that improvement (1). There's still some way to go before the test becomes widely available; it needs further validation and regulatory approval.

"The current prostate cancer test often leads to […] significant harm to patients and a waste of valuable healthcare resources. There is clearly a need for better selection of patients to undergo the biopsy procedure," Lu said in a recent press release (2). "By combining the new CTC analysis with the current PSA test, we were able to detect prostate cancer with the highest level of accuracy ever seen in any biomarker test, which could spare many patients unnecessary biopsies."

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A Mouthwatering Malaria Test

Could the world's first saliva-based RDT for malaria boost eradication efforts?

Malaria claims over 435,000 lives around the globe each year. In our fight to eradicate the disease, early detection of subclinical and asymptomatic infection (and of those who carry the parasite without falling ill) is vital. However, current blood-based tests are invasive, require administration by clinicians, and often cause patients stress. Now, the world's first saliva-based rapid diagnostic test (RDT) for malaria – backed by a US$1,199,161 (¥138,269,665) grant from Japan's Global Health Innovative Technology (GHIT) – seeks to offer a simpler, less invasive alternative (1).

A recent report from the World Health Organization's Strategic Advisory Group on malaria eradication called for more research and the development of innovative diagnostic tools to replace existing blood tests (2). Rhoel Dinglasan and his team at the University of Florida have answered the call by laying the groundwork for a new saliva test called SALVA!. "We set out to discover and identify protein biomarkers specific to Plasmodium falciparum – or the different phases of the parasite in the human body – in fluids other than blood," says Dinglasan. Their discovery? A new protein biomarker, PSSP17, that is present in saliva and identifies asymptomatic infected individuals who are likely to progress to malaria within a week.

The testing device is designed to allow healthcare professionals, teachers, and parents to carry out the procedure by taking a small saliva sample – no specialist training is required. Thanks to GHIT's funding, the next step will be to produce 2,000 SALVA! kits, each containing high-affinity recombinant humanized monoclonal antibodies to detect PSSP17 on a lateral flow test. The devices are then set to be tested in either the Democratic Republic of Congo or Uganda in 2020.

"Once launched, we anticipate the tests will be used globally, but specifically in all endemic areas," explains Dinglasan. "Mass screening for carrier detection will be the first step in the regional elimination process, but detecting early-stage asymptomatic acute disease – in addition to symptomatic acute disease – will require global roll-out." The test's accessibility is a particularly enticing goal. "RDTs are crucial in curtailing malaria and, in this case, we have a minimally invasive saliva-based test that is easy to use and doesn't have to be administered by a healthcare professional. We hope this early detection can finally make the eradication of malaria a reality."

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In My View

In this opinion section, experts from across the world share a single strongly held view or key idea.

Submissions are welcome. Articles should be short, focused, personal and passionate, and may deal with any aspect of laboratory medicine. They can be up to 600 words in length and written in the first person.

Contact the editors at edit@thepathologist.com

The Road to Augmented Pathology

Paving the way for virtual and augmented reality in medicine

By Laszlo Igali, Consultant Histopathologist at the Norfolk and Norwich University Hospital, and Ferenc Igali, Lead Technician of the School of Education, Faculty of Social Science, University of Sheffield, UK

As a cellular pathologist, Laszlo began his career at a time when the microscope required a table lamp as its external light source and a mirror on its base to make sense of histology and cytology slides. But thanks to relentless technological development, the field has evolved considerably in the space of just a single generation – and new technologies continue to make their mark in pathology today.

But what does the future hold for this precise specialty that uncovers the secrets behind human tissue? Pathology's ultimate aim is to use imaging techniques to link what we see in the tissue with what we know about disease so that we can diagnose our patients and recommend the most effective treatments.

To do this successfully, information is key. We interrogate tissue to reveal any underlying information that contributes to identification of the disease or neoplasm. But there is one major constraint: we can only examine tissue taken from a single point in the course of a disease, removed from its environment, and frozen in time. The resulting sample represents only a minuscule portion of an organ or tissue. A frozen section is a tissue wafer no more than 2.5 cm in diameter and approximately 3-4 µm thick, or half the diameter of a red blood cell. It's no wonder that, with this alone to go on, we can't always find the answers we seek.

"Imagine if we could view tissues inside he patient, using in vivo microscopy to link cellular features to radiological images."

Morphology is based on tissue structure, which we visualize through our toolkit of processing methods and

"Stepping into a bold new frontier where 3D data is beamed directly into a convenient headset – that you can pick up as easily as your phone – is right around the corner."

microscopy. Although the microscope is increasingly being replaced by digital scanning and display technologies, the basic principle of information visualization – the hematoxylin and eosin-stained tissue – stays the same. In our view, the future of pathology lies in viewing tissue without the need for processing, speeding up the time to diagnosis. But it would require a huge leap for the field into 3D visualization of tissue through augmented or mixed reality. Imagine if we could view tissues inside the patient, using in vivo microscopy to link cellular features to radiological images.

Artificial intelligence (AI) has an integral role to play in this modernization of pathology visualization. As AI matures, it takes on increasingly difficult tasks, often with unimaginable precision and accuracy. But AI only does what it is programmed to – and currently, it carries out repetitive tasks deemed "boring" by humans, sifts through tons of data to find common features and denominators, and makes conclusions based on statistical probability. Its efficacy for these tasks is undisputed – and we are now entering a new era of augmented intelligence (AuI), whereby AI will work alongside clinicians in the decision-making process. However, AI still struggles with edge cases. It lacks the ability to choose its own research questions or select areas of a 3D object that deserve further study.

And that's exactly where virtual reality (VR) and augmented reality (AR) will shine. Rendering whole-slide images in 3D to generate a model that can be the size of a room will completely change the game. And it is not only in the visualization of morphology that VR and AR will take over. Many AR companies dream of a world in which we abandon our desktop computers and spatially interact with floating holograms – a reality that is truly on the horizon. Many of the projects with which we are currently involved aim to develop tools for situations ripe for AR exploitation. For example, in the frozen section room, an AR headset could record the user's actions, generate useful information from various data sources, take photos for a 3D render, transcribe, and make video calls to discuss where and how to cut the sample (3D-rendered for the caller's convenience). It could also deal with patient safety tasks and even the volumetric measurement of biological samples.

As VR headsets get lighter and computers get smaller and more powerful, we enter another phase of human-computer interaction. AR and VR will take their place as the new canvas upon which diagnosticians work. They will be especially transformative for training laboratory professionals of the future, throwing teaching into a whole different dimension. Imagine a scenario in which students can follow a holographic model with their phones and simultaneously record the visuals, transcribe the audio, and record any volumetric measurements through 3D modeling. Clinicians could describe and explore every aspect of the sample and even manipulate it manually.

One of the projects we have worked on involves the world's first AR patient controlled by AI and a dialogue management system. It takes a holistic approach to teaching; you can speak to the patient and then work down to the microscopic level and watch as the layers of skin under a lesion expand out, like a computer-aided design model. You can even touch each element to receive information about it.

Stepping into a bold new frontier where 3D data is beamed directly into a convenient headset – that you can pick up as easily as your phone – is right around the corner. VR and AR open the door to personalized, easily maintainable workspaces with context-sensitive tools at your fingertips. You will no longer be tied to a desk, instead able to work standing up or on the move. Being in an empty (virtual) office space, you will be able to design and use tools as you see fit in an almost unlimited environment that will be entirely customizable. Imagine being able to replay a full 3D holographic render of a cut-up sequence with volumetric measurement.

Eventually, we will even be able to record a patient's skin lesions in a 3D render that can be played back or referred to in the future. VR and AR will enable a radical shift in the delivery of frontline medicine – and it's going to produce a brave new (augmented) world.

A Distant Dream

India's laboratory infrastructure requires regulation and standardization to make it safe for billions of patients

By Rohit Jain, Consultant Pathologist at Santokba Durlabhji Memorial Hospital and Founder Secretary of the Practicing Pathologists Society, Jaipur, Rajasthan, India

What exactly is an in vitro diagnostic medical device (IVD)? It's the instrumentation needed to carry out a particular pathology test (or tests) on human samples to assist in clinical diagnosis or treatment decision-making. These devices include the laboratory or point-of-care devices, calibrators, controls, kits, reagents, and accessories used to perform diagnostic tests. IVDs are distinct from medical devices in that they never come into direct contact with the patient; however, they still have an impact on life-changing, and potentially life-saving, treatment decisions.

The World Health Organization (WHO) published the first edition of its Model List of Essential In Vitro Diagnostics in May 2018, recognizing that IVDs are an essential component to their three strategic priorities: advancing universal health coverage, addressing health emergencies, and promoting healthier populations. Now, India has become the first country to compile a National Essential Diagnostics List (NEDL) to guide the government on the diagnostic tests required by healthcare facilities in villages and remote areas.

Factors including a growing demand for personalized medicine, innovations in diagnostic techniques, an increasing preference for point-of-care testing among the general population, a growing geriatric population, and an increase in disposable income are driving the growth of India's IVD sector. With a population of more than 1.33 billion, India is the world's second-largest country and Asia's fourth-largest (and rapidly growing) market for IVDs. The global IVD market is estimated to reach US$97 billion in 2022 – a market share of which India held just 1 percent five years ago, but anticipates doubling by 2020. India's IVD market is likely to exceed US$ 1.8 billion by 2025.

Pathology is the cornerstone of modern medicine, ensuring that patients are correctly diagnosed and given appropriate treatment. However, a recent series in The Lancet (1) highlights the frequency of presumptive treatment (that is, treatment without a confirmed diagnosis) in many low- and middle-income countries. Why? Because of unregulated laboratory services and basic medical tests. Although India's new NEDL provides a list of important tests required at various levels of the healthcare system, the list cannot have an impact without an integrated, connected, tiered laboratory system, adequate human resources, training, laboratory infrastructure, and regulatory/quality assurance systems.

At the moment, the Indian healthcare sector (particularly with regard to clinical/pathological laboratories) is completely unregulated and has no clear rules for regulating registration, inspection, and penalties. Even the WHO has recommended that India develop a national health laboratory policy to regulate clinical laboratories in India. Some areas where medical diagnostic laboratories lack standards include: minimum qualifications for human resources in basic labs that cater to over 90 percent of the country's population; sample collection centers and sample transport; use of scanned/electronic signatures; number of laboratories a pathologist may visit in a day; daily internal quality control; the unregulated sale and purchase of IVDs; and health insurance claims on the basis of illegal laboratory reports. There is no central allied health, paramedical, or medical lab technology council. No data are collected on the numbers of medical lab technicians, trained medical postgraduates in pathology, or institutes offering medical lab technology courses.

In my view, this degree of unregulated operation leads to quackery in medical diagnostics – and the government of India turns a deaf ear, putting the lives of billions of patients in jeopardy. Even with the NEDL, we lack the necessary infrastructure to offer our citizens and visitors universal health coverage in a safe, effective, and regulated way. Only by developing these standards and regulations can we close the gap between the services we offer and the services our patients need. And for this, we need a global alliance for medical diagnostics. In resource-limited settings where pathologists play a key part in disease diagnosis and treatment, such an alliance would allow us to step into leadership and advocacy roles by setting standards for appropriate test type and frequency, maximizing the quality of the laboratory systems available, and ensuring that scarce health testing resources are used in the best way possible.

Reference

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Giving to Others – and to Ourselves

Charitable giving not only helps our friends and colleagues, but also our profession as a whole

By E. Blair Holladay, CEO of the American Society for Clinical Pathology, Chicago, USA

The holiday season is traditionally one of giving. We give the tangible – money, food – and the intangible – time, goodwill – to those in need. We step outside ourselves and share what we have for the greater good, knowing as we do so that we are contributing to the success and happiness of others. Although the holiday season is a great reminder to donate, it's worth remembering that, come January 1, these needs don't stop – they are often long-term or sometimes even lifelong.

As a patient-centered organization, we spend much of our time focusing on how we can improve the patient experience and how we can contribute to fulfilling patients' needs. We continually educate ourselves so we are up to date on the latest research that informs our pathology and laboratory science practice. We collaborate with peers and colleagues to share knowledge and ensure that we are providing patients with the right test, the right diagnosis, the right care plan, at the right time.

But, too often, we overlook how we can fulfill the needs of the people within our own profession.

In 2017, we launched the ASCP Foundation with a three-pronged intent: i) to support pathology and laboratory medicine students on their educational journey; ii) to increase the visibility of the profession; and iii) to improve global health by supporting increased implementation and improvement of diagnostics in underserved and underdeveloped countries.

Supporting those within pathology and laboratory science is crucial to our profession's success. The scholarships the Foundation provides help lift a mantle of worry from students who are passionate about the profession, but struggle to pay for essentials like books and study materials. The Foundation also provides opportunities for travel to conferences and events that help shape a young professional's career path and inform their practice. Foundation donations have helped the Partners for Cancer Diagnosis and Treatment in Africa Initiative enhance laboratories and train the personnel needed to create a sustainable workforce.

In the three years that the Foundation has been running, we have seen great success. We've had thousands of donations and have given away more than half a million dollars to fulfill the missions we established at its launch. The success we've seen lies squarely in the hands of the individuals and outside organizations who have embraced our mission and contributed both money and time to support those in our profession who need it most.

"Supporting those within pathology and laboratory science is crucial to our profession's success."

Donating to the ASCP Foundation is a fundamental and indispensable way that pathology and laboratory science professionals can help support each other. Together through the ASCP Foundation, we can – and do – foster the growth of not only our future colleagues, but also the profession as a whole. I invite and encourage you to contribute not just during this holiday season, but throughout the year: ascp.org/foundation.

What Is the Real Impact?

Experts share their opinion on the value of fully automated NGS results in a single day

At this year's Association for Molecular Pathology meeting in Baltimore, Thermo Fisher Scientific launched the Ion Torrent™ Genexus™ System, a first-of-its-kind, fully integrated, next-generation sequencing (NGS) platform. The system, for research use only, features an automated specimen-to-report workflow that delivers results economically in a single day and holds the potential to advance precision medicine. Its unprecedented turnaround time – as low as 14 hours to final results – making speed the quintessence of the system*. That speed, along with a fully automated workflow and the ability to return data with only minimal sample input, provides a cost-effective turnkey solution that may ultimately broaden NGS adoption to local and community hospital pathology labs in the future.

Luca Quagliata, Global Head of Medical Affairs at Thermo Fisher Scientific, asked NGS expert users for their thoughts on the newly launched Ion Torrent™ Genexus™ System and how obtaining a complete tumor sample molecular profile within a single day might impact precision medicine in the future.

Nicola Normanno of the Department of Translational Research, INT-Fondazione Pascale, Naples, Italy, has longstanding expertise in molecular testing, especially in the context of clinical trial-associated transitional research. His reaction to the system: "I was really impressed by the Ion Torrent™ Genexus™ System for a number of reasons. The first is that it's very easy to use. Even a person with low experience could load it in an extremely simple way, and it's very difficult to make a mistake because the system will alert you if there is an error."

Was the instrument intuitive? Approachable?

Jose Luis Costa, Clinical Researcher at the Ipatimup Center and an Affiliated Professor at the Department of Pathology, University of Porto Faculty of Medicine, Portugal, was an early tester of the Ion Torrent™ Genexus™ System. He says, "The instrument is extremely intuitive. I would say that it is even childproof, so anyone – even without any expertise – can just plug in the instrument and start workin g with it. All the instructions are fairly simple to follow. The instrument tells you exactly what to do, step by step. So you don't really need to prepare in advance to work with it. In fact, the only thing you need is a pipette to transfer the samples into the system."

What kind of advantage would such a system bring to your laboratory?

Costa says, "What the Ion Torrent™ Genexus™ System brings to the laboratory is more time for people to do things other than just jam in processing samples for NGS testing. As well, because the system goes from sample to final report with little to no intervention, no errors are introduced in the process. This offers great performance robustness along with high reproducibility. So, to wrap it up, time and robustness are area where we have major advantages, I would say."

What are the main barriers to NGS adoption in smaller laboratories?

Costa says, "The barriers to NGS adoption are the same as for larger laboratories. The difference is the resources to overcome them. In a nutshell, I think it's the expertise that is needed, from both a molecular biology and a bioinformatics standpoint, including result interpretation. Also, the cost related to both the instruments and the sequencing itself forces the need to batch a lot of samples to be cost-efficient in running samples. Usually, small laboratories do not have enough samples to be cost-efficient – sometimes, even large laboratories don't! The Ion Torrent™ Genexus™ System offers a solution to all these barriers."

"The machine does everything, including providing a full annotated report for final interpretation."

How does the Ion Torrent™ Genexus™ System help overcome those barriers?

Costa says, "The way the Ion Torrent™ Genexus™ System overcomes these barriers is essentially by tackling all these different aspects. The expertise needed to run it is essentially none, because it's a fully automated system. The machine does everything, including providing a full annotated report for final interpretation. Notably, you no longer need to batch samples. In principle, you can run the system with a single sample! But it is when you have just a handful that it becomes extremely cost-efficient. When I think of costs – not just the reagents, but time needed to process samples – that is a major component."

So labs that don't have any experience with NGS can use the Ion Torrent™ Genexus™ System?

Phillip Jermann of the Institute of Medical Genetics and Pathology, University Hospital Basel, Switzerland, commented,"The Ion

Torrent™ Genexus™ System enables laboratories that want to implement next-generation sequencing into their laboratory workflow and do not yet have the background and the knowledge around NGS to do that easily. That is because the system is basically a fully automated end-to-end workflow that requires very little human input. Therefore, it is very difficult to make any errors and, at the same time, it is very easy to learn how to use it, making it quickly implementable."

And what about experienced laboratories?

Jermann says, "Experienced laboratories like ours can also benefit from the from Ion Torrent™ Genexus™ System because it allows us to automate many steps that are otherwise error-prone when done manually, even by skilled users. So, again, it's the automation that benefits us most. And of course, that goes along with another big advantage of the system – the short turnaround time. This will enable us to generate results much faster than we currently can. No need to pile up cases and then hurry to analyze them all at once. We can better distribute the workload in the laboratory."

"The system is basically a fully automated end-to-end workflow that requires very little human input. Therefore, it is very difficult to make any errors and, at the same time, it is very easy to learn how to use it."

An important aspect of today's NGS-based molecular profiling is the percentage of failed tests. Does the Ion Torrent™ Genexus™ System reduce that percentage?

Jermann says, "The Ion Torrent™ Genexus™ System is based on technology that has evolved over the last 10 years. I was an early adopter, so I have followed its entire development. The method, to the best of my knowledge, has been cited in more than 6,000 scientific papers. Recently, a seminal retrospective study from the University of Heidelberg in Germany that used the Ion Torrent technology demonstrated a nearly 97 percent sequencing success rate across >3,000 non-small cell lung cancer samples, and a rejection rate, mostly due to quantity not sufficient errors, of only around 3 percent (1). The Ion Torrent™ Genexus™ System represents a further evolution of that robust methodology, so it is conceivable to expect it will deliver excellent results."

The Ion Torrent™ Genexus™ System is a Research Use Only platform. However, Luca Quagliata stated, "Thermo Fisher intends to seek regulatory marketing authorization of the system so that it can potentially be made available in every clinical setting. Additionally, we plan to develop and seek approval for a broad portfolio of diagnostic assays in oncology. The Ion Torrent™ Genexus™ is made to shift the cancer testing paradigm. That is what we have worked for – and we will keep on working for it."

For research use only. Not for use in diagnostic procedures.

**Specimen-to-report workflow will be available after the Genexus™ Purification System and integrated reporting capabilities are added in 2020.*

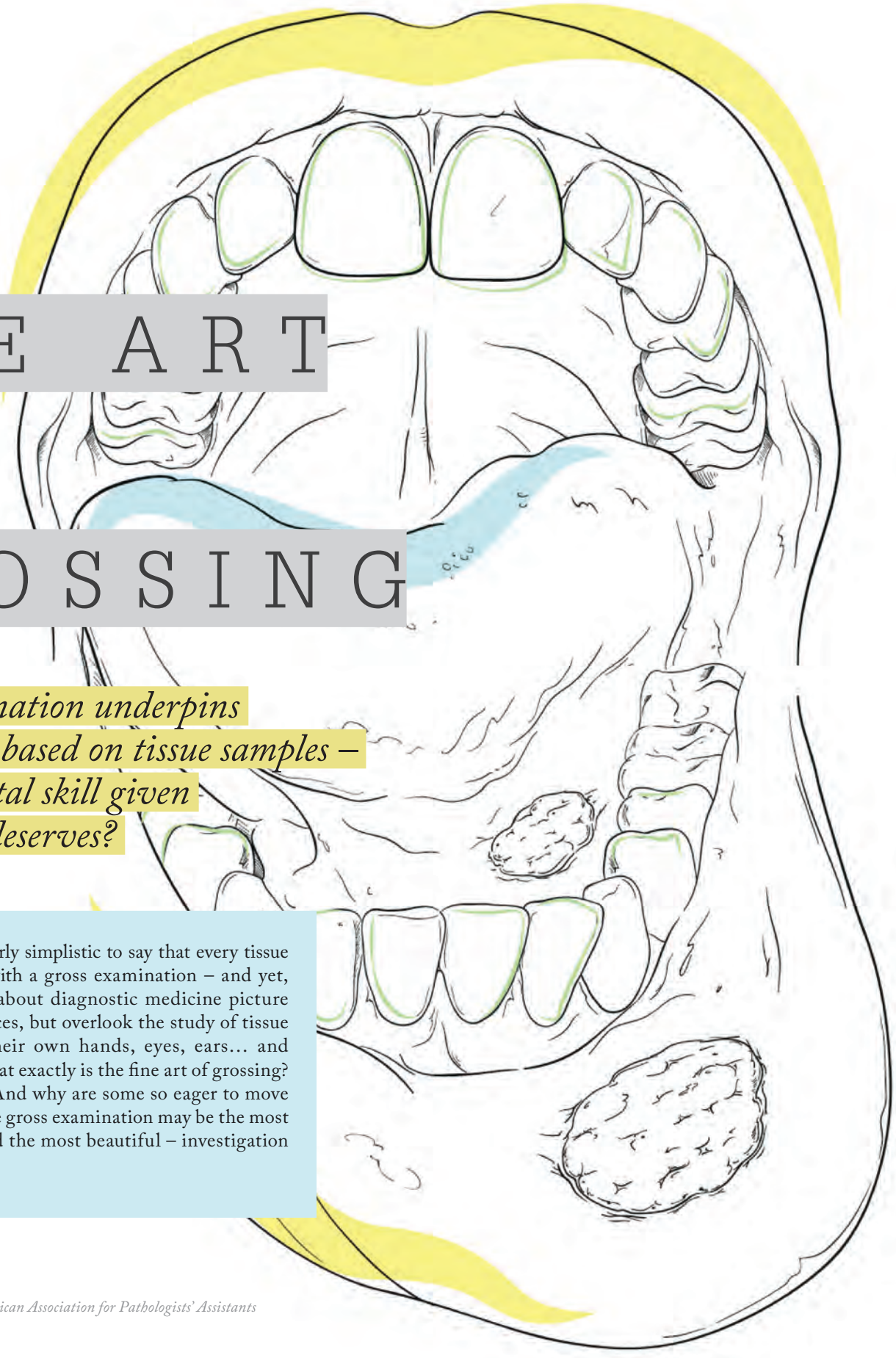
Reference

1. *AL Voclkmar et al., "Combined targeted DNA and RNA sequencing of advanced NSCLC in routine molecular diagnostics: Analysis of the first 3,000 Heidelberg cases", Int J Cancer, 145, 649 (2019). PMID: 30653256.*

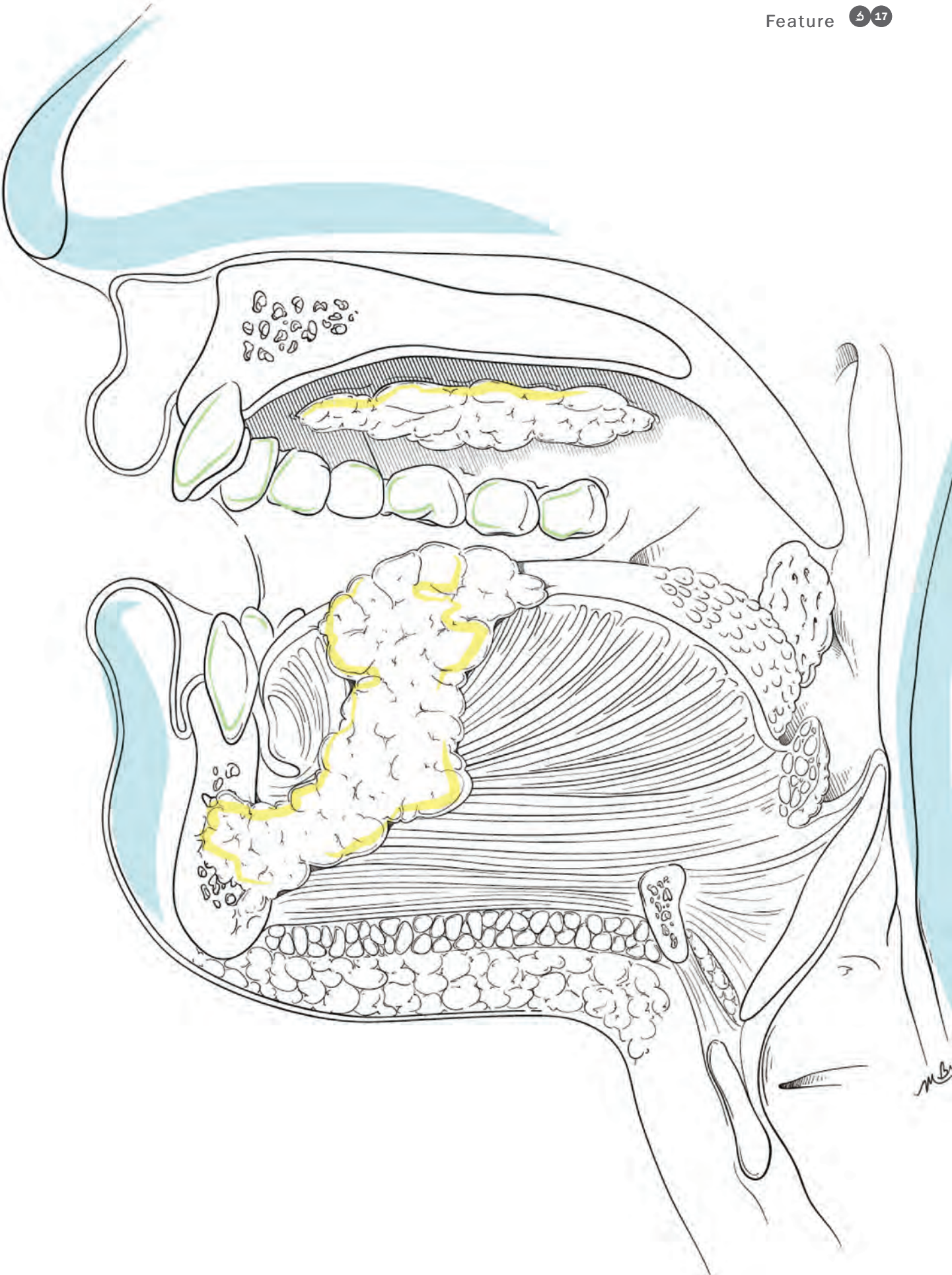
THE ART OF GROSSING

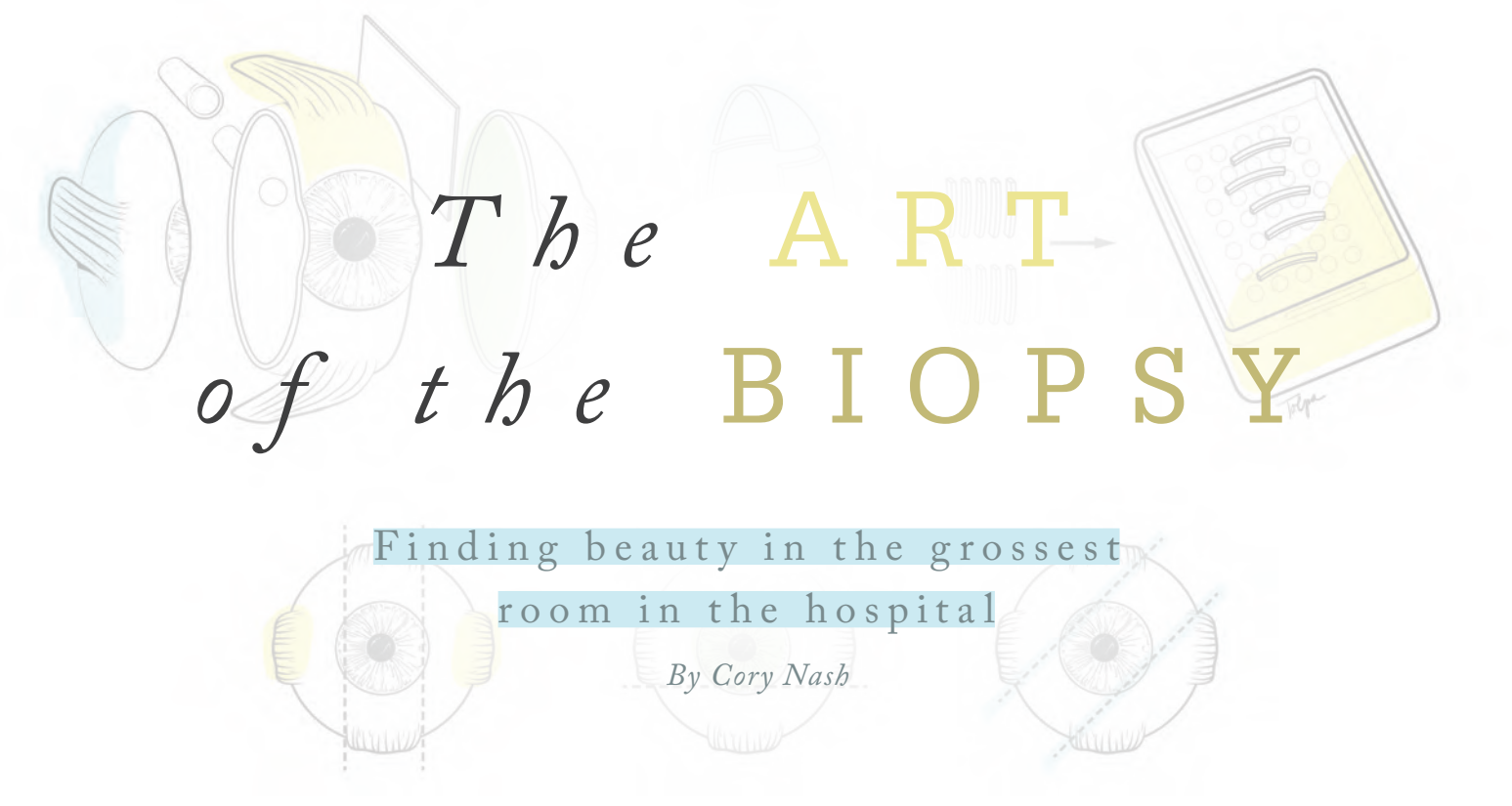
Gross examination underpins all diagnoses based on tissue samples – but is this vital skill given the credit it deserves?

It seems almost overly simplistic to say that every tissue diagnosis begins with a gross examination – and yet, many who think about diagnostic medicine picture screens, stains, sequences, but overlook the study of tissue samples using only their own hands, eyes, ears… and occasionally noses. What exactly is the fine art of grossing? How is it performed? And why are some so eager to move past it when, in fact, the gross examination may be the most important – and indeed the most beautiful – investigation they perform?



All images courtesy of The American Association for Pathologists' Assistants





The ART of the BIOPSY

Finding beauty in the grossest room in the hospital

By Cory Nash

Looking around the surgical pathology lab, the uninitiated might think that the term "gross room" is self-explanatory – used to describe the plethora of specimens you might see strewn about the lab. After all, from biopsies to multi-organ resections and everything in between, you may see things that would give Wes Craven nightmares. Despite appearances, the term "gross room" does not, of course, refer to the awful things you might find in the lab, but to the act of gross examination – the macroscopic examination of organs, describing the size, shape, color, and consistency of tissue. It requires the use of your five senses (or rather, four – taste being the exception) and nothing more. For context, the antithesis of this is the microscopic examination, which requires the eponymous tool.

"There is immense beauty to be found in the surgical pathology lab – if you know where to look."

Making sense of chaos

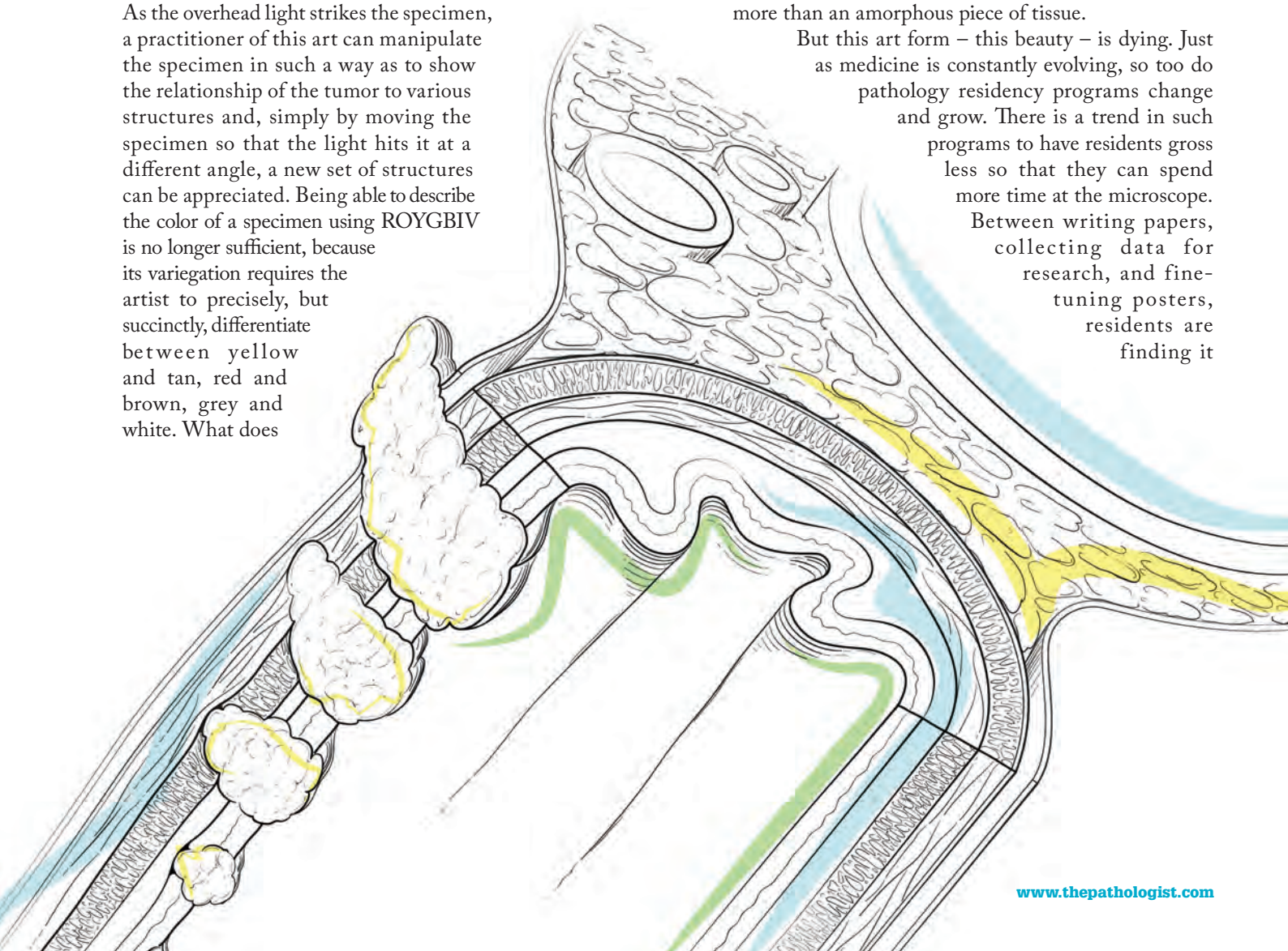
To some who walk into a gross room, the lab is nothing more than organized chaos. Technicians type away at computers as they accession specimens. Pneumatic tubes drop in the background, dumbwaiters arrive and leave with the "ping!" of a bell, and doors constantly open and close as specimens are dropped off. All the while, surgeons are coming in and out of the lab wanting to orient specimens or to know where the results are on their frozen section. Residents scurry back and forth, almost as if they are partaking in a strange, ritualistic dance to appease the surgical pathology gods (all hail Virchow). Between grossing,

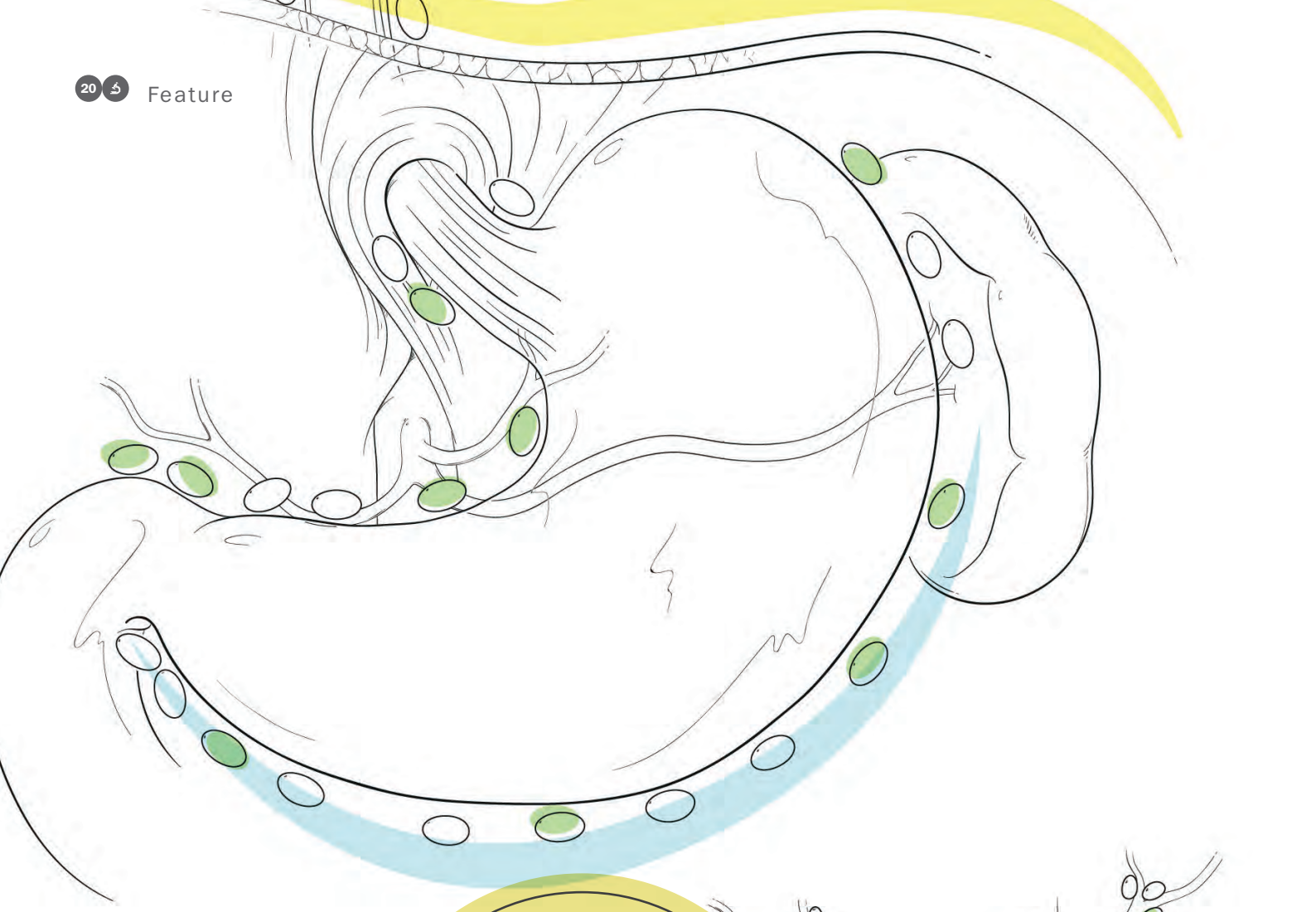
frozens, and answering pages, residents are in a constant whirlwind of movement, trying to stay ten steps ahead in the hopes of finding a second to use the bathroom or grab some food. Pathologists' assistants pace the gross room as if it is a battlefield and they are commanding an army, rotating between grossing a specimen, helping a resident, and answering a question from a technician. Instruments are making all kinds of sounds, there are people talking at a bench about the best way to approach a specimen, and Stryker saws and band saws intermittently cry out, "Hear me roar!"

Despite the inherent "grossness" and commotion, there is immense beauty to be found in the surgical pathology lab – if you know where to look. The stainless steel benchtops are adorned with vials of ink in every color of the rainbow, displayed like a "House Pathology" banner. Specimens large and small are laid out on these benches, waiting for an artist to come along and perfect their craft. As the overhead light strikes the specimen, a practitioner of this art can manipulate the specimen in such a way as to show the relationship of the tumor to various structures and, simply by moving the specimen so that the light hits it at a different angle, a new set of structures can be appreciated. Being able to describe the color of a specimen using ROYGBIV is no longer sufficient, because its variegation requires the artist to precisely, but succinctly, differentiate between yellow and tan, red and brown, grey and white. What does it mean to measure a tumor as 2.3 versus 2.4 cm in greatest dimension? Does a discrepancy as small as 0.1 cm really mean anything? Is it okay to just round to the nearest half or even whole centimeter?

Gross examination, often just called "grossing," is an art form that is all too often overlooked as nothing more than a barbaric act – but there is value in it. There is beauty in something as simple as a stroke of the scalpel blade or the flick of an applicator stick as ink is applied to the rim of the resection margin, stopping just short of the mucosa. With that same overhead light shining off the scalpel, an expert artist can use these blades with such fine precision as to cut a piece of tissue only a few millimeters thick, yet still maintain all the appropriate margins and structures. To these artists, the scalpel blade is an extension of themselves. It is this blade that allows for the precise, yet complex manipulation of multi-organ resections that, to outsiders, may appear to be nothing more than an amorphous piece of tissue.

But this art form – this beauty – is dying. Just as medicine is constantly evolving, so too do pathology residency programs change and grow. There is a trend in such programs to have residents gross less so that they can spend more time at the microscope. Between writing papers, collecting data for research, and fine-tuning posters, residents are finding it





harder to balance grossing and microscopy. Most pathology residents, if asked, would want more time at the microscope; few, if any, would ask for more time grossing specimens. And that's understandable. If residents spend more time reviewing cases under the microscope, they will feel more confident in their ability to sign out cases when the time comes. For those pursuing surgical pathology, this will make the transition to becoming an attending much smoother. At what cost, though, do we take residents away from grossing? This is a delicate balance that must be maintained to ensure that residents are leaving their programs adequately trained in every respect. One of the first things to feel the burden of this transition is the reduction – and eventual elimination – of biopsy grossing in residency.

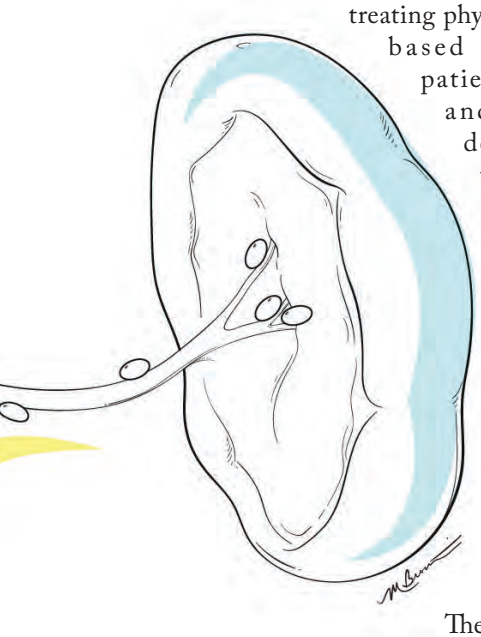
"We need to re-instill in our trainees' minds not only the importance of the biopsy, but also its beauty."

The value of grossing

Some medical students have said that they do not want to apply to certain pathology residency programs because "they make their residents gross biopsies and that is a red flag." Online medical student residency forums suggest that all such residency programs should be avoided.

Although some in these groups may claim to understand the importance of the biopsy, their willingness to overlook the importance of grossing suggests otherwise. It goes without saying that biopsies are arguably the most important specimens you will receive in a surgical pathology lab. The "more grossable" organs are resected because a biopsy has already been

performed to provide a diagnosis. Biopsies help determine whether a mass is benign or malignant, whether a specimen needs to be resected, and whether further treatment is necessary. The results of a biopsy can help support and comfort a patient in their time of need and, irrespective of outcome, radically change their future. Grossing biopsies is not just about putting pieces of tissue into cassettes for processing. It is about understanding why the treating physician, based on the patient's history and presentation, decided to take a piece of tissue from this site rather than any other. It is about differentiating why certain stains are ordered up front on one kind of biopsy, but not another that is taken from the same exact location on a different patient. It is about understanding how, even in tissue measuring only a few millimeters, you can determine a mucosal surface, a resection margin, inking, and even orientation. The tiniest details on the smallest piece of tissue can be overlooked by someone who does not take into account the art that goes into grossing – someone who may not understand how that single piece of tissue can convey an overwhelming amount of information.



"We may not be the poster children of medicine, but what we do in the surgical pathology lab is important."

We need to re-instill in our trainees' minds not only the importance of the biopsy, but also its beauty. If you tell a resident that they need to start grossing biopsies again, but you don't take the time to explain to them what can be learned simply by looking at a biopsy, then you have failed before you begin. We, as humans, innately want to learn. We want to teach and, in turn, be taught. We want to take pride in what we do and know that our actions have an impact. If a resident takes a rectal biopsy for an infant patient with a history of constipation, they might know that there is a possibility they are looking for Hirschsprung's disease. Will they, however, know by looking at the biopsy that it needs to be embedded a certain way – or that, more likely, there may be a piece of submucosa attached that will help them determine how it should be embedded? If a resident were to see this rectal biopsy, would they even know to look for submucosa in the first place? If they did see the submucosa, would they ignore it as just an aberration of the mucosa and nothing more?

The key to re-establishing the importance of grossing biopsies with residents is to have them take pride in that tan-pink "scrap" of tissue, and know that what they are doing will affect someone's life. We need to get residents excited about finding that submucosa to the point that, when they do find it, they feel a sense of accomplishment and say to themselves, "I got it!" I have seen this excitement on residents' faces when they are able to orient a difficult specimen, or when they find a ureter on a cystoprostatectomy specimen. Why should that excitement and sense of accomplishment be limited to complex cases when the same sense of elation can be felt with an everyday biopsy?

Patients may not know what we do in the surgical pathology lab. They go into their doctor's office, have a biopsy performed and, magically, a few days later, they have their answer. They do not know how the doctor got that answer, or that there was a team of highly trained, highly motivated professionals working behind the scenes to provide it. We are the unseen healthcare providers critical to their diagnosis. This is unlikely to change soon, but we need to make sure residents know this, and remind them of why we went into medicine in the first place: to help patients. We may not be the poster children of medicine, but what we do in the surgical pathology lab is important. Perhaps by reminding our residents of the beauty that can be found in the gross room, we can slowly start to change their frame of mind. That tan-pink piece of tissue sitting at your bench has a hidden beauty to it that is just waiting to be uncovered.

Cory Nash is a pathologists' assistant in the Department of Pathology at the University of Chicago, USA.

Behind the GROSSING GUIDELINES

The Macroscopic Examination Guidelines from concept to delivery

By Jesse McCoy

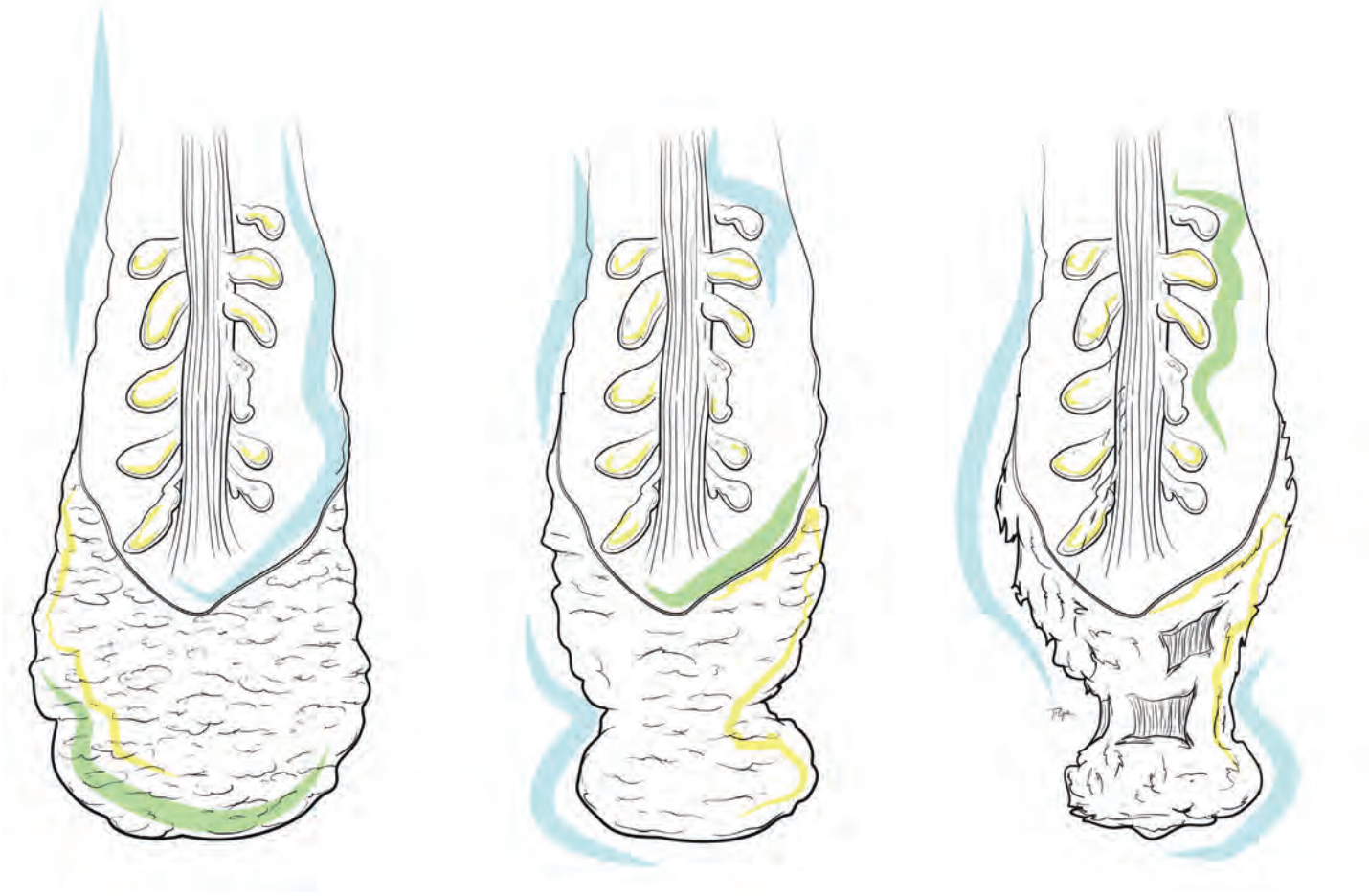
As a pathologists' assistant, an evolving "lab hero" (1), I serve as a key provider in the medical laboratory diagnostic continuum. As part of that role, I provide critical diagnostic information through the macroscopic gross examination, evaluation, and dissection of surgical cancer cases. That information provides pathologists with essential diagnostic information that, in turn, yields prognostic criteria to dictate treatment protocols and outcomes.

To align with the highest standards of patient care, the information we provide at the gross bench must be compliant with the criteria established by both the American Joint Committee on Cancer (AJCC) Cancer Staging Manual and the College of American Pathologists (CAP) Cancer Reporting Protocols. Recognizing quality patient care as a primary core value, the American Association of Pathologists' Assistants (AAPA) spearheaded a project to provide a source document integrating both sets of established criteria for those "involved in the macroscopic handling of surgical cancer cases" (2). The AAPA Macroscopic Examination Guidelines: Utilization of the CAP Cancer Protocols at the Surgical Gross Bench, colloquially known as the "Grossing Guidelines," is not only a wonderful practice aid and teaching tool, but also a catalyst for many new relationships between the AAPA, AJCC and CAP. The guidelines have strengthened professional relationships among the vast network of contributing volunteer PAs and validated our long-sought-after sense of belonging to the anatomic pathology and laboratory medicine community (3).

> *"The first edition of the Grossing Guidelines was a six-year labor of love."*

Laying the groundwork

I have had the honor of serving alongside over 100 volunteers (and counting) in developing this immense working tool. I serve as Art Director and Illustration Liaison, a position I have held since 2012. The first edition of the Grossing Guidelines was a six-year labor of love and commitment – and a true marriage between my passions and professions as a medical illustrator and pathologists' assistant.



The guidelines were conceived in 2011 by a number of AAPA Board of Trustee members, including Editor-in-Chief Jon Wagner, the foremost driver of the project (4). Their vision was to provide a standardized, systematic approach to support medical professionals engaged in the macroscopic examination of cancer resection specimens (2).

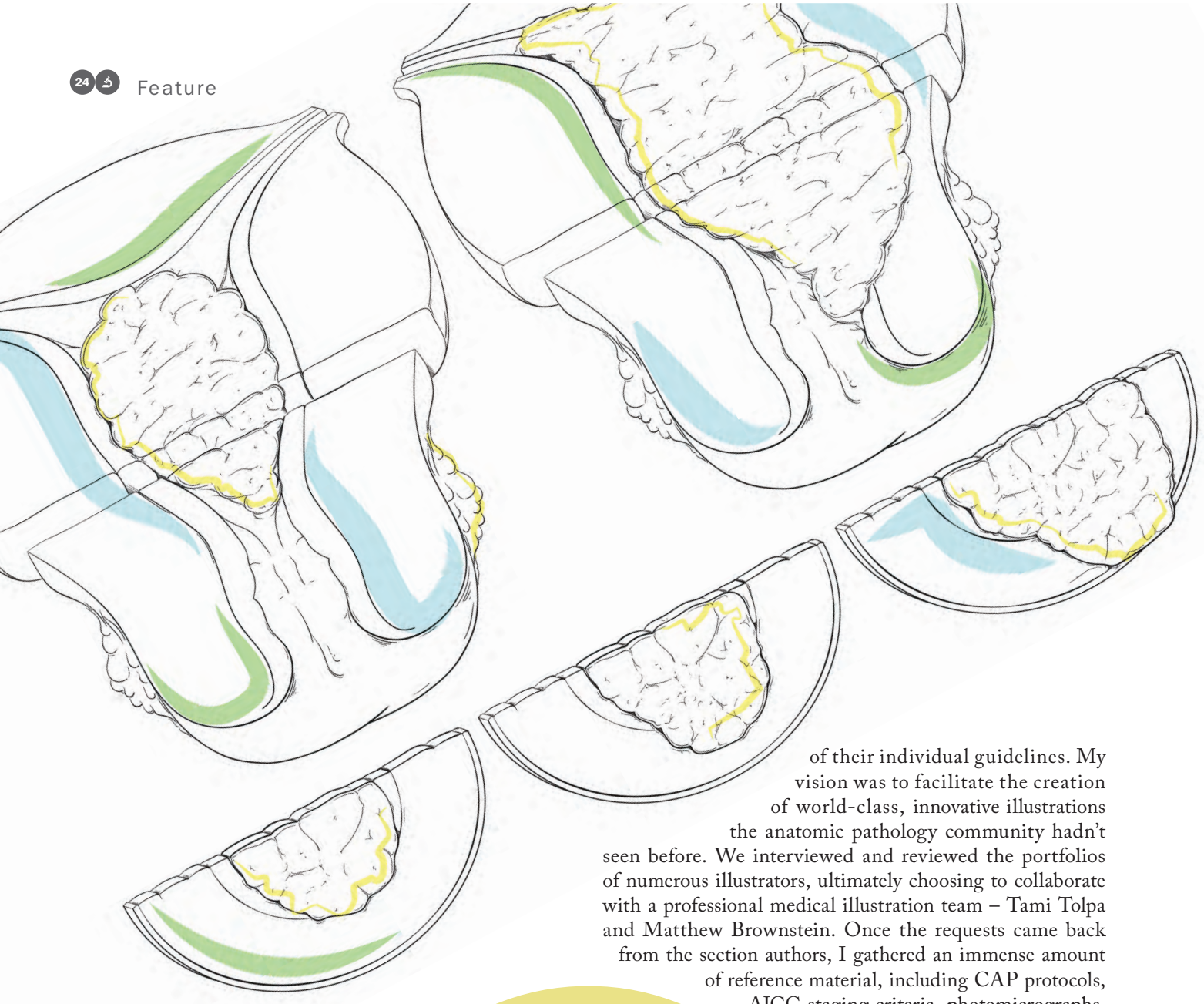
The scope of this project was beyond anything the AAPA had previously attempted. With 67 protocols to cover, an initial call for volunteers went out to the membership. Contributions would be "non-paid, time-intensive, and peer-scrutinized… however, there was an overwhelming response" (5). Each of the protocols required authors, content reviewers/editors, illustrators, publishing editors, managing editors, molecular considerations editors, technical support, and project managers. I've said before that what sets those who choose the PA profession apart is our variety and versatility (1) – and the Grossing Guidelines was an endeavor that demanded the versatility our profession offers.

The guidelines mirror the applicable CAP Cancer Protocols and include molecular and immunohistochemical considerations. Each guideline includes procedures and general anatomic considerations, content that address ambiguous terminology, and methods and procedures for grossing cancer specimens. Each section is color-coded based on the AJCC tumor, lymph node, and metastasis (TNM) schema.

The making of a guideline

The vaginal protocol was chosen to be the proverbial guinea pig. A shorter and less commonly used protocol, it seemed ideal for the first flex of our Grossing Guidelines development muscles – so we assembled a small team of authors and began developing content. Endless emails and teleconferences ensued. I served as the illustrator for this first protocol. Everything was a journey through trial and error – content development, editing, formatting, illustration creation, basic organization skills, and even navigating the novel cloud file-sharing system we chose to use. Even after we had the first draft in place, we still faced seemingly endless revisions, additions, and modifications.

Once the vaginal protocol was complete, we began development on the remaining protocols. That step opened the project up to our large volunteer base – almost 10 percent of the AAPA's total membership! Once content for each of the protocols was generated, a content review team was organized



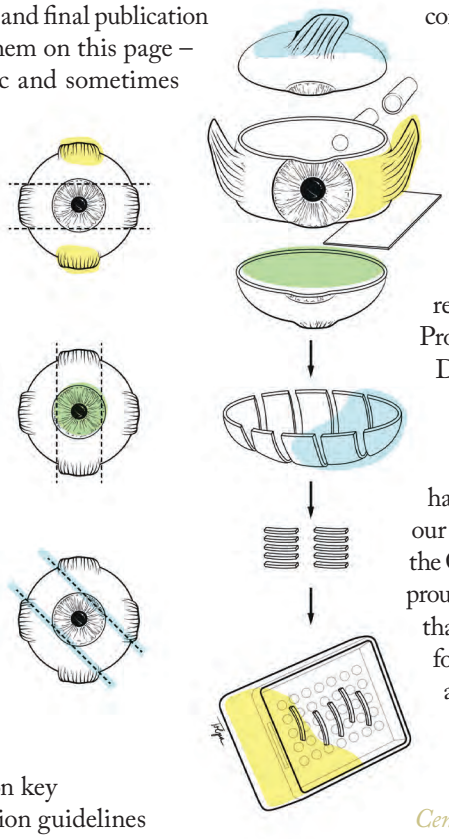
and acted as an editorial board. The group consisted primarily of PAs based out of the Mayo Clinic; they assembled in conference rooms before work to scrutinize each protocol, dedicating countless hours to finessing the massive influx of content.

Then came the need for the remaining 90+ illustrations. I drafted an illustration request form, which the primary section authors used to communicate the needs of their individual guidelines. My vision was to facilitate the creation of world-class, innovative illustrations the anatomic pathology community hadn't seen before. We interviewed and reviewed the portfolios of numerous illustrators, ultimately choosing to collaborate with a professional medical illustration team – Tami Tolpa and Matthew Brownstein. Once the requests came back from the section authors, I gathered an immense amount of reference material, including CAP protocols, AJCC staging criteria, photomicrographs, gross images, radiographs, sketches from section authors, and anatomic atlas illustrations. In fact, a large part of the Netter CIBA collection of medical illustrations adorned my coffee table for well over a year! With that information, I developed revised requests easier for the illustration team to understand. Using a web-based project and file management system, I oversaw the creation and revision of every illustration needed for the guidelines. The artists created an amazing collection of beautiful illustrations, making the Grossing

"The Grossing Guidelines has served as a conduit, broadening inter-professional relationships in anatomic pathology."

Guidelines truly come alive.

Once the illustrations were complete, I partnered with the AAPA executive team to oversee their placement in the guidelines, textual annotations, labeling, and overall layout. We also relied on the administrative expertise of the AAPA executive team to manage publication. As the project progressed, we added a vast network of specialized editors, each in their respective specialties. Additionally, since the development of the second edition, we have continued to consult with CAP pathologist expert reviewers and incorporate their comments, suggestions and edits. The process of content development, editing, illustration creation, layout, and final publication may seem simplified as you read them on this page – but I assure you, it was an organic and sometimes overwhelming process, taking many years to streamline the coordinated efforts of such an enormous and high-caliber project. The dedication to both our patients and our profession are evident in the work our tireless group of volunteers continues to devote to this project.



And the story isn't over yet; the Grossing Guidelines are continually evolving. We currently use the second edition, but the third revision is already in development. This new edition will have a host of significant additions (6), including:

- macroscopic photographs
- macroscopic structured data reporting
- a recommended block allocation key
- specimen handling and dissection guidelines
- an educational/background information section
- TNM criteria in appendices
- ancillary testing information
- frozen section considerations, and
- sample gross narrative descriptions.

The evolution of the Grossing Guidelines continues to align with AJCC Staging and CAP Cancer Protocol revisions. In particular, the second edition featured significant changes to the AJCC lung cancer staging, which affected both written content and illustrations, and required significant modifications to the protocol.

More than just a protocol

The Grossing Guidelines has served as a conduit, broadening inter-professional relationships in the anatomic pathology realm and opening active dialog between the AAPA and both CAP and AJCC. Since the release and subsequent revision of the guidelines, the AAPA now serves as an Association Member of the AJCC. Our relationship with CAP has also strengthened, particularly through our relationships with expert pathologist reviewers and staff. CAP has been instrumental in driving this project forward, and we are immensely grateful for this continued support and recognition.

I would be remiss if I did not thank the hundreds of volunteers who made this amazing vision come to fruition. To name them all would go beyond the constraints of print publication; however, there are a few who have served not only as key contributors on the Grossing Guidelines, but also as source material for this article: Jon Wagner, Editor in Chief; Mike Sovocool, Editor – responsible for recruiting me so many years ago; Connie Thorpe, Project Manager; and Michelle Sok, AAPA Executive Director. I would like to thank every one of these people for their unwavering commitment and diligence to our patients and profession.

Echoing sentiments expressed by Jon Wagner, this has been a profound experience, energizing and inspiring our practice habits (4). I look forward to future editions of the Grossing Guidelines with eagerness and will always be proud to contribute to this world-class teaching tool. I know that, for many years, the guidelines will set the standard for the macroscopic examination of cancer resections and, ultimately, drive the best possible patient care.

Jesse McCoy is a Pathologists' Assistant for Hampton Roads Pathology at Chesapeake Regional Medical Center, Chesapeake, Virginia.

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THE INNOVATORS 2019
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The FS-Live system improves caseload efficiency by bringing the lab and operating room directly to the off-site pathologist, eliminating hours of travel and on-site time for experts. The continuous autofocus feature is an industry breakthrough innovation that eliminates the need for lengthy pre-mapping. Instead, FS-Live delivers a completely clear, in focus slide image within seconds. The system also leaves control entirely in the pathologist's hands: change objectives, correct over-staining, measure, annotate, and drive the stage all from offsite. If users wish to send an image for a speedy second opinion, they can also capture snapshots of single layers or complete z-stacks without ever leaving the live interface.

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In 2006, formaldehyde was declared carcinogenic and mutagenic to humans by the International Agency for Research on Cancer. Despite this, in today's labs and operating rooms, formaldehyde remains the standard fixative for collecting and storing biospecimens, exposing personnel to high levels of formaldehyde fumes. It has become crucial for hospitals and clinics to adopt precautions to ensure the safety of their personnel.

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The Oncotype DX test is the third predictive marker after hormone-receptor (HR) status and HER2-receptor status to guide precise treatment decisions in early breast cancer (4).

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The Oncotype DX test is now an essential tool for completing a pathology workup and providing a clear recommendation for every patient.

The Oncotype DX test is performed by Genomic Health, Inc., an Exact Sciences company.

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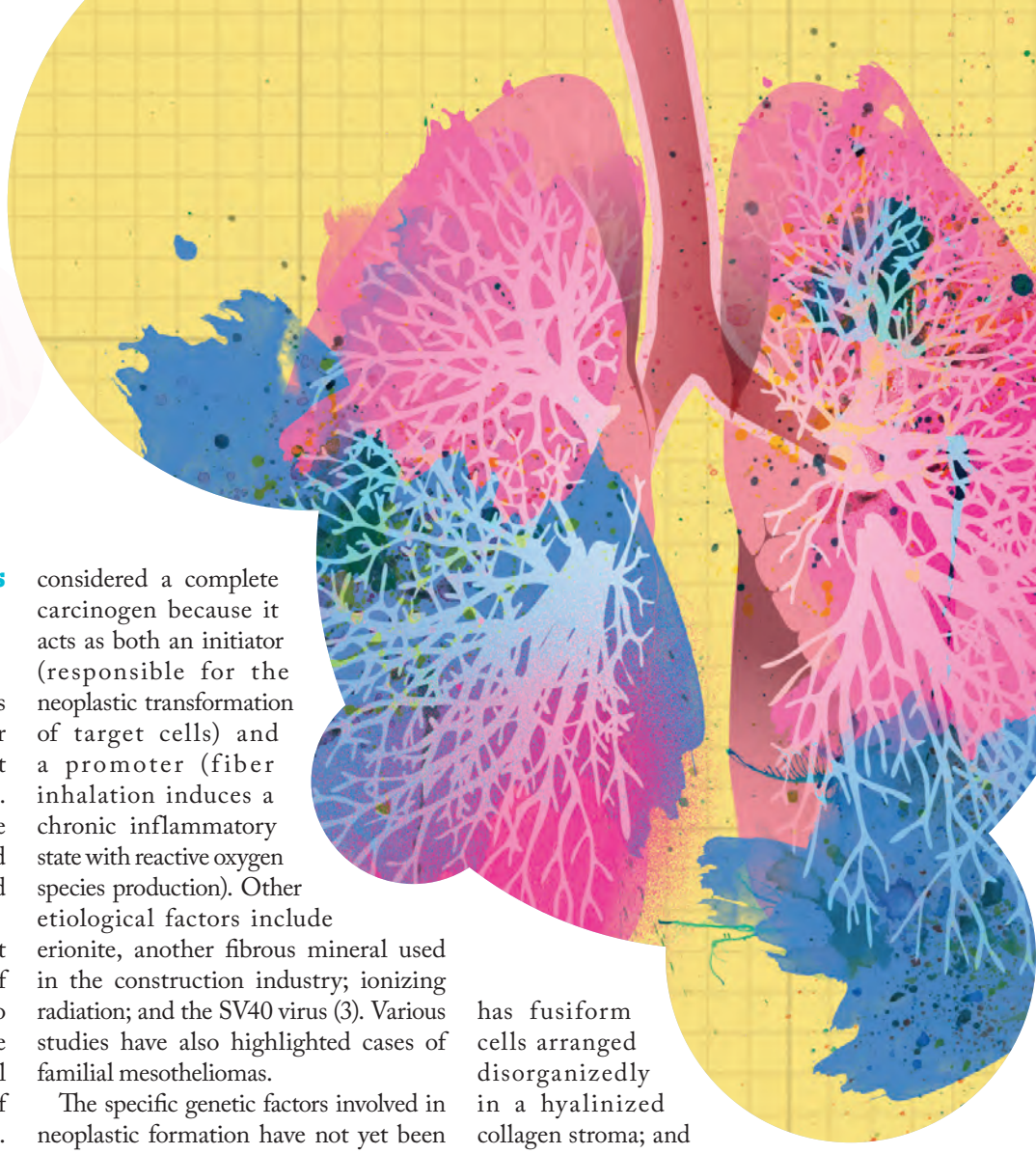

Molecular Drivers of Mesothelioma

The search for factors implicated in pleural mesothelioma carcinogenesis

By Stefania Erra and Carolina Pelazza

Mesothelioma is a cancer that originates from the mesothelium, a tissue cover that protects the lungs (pleura), heart (pericardium), and abdomen (peritoneum). Although still a rare disease, the worldwide incidence of mesothelioma has increased steadily over the last decade and is expected to peak in 2020.

This lesion has greater incidence at the pleural site (1), where two sheets of mesothelium fold over one another to form a serous membrane that covers the lungs. Between these sheets, a virtual cavity containing a small amount of liquid allows regular lung function (2). Pleural mesothelioma is highly correlated with exposure to asbestos, a substance considered a complete carcinogen because it acts as both an initiator (responsible for the neoplastic transformation of target cells) and a promoter (fiber inhalation induces a chronic inflammatory state with reactive oxygen species production). Other etiological factors include erionite, another fibrous mineral used in the construction industry; ionizing radiation; and the SV40 virus (3). Various studies have also highlighted cases of familial mesotheliomas.

The specific genetic factors involved in neoplastic formation have not yet been determined, but many cases show recurrent mutations in *BAP1, NF2, CDKN2A*, and *TP53* – all genes involved in important cell regulatory pathways (4–6).

The diagnosis of mesothelioma can be complicated. Formalin-fixed paraffin-embedded (FFPE) tissue sections are stained with hematoxylin and eosin (H&E), followed by additional immunohistochemical investigations fundamental to differentiating between mesothelioma, pulmonary adenocarcinoma, pleural metastasis of extrathoracic carcinoma, and sarcoma (7,8).

From H&E staining, we can distinguish three different histological structures. The most widespread is the epitheliomorphic histotype, which presents globose cells aggregated in tubulopapillary structures and immersed in a dense and fibrous stroma; the much rarer sarcomatous histotype has fusiform cells arranged disorganizedly in a hyalinized collagen stroma; and the biphasic morphology has at least 10 percent of each of the previous components (9).

In our study in particular, selected samples additionally underwent immunohistochemistry (IHC) to investigate their expression of several proteins: PD-L1, PMS2, MLH1, MSH2, and MSH6. PD-L1, the major PD-1 receptor ligand expressed by immune cells, participates in T-cell stimulation as a negative regulator of the immune response (10,11). PMS2, MLH1, MSH2, and MSH6 are all part of the DNA mismatch repair system; the lack or dysfunction of such proteins leads to microsatellite instability and the onset of mutations due to errors in the replicative phase (12,13).

Taking a closer look

My colleagues and I saw the need to better

At a Glance

- *Pleural mesothelioma has three histotypes: epitheliomorphic, sarcomatous, and biphasic*
- *About half of pleural mesotheliomas exhibit PD-L1 expression and may be treatable using targeted immunotherapies*
- *Although epitheliomorphic mesothelioma morphologically and biologically mimics adenocarcinoma, there are no DNA mismatch repair defects*
- *This case series provides greater insight into the molecular factors in mesothelioma carcinogenesis and may lead to improved treatment*

understand the molecular contributors to pleural mesothelioma, so we turned to IHC. Our study took place at the Santo Spirito Hospital in Casale Monferrato, Italy, where we examined 37 selected cases of malignant pleural mesothelioma diagnosed between 2015 and 2017.

Each biopsy specimen was prepared through a multi-step process:

1. Formalin fixation to preserve the morphological and molecular characteristics that the tissue presented in vivo.
2. An automatic processor dehydrated the tissue in an ascending scale of alcohols (from 25 to 100 percent ethanol).
3. Tissue clarification using diaphans (including xylene, benzene and toluene) to give the samples a transparent – or diaphanous – appearance.
4. Paraffin embedding and sectioning at intervals of 1–3 µm using a microtome.
5. De-paraffinizing and rehydrating the tissue sections.
6. Collecting the tissue sections on a slide.

Once the slides were ready for staining, we applied H&E for routine diagnostics. In the case of suspected neoplasia, we carried out further IHC investigations – monoclonal antibodies for the differential diagnosis of mesothelioma and antibodies against PD-L1 and the mismatch repair proteins (14).

For our anti-PD-L1 antibody, positivity was evaluated based on percentage of PD-L1 expression relative to the amount of mesothelial tissue present. According to the International Association for the Study of Lung Cancer (15), <5 percent expression indicates a negative evaluation, whereas > 10 percent indicates low expression and > 50 percent indicates high expression. For our anti-mismatch repair protein antibodies, we evaluated positivity or negativity of staining at the nuclear level in neoplastic cells, but quantification was not necessary because the nuclear positivity of the tumor on IHC slides tested with monoclonal antibodies against mismatch repair proteins means that those proteins are expressed – and that the DNA can repair its own replication errors, an ability that is not dose-dependent. As long as the neoplastic cells retain their DNA repair function, microsatellite instability is not established.

What we found

The patients in our study ranged from 44 to 89 years old (with an average age of 73). They included 20 male and 17 female patients. Over two-thirds of cases (26; 70 percent) were the epitheliomorphic histotype, whereas nine (24 percent) were biphasic and two (6 percent) sarcomatous. IHC investigations showed that the four proteins involved in the DNA repair system were all expressed – and presumably functioning – in the samples we analyzed. At the microscopic level, we were able to determine differences in color intensity that indicate variable expression of the proteins under examination (see Figures 1 and 2), but these were not considered in the evaluation of positivity.

PD-L1 was expressed in 20 samples (54 percent), 11 of which showed high expression and nine low (see Figure 3). Of the samples expressing PD-L1, 14 were epithelioid, five biphasic, and one sarcomatoid. Thus, approximately half of mesotheliomas present anti-PD-L1 antigens to stimulate the lymphocyte-mediated immune response.

"With the rarity of [mesothelioma], it's unsurprising that we have not yet identified the genes or gene complexes involved in its carcinogenesis."

Spotting the protein culprits

Pleural mesothelioma is an aggressive neoplasm with a poor prognosis. The patients examined in this study all had environmental or occupational exposure to asbestos, which further emphasizes the chemical's key role in mesothelial carcinogenesis – and explains the cancer's high incidence in the Casale Monferrato area, where numerous companies have worked on asbestos for decades. Few of the patients reported having smoked and, although mesothelioma is more common in men at the national level (16), the cases studied showed no particular correlation with gender.

Histological classification carries particular importance in mesothelioma because recent studies have determined that patients with PD-L1-positive sarcomatous pleural mesothelioma have lower survival rates (17–19). Although PD-L1 expression is associated with a worse prognosis, it has a silver lining; novel immunotherapies that target PD-1 and PD-L1 are permeating the market, so PD-L1 expression in pleural mesotheliomas could lead to targeted treatment that acts on the tumor microenvironment. At the moment, three

available antibodies act on PD-1 or PD-L1: pembrolizumab, nivolumab, and atezolizumab. Although none of these three drugs is currently approved for the treatment of mesothelioma, several studies are in progress, and preliminary results suggest slight improvements in lifespan and prognosis for eligible patients (20).

DNA mismatch repair proteins correct errors in the pairing of nucleotides and nucleotide loops, the latter of which form at repeated sequences of nucleotides (microsatellites), where the DNA polymerase can introduce errors by inserting or deleting nucleotides. A deficiency in one or more of these proteins causes microsatellite instability (the progressive elongation or shortening of microsatellite sequences), which is present in many tumor suppressor genes. Defects in the production and function of mismatch repair proteins can therefore influence carcinogenesis, as has been shown in several cancers (21). Mismatch repair proteins are currently understudied in pleural mesothelioma; however, one study has shown tumor cells' reduced ability to correct DNA defects after platinum-based chemotherapy, demonstrating an increased sensitivity to treatment (22).

In our study, every sample showed expression of the four proteins in the mismatch repair complex, indicating that there is no loss of DNA mismatch repair – so it's unlikely that these proteins are responsible for pleural mesothelial carcinogenesis. It is therefore also unlikely that the RAS genes play a role; although they are the main culprits in epithelial carcinogenesis, other cancers with RAS oncogene involvement also exhibit mismatch repair complex deletions.

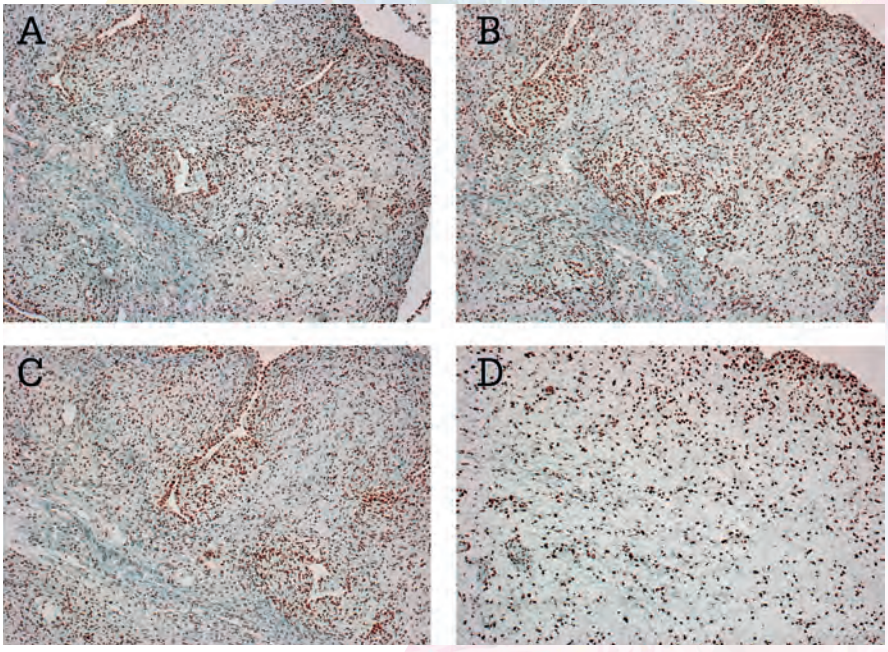

Figure 1. Sarcomatous pleural mesothelioma as determined by IHC stains for a) PMS2, b) MLH1, c) MSH2, and d) MSH6. 100X magnification.

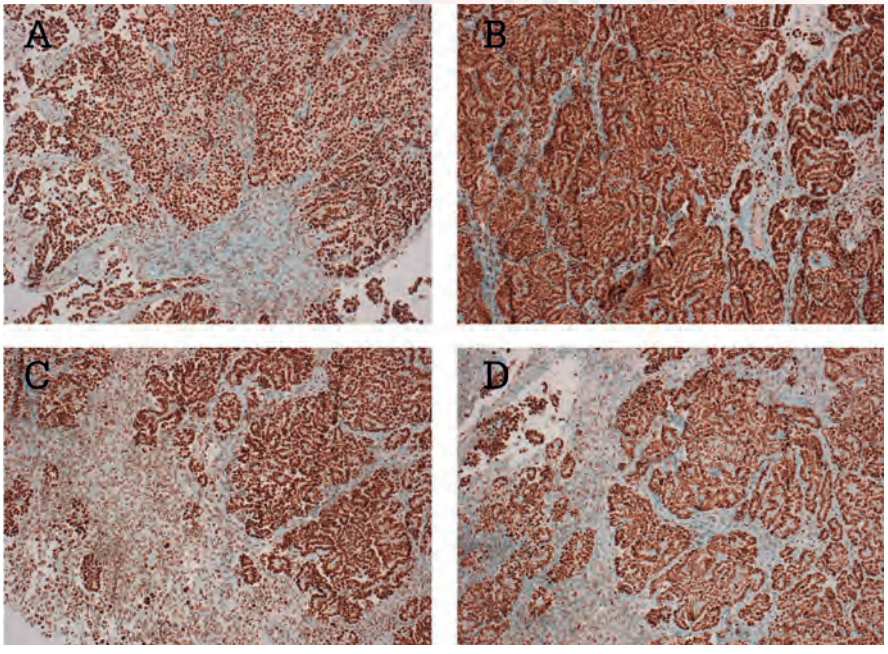

Figure 2. Epitheliomorphic pleural mesothelioma as determined by IHC stains for a) PMS2, b) MLH1, c) MSH2, and d) MSH6. 100X magnification.

Lessons learned

We still lack effective treatments for pleural mesothelioma; fewer than 10 percent of patients survive five years after diagnosis (23). And that's why my colleagues and I wanted to identify molecular factors implicated in carcinogenesis. We opted for PD-L1 evaluation because of the increasing availability of immunotherapies targeting immune checkpoint inhibitors, such as PD-1/PD-L1, and explored the mismatch repair proteins because of the epitheliomorphic histotype's similarity to adenocarcinomas of the gastrointestinal tract – most of which have defects in the mismatch repair complex.

Approximately half of the cases we examined were positive for PD-L1, meaning that immunotherapy is a possible treatment option for these patients. None of the cases showed a DNA mismatch repair deficiency, indicating that, despite morphological and biological similarities between

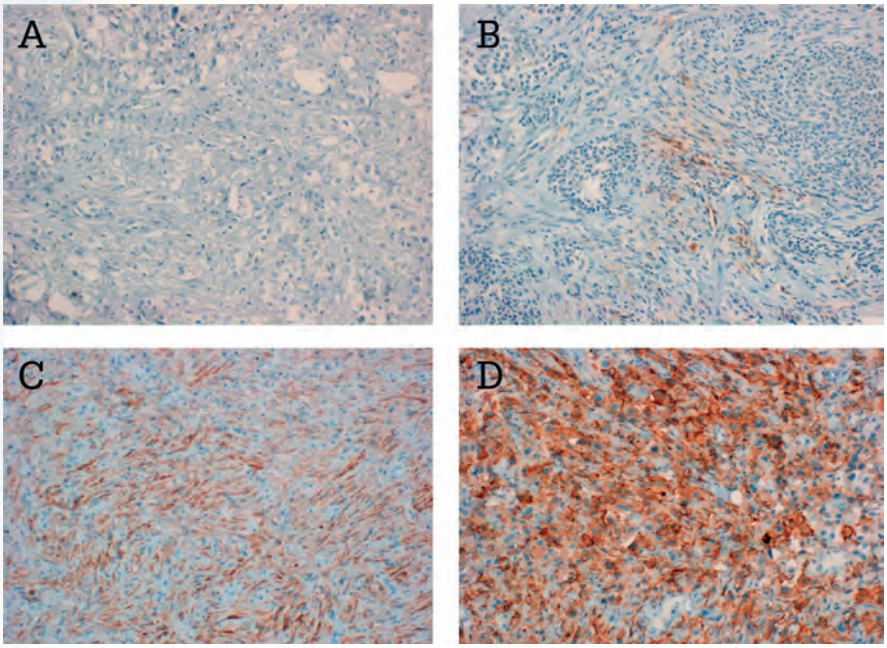

Figure 3. Pleural mesothelioma samples with IHC staining for PD-L1. Samples show differential expression with a) negative, b) low – 10 percent, c) high – 50 percent, and d) very high – 70 percent expression. 200X magnification.

adenocarcinoma and epitheliomorphic mesothelioma, the latter does not follow the epithelial carcinogenesis channels.

The oncogenes mutated in mesotheliomas are numerous; with the rarity of the disease, it's unsurprising that we have not yet identified the genes or gene complexes involved in its carcinogenesis. With the availability of more cases and the increasing communication between laboratories across the world, though, we anticipate expanding and improving our research to identify the involvement of specific molecular pathways that allow the disease to take hold.

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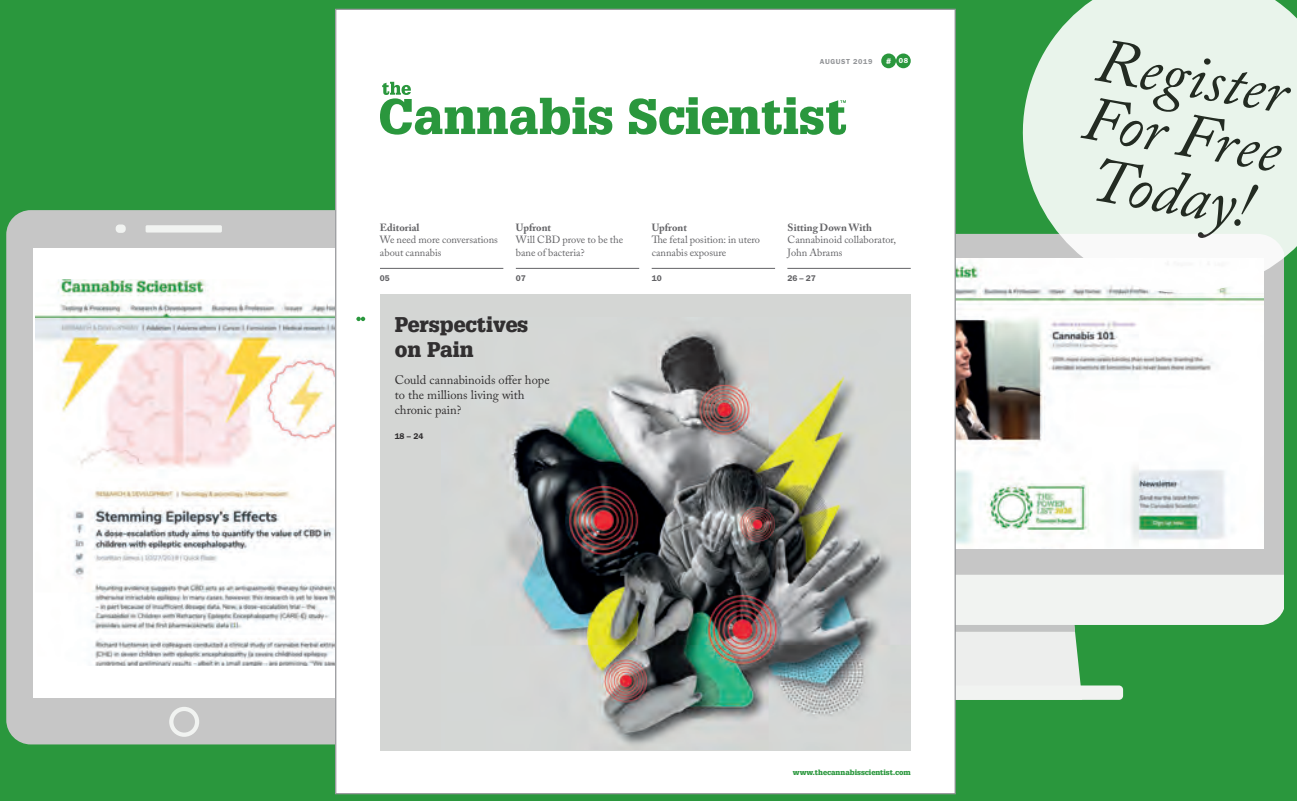

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The Road to Mass Spec Imaging in the Clinic

Moving MALDI MSI-based tissue typing from the research lab into clinical pathology

By Alice Ly

Until relatively recently, matrix-assisted laser desorption/ionization (MALDI) mass spectrometry imaging (MSI) was restricted to basic science – and it has yet to be widely accepted for clinical analysis. For MSI to migrate from a research platform to a universally accepted clinical diagnostic tool, it requires a standardized procedure for everyone using the technique and concerns regarding reproducibility must be addressed. Pathology laboratories increasingly rely on molecular testing that uses genomic technology; emerging molecular technologies, such as MSI, that provide dynamic, untargeted information about the cell's active state are likely to follow suit in the coming years.

The power of MSI

Many of MSI's features make it ideally suited to clinical pathology applications. Importantly, it can use the formalin-fixed paraffin-embedded (FFPE) tissue sections routinely collected during hospital care. These specimens maintain excellent tissue morphology and allow the direct collection of both spatial and molecular information. And, because this tissue acquisition method doesn't require analyte-specific reagents, MSI can even be used for biomarker discovery.

Traditional LC-MS/MS analyses of FFPE tissues require large sample sizes – impractical in the clinical setting – and sample preparation procedures may result in the loss of spatial information. MSI experiments, in contrast, retain the spatial distribution of the multiple molecules detected, because the measurements are conducted on intact tissue sections. One example is MALDI MSI-based tissue typing experiments, in which tissue- or clinically specific molecular profiles are created. MSI's label-free and nondestructive nature make it an ideal technique for preserving tissue material, such as cancer biopsies, for subsequent analyses.

Standardizing clinical proteomics

Despite MSI's advantages for molecular analysis, the variability of results currently restricts its clinical use. To apply the analytical benefits of MSI to clinical pathology, the technique's reproducibility across multiple laboratories and geographical locations must be demonstrated; many basic science laboratories optimize methodologies to their local conditions. A simple way to examine reproducibility is to apply a completely standardized sample preparation and imaging workflow across multiple sites. A recent study did just that when it examined whether several laboratories could achieve reproducible results by analyzing FFPE samples with a standardized MSI workflow (1). The aims of the study were threefold: i) to confirm whether the MSI protocol can maintain spatial resolution across experiments, ii) to confirm application to clinical samples, and iii) to assess the reproducibility of results across multiple sites.

The study's authors assumed that trypsin application and digestion were sources of variation and loss of spatial resolution in the MSI of FFPE samples – but results indicated that, when using a standardized workflow, they could discriminate discrete histological features in different tissues, eventually enabling different sites to generate images of similar quality. Using the integrated MSI tissue typing workflow for tryptic peptides from FFPE tissues, specific m/z features were detected in discrete histological features in mouse intestine, human ovarian teratoma, and human squamous cell carcinoma of the lung (see Figure 1).

When applied to the multicenter study, the MSI workflow could delineate the same histological features on the mouse intestine across five different sites, demonstrating the technique's reproducibility when laboratories adhere to stringent sample preparation and standard operating procedures. The study's results show a reduced likelihood that MSI-based tissue typing-derived classifications will differentiate samples based on technical differences, such as processing origin site, rather than biological or pathological differences – crucial if MSI is to be used as a clinical tool.

Because clinicians often make crucial decisions based on the results of a wide variety of tests, the non-destructive and tissue sample-preserving aspect of MSI may also benefit personalized medicine. For example, the development of novel therapies targeting oncogenic driver mutations has the potential to improve patient prognosis. Digital polymerase chain reaction (dPCR) is commonly used to reliably detect genetic mutations, and its combination with MSI has great potential for patient stratification. Researchers have demonstrated the ability to carry out MSI and dPCR analyses from the same tissue

At a Glance

- *Mass spectrometry imaging could be valuable in the clinic – if existing concerns can be addressed*
- *MSI allows measurement of small-sized samples and good specimen preservation for additional studies*
- *It can also be combined with other techniques, such as digital PCR, to make best use of limited biopsy tissue*
- *Although MSI shows promise for clinical use, standardization efforts are needed, because results remain variable*

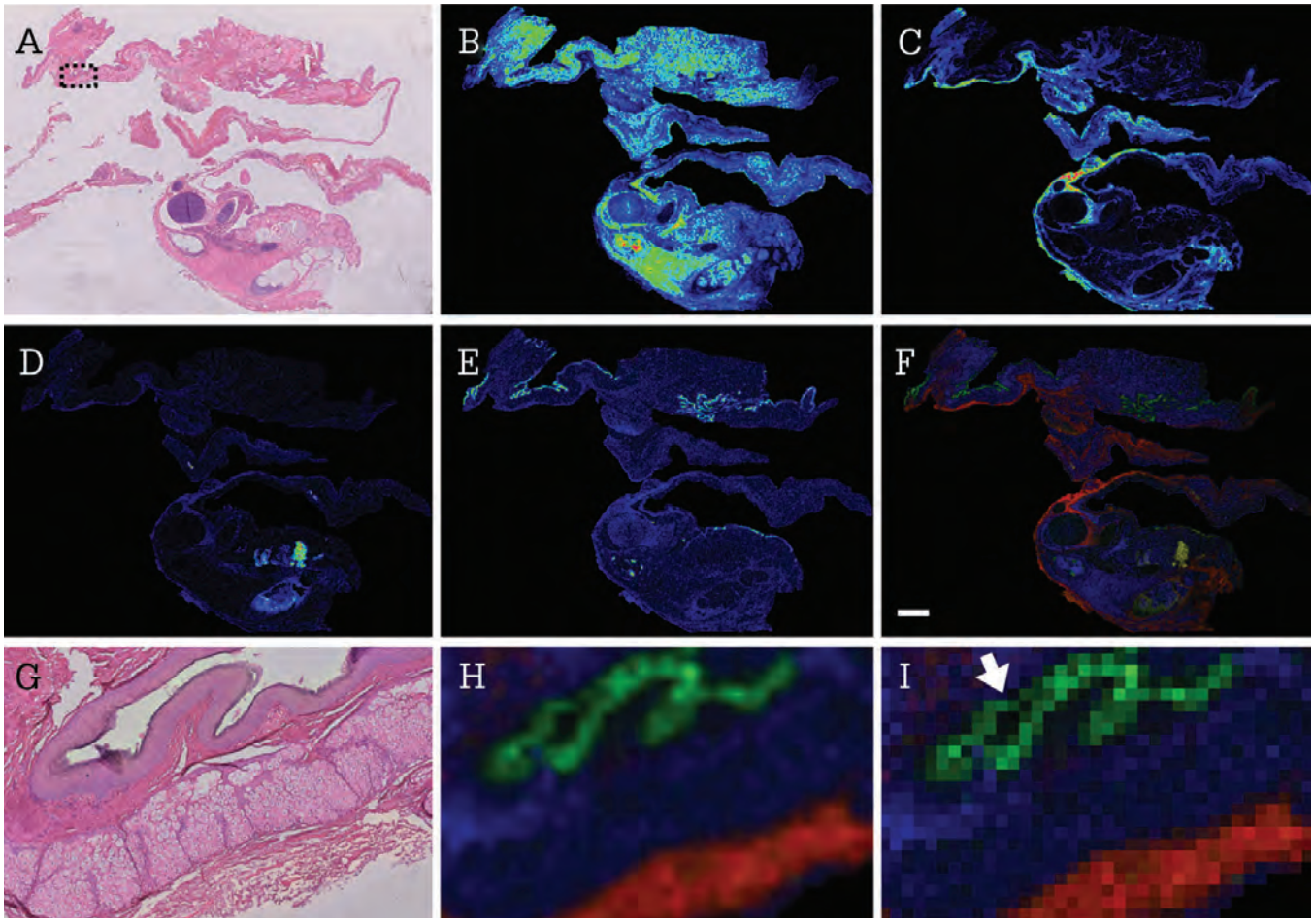

Figure 1. MALDI-MSI of human ovarian teratoma. a) Post-measurement stained H&E human teratoma; b) MALDI-MSI image of m/z 1249.2 corresponding to smooth muscle and glands; c); m/z 1095.7, connective tissue; d) m/z 1127.7, mucus; e) m/z 1324.63, epidermal stratum corneum layer. f) Overlay of the preceding ion images showing individual localizations. Scale bar = 2 mm. g) Higher magnification of H&E stained sample – region indicated by dotted black box in A; h) Overlay image of corresponding region from G shows the discrete localizations of the ion signals; i) Image of corresponding region with pixels representing individual mass spectra. In this view, it is possible to see that some ion signals are limited to a 50 µm region (arrow). Scale bar = 100 µm. Reproduced with permission from (1).

section (2), which is highly advantageous, given that biopsy material is often limited. This combination of proteomic and genetic analysis in one workflow is made possible by MSI's noninvasive nature, which has been shown to maintain DNA quality for subsequent analysis.

Clinical MSI in the future

If MSI is to be adopted for wide-scale clinical applications, such as diagnostics, its ability to generate the same results from samples collected and measured at different sites is crucial. However, being reproducible is one piece of the puzzle; having a relevant role in the pathologist's toolbox is another. For example, MSI has been shown to differentiate between adenocarcinoma and squamous cell carcinoma of the lung (3) – a challenging task for traditional immunohistochemistry (IHC) techniques. Additionally, MSI requires only one slide (unlike multi-slide IHC), allowing tissue to be saved for subsequent predictive molecular testing.

The continuing development of mass spectrometers, particularly with respect to improvements in spatial resolution, sensitivity, and sample throughput, is opening the field of MSI to clinical pathology. The speed and robustness of modern mass spectrometers allows large specimens to be analyzed quickly over large patient cohorts with good spatial resolution – imperative for driving this technique forward in diagnostics, prognosis, and monitoring treatment responses.

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Peer-to-Peer, Featuring Fred Plapp

How to navigate the clinical laboratory – and the resources that can help

Ivan Damjanov interviews Fred Plapp

Fred Plapp is a man who wears many hats – researcher, inventor, clinical pathologist, transfusion medicine physician, and even web guru. His professional history is similarly varied; he has practiced at a community blood center, a large private health care system, and an academic medical center. His primary areas of academic interest are clinical chemistry, immunology, transfusion medicine, and apheresis – but because of his wide experience, he also brings a unique perspective to education in pathology and laboratory medicine. Many of you may be aware of his inventions, his peer-reviewed publications, or the web resource he has developed to educate medical professionals about lab test results. Here,

At a Glance

- *The clinical laboratory is an invaluable health care resource with a wide range of responsibilities*
- *Similarly, clinical pathologists play a vital role in everything from test utilization management to inspection readiness*
- *Innovative clinical laboratorians have much to contribute to health care advancements such as the development of new techniques*
- *We can also provide a unique educational perspective to our colleagues and other medical professionals*

Ivan Damjanov uncovers the history behind the advancements…

How do you view your role as clinical pathologist and medical director?

The clinical laboratory plays a vital role across the entire continuum of health care. Virtually every practicing physician depends upon it for the care of their patients. And so, clinical pathologists provide consultation to referring physicians regarding:

- Maintenance of an up-to-date laboratory test menu
- Introduction of new tests and deletion of obsolete ones
- Inclusion of laboratory tests in clinical order sets
- Appropriate test utilization
- Interpretation of clinical laboratory test results
- Investigation of discrepant or unexpected results
- Lab results reporting in the electronic medical record

A clinical pathologist also needs to be accessible to the laboratory staff 24/7. We maintain an effective working relationship with laboratory management and hospital administration by actively participating in their meetings and assisting them in developing goals, objectives, policies, and procedures. We also advise in long-range planning and the acquisition of capital equipment.

Clinical pathologists monitor and evaluate the quality and appropriateness of laboratory services rendered within the context of an institution's overall quality management plan. We assure the quality of laboratory results by reviewing quality control, proficiency surveys, and patient data.

The medical director must make certain that the laboratory maintains a constant state of inspection readiness – after all, accreditation agencies may make unannounced inspections at any time. Not only is it vital to be prepared for such eventualities, but it also improves the overall performance of the laboratory. Last – but certainly not least – an important aspect of the medical director's job is to demonstrate to hospital administration how the laboratory provides added value for hospital operations, safety, and patient care.

When I am covering the transfusion service, I see patients almost every day for apheresis procedures including plasma exchange, red blood cell exchange, and white blood cell removal. Many of these patients are critically ill, so we work closely

with our critical care physicians. One of my fondest memories is caring for a young woman who developed life-threatening autoimmune hemolytic anemia after a hematopoietic stem cell transplant. She was admitted comatose with a hemoglobin level of 2.8 g/dL. She fully recovered following several therapeutic plasma exchanges and a complete red blood cell exchange. Several months later, I received a wonderful Christmas card thanking me for helping her enjoy the holidays with her family.

What contributions have you brought to hospitals and blood banks?

An increasingly important role of the medical director is active participation in utilization management initiatives, such as the Choosing Wisely campaign, that seek to eliminate unnecessary laboratory tests. I worked with our medical informatics team to develop a multi-pronged strategy for test utilization. We established duplicate alerts for tests that should only be ordered once per admission and high-volume test alerts for commonly ordered tests, such as complete blood counts and chemistry panels. We also added best practice alerts for expensive tests (those costing more than US$500) and send out tests with long turnaround times. So far, these test utilization initiatives have resulted in annual cost savings of $920,000.

After completing my pathology residency, I wanted to pursue basic research. I became interested in determining the biological function of red blood cell antigens, so my graduate students and I developed several innovative techniques to purify and identify blood group antigens. Eventually, we realized that some of these methods could be used to automate blood group serology, which at that time was performed manually in individual test tubes. Over the next five years, our small research team invented the solid phase red cell adherence method for pre-transfusion serologic testing. Once we realized its potential commercial value, we worked with a local intellectual property attorney to patent every facet of this technology. Gradually, we also invented blood grouping dipsticks and image recognition software to automatically interpret solid phase reactions.

I think that my first patent, for solid phase red cell adherence, has also been the most consequential one I've obtained. After patenting that technology, we met the three founders of a startup company looking for a novel technology to distinguish them from the established blood bank companies. After we transferred our technology to them, they became a leading international blood banking company. In fact, they still use our technology today in their workstations and automated analyzers. My research team was awarded the Morton Grove-Rasmussen Memorial Award by the American Association of Blood Banks in 1999 in recognition of our invention of solid phase blood banking. It was a very interesting experience, because I sat next to Kary Mullis, who received the Karl Landsteiner Memorial Award for the invention of the polymerase chain reaction (PCR). However, far more than the award, I value the fact that our work is still being used 35 years on – so it has clearly withstood the test of time.

But not all good inventions make it through the commercialization maze. In the early days of HIV, I invented technology to open vacutainer tubes safely without creating an aerosol. I sold this patent to a local company, which was soon bought out by a major pharmaceutical company. They shelved this project and, unfortunately, it was never pursued commercially.

How important is teaching as part of your role?

I have always enjoyed teaching. During my career, I have had the opportunity to teach medical students, residents, faculty, medical laboratory scientists, and nurses. Although I have given many lectures to large classes over the years, I particularly enjoy one-on-one teaching. I never pass up the opportunity to introduce young minds to the exciting field of pathology and laboratory medicine.

All of us who teach pathology have spent endless hours preparing teaching materials. Over the years, I have written descriptions of hundreds of laboratory tests, test utilization recommendations, and transfusion guidelines – and, eventually, I decided that I wanted to find a way to disseminate this educational material to a wider audience. Fortunately, my son Chris acquired the skills for website development in high school and began to host websites for several small businesses. In college, he majored in both fine art and computer science – a unique combination of interests that enhanced his ability to design websites that were both functional and aesthetically pleasing.

Together, we founded a company and created the website ClinLabNavigator.com. My son provides the technical expertise and I write the medical content. Chris has crafted a site that is very easy to use, even for those of us who are less technologically inclined, so all I have to do is tell him what content I would like to include and he determines the best way to display it. The site has steadily evolved over many years because of the changes he has made to improve readership. Today, thanks to our complementary skills and good working relationship, ClinLabNavigator.com contains over 1,000 laboratory test interpretations and guidelines. We're now looking into growing our organic search traffic and even experimenting with mobile applications. Our little web page has evolved into a comprehensive resource for healthcare professionals!

Fred Plapp is Clinical Professor and Medical Director of Clinical Laboratories at the University of Kansas School of Medicine. Ivan Damjanov is Professor of Pathology at the University of Kansas School of Medicine, Kansas City, USA.

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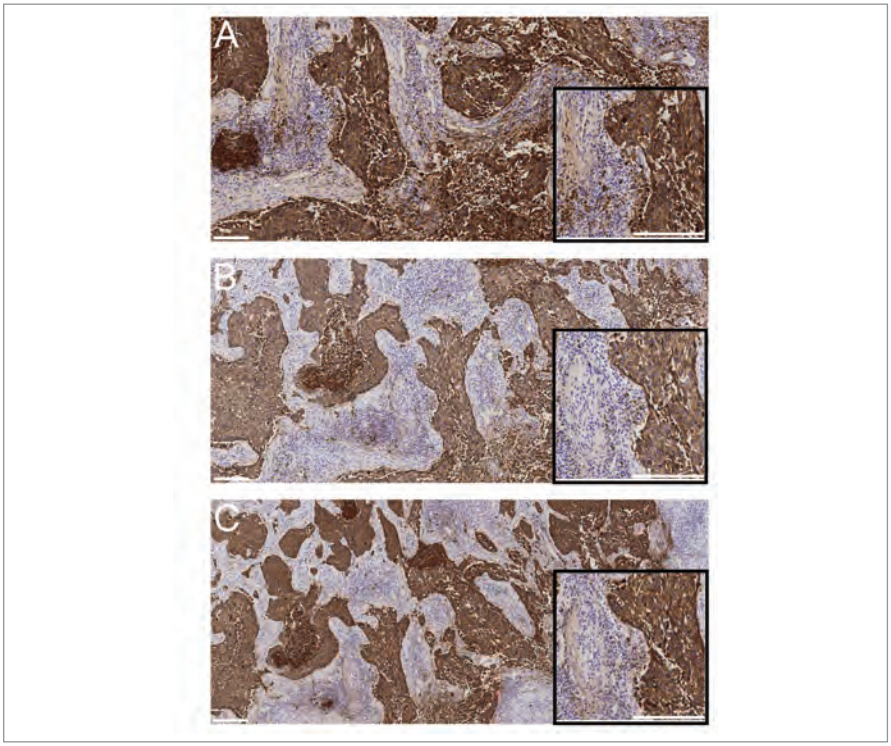
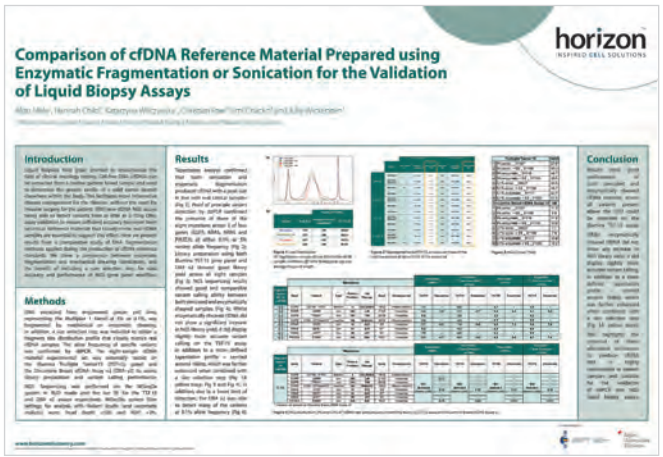


Figure. Expression of pan-cytokeratin in human lung carcinoma. Immunohistochemistry staining of Pan-cytokeratin in formalin-fixed paraffin-embedded human lung carcinoma using detection reagents and chromogens from Enzo Life Sciences (A), Dako (B) and Vector Laboratories (C).

Immunohistochemistry is an important diagnostic, prognostic, and research tool to analyze the anatomy of the tissue of interest but also to visualize the distribution, the localization, and the intensity of the expression of a specific antigen or cellular components in tissue sections. When done on a bench, it can be a lengthy and not always identically reproducible process. For a histopathology laboratory to deliver IHC results to the clinicians in a consistent and timely manner, it needs to be able to process hundreds of samples in a very short period of time. Researchers also face, a prerequisite to study dozens of specimen materials in order to get true statistical significance when establishing new biomarkers for a disease or a specific disease state. Cost-saving and reliable high-throughput staining capabilities are therefore essential for histopathologists and researchers alike. Automated slide strainers have been specifically developed for such a complex and time-consuming process. They provide an experimental environment for reagents to react with the sample during timed periods of incubation, and are capable of applying unique reagents in a predetermined manner as well as rinsing/washing buffers in between periods of incubation. Systems, such as the Autostainer Link 48 from Dako or the intelliPATH™ from Biocare Medical, possess opened operating modes providing them with a flexibility in protocol programming and stain sets. They allow the end user to optimize staining conditions in terms of primary antibody dilution, detection reagents, and chromogens for each individual marker with the main goals being to reach maximum sensitivity as well as, minimize non-specific binding while reducing time to result and cost. IHC reagents are not, however, always easily adapted to high-throughput staining methods.

Hence, the main objective of this study was to look at the suitability of POLYVIEW® IHC detection reagents and HIGHDEF® IHC chromogens for these autostainer platforms and their potential in terms of sensitivity and quality of staining. Data obtained with Dako Autostainer Link 48 correlated with results obtained with Biocare Medical intelliPATH™ FLX. Application of the POLYVIEW® IHC detection reagent and HIGHDEF® IHC chromogen resulted in the successful detection of BrdU, Ki-67, and p53 in murine intestine tissue and pan-cytokeratin in human lung tissue. The results also demonstrated that improved sensitivity and high intensity color development were achieved with detection reagents and chromogens from Enzo Life Sciences when compared to other detection reagents and chromogens from competitors, thereby validating their use as ideal IHC reagents for automated staining regardless of the autostainer platforms. The Beatson Institute for Cancer Research is one of Cancer Research UK's core-funded institute and which delivers a range of histology and immunohistochemistry services for research groups and large-scale IHC investigations thanks to top-of-the-range instruments including automated slide stainers.

A comparison study of cfDNA reference material preparation methods



The growing field of liquid biopsies has huge potential to transform the clinical oncology space. In order to realize the full potential of this emerging technology, sequencing labs need to ensure accuracy by validating a range of challenging new techniques.

This includes the ability to extract cfDNA from blood samples, sequence it at new levels of sensitivity (down to 0.1 percent limit of detection) and establish effective bioinformatics pipelines. Reference materials that closely mimic real cfDNA samples are critical to support this effort.

We have investigated the use of sonicated and enzymatically sheared cell-line derived DNA as alternative methods to create the most commutable cfDNA reference material for the validation of liquid biopsy assays

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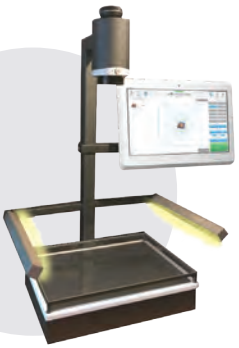

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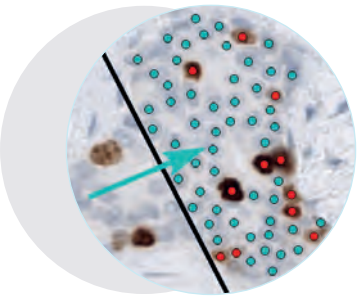

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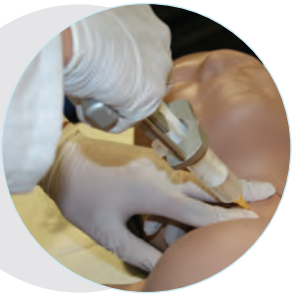

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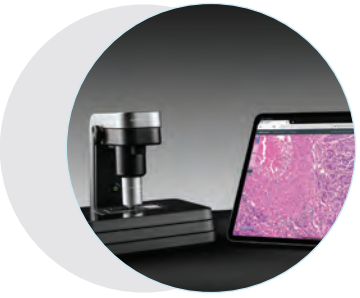

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Leading the Pack

Sitting down with… Jim Lanier, Retired Pathologist of 33 years at Providence Hospital, Anchorage, USA

How did you first get into pathology?

I did not consider pathology at all while in medical school. But, by the late 1960s, after gaining some general practice experience in the US Public Health Service in Alaska, I realized that caring for sick and terminally ill patients was not for me. I enjoyed basic science and I figured pathology would be more of the same. In 1969, I began a pathology residency at Mayo Clinic in Minnesota. Even then I had doubts about whether I had made the right choice – and it wasn't until 1974, when I started working as a pathologist at Providence Hospital in Anchorage, that I finally felt comfortable and confident at the microscope.

And you're an avid sled dog racer…

Growing up in Fargo, North Dakota, I was never allowed any pets, so when I became an Alaskan, my yearning for canine companionship became palpable. Soon enough, my back yard was brimming with dogs. The Iditarod is an annual sled dog race from Anchorage to Nome – a 938-mile journey across Alaska in early March. You might think this sounds daunting – and it often is – but I can't get enough, even at the age of 79! I have competed at least once every decade since 1979, with a current total of 20 races. I enjoy training with the dogs to prepare for the race, planning and executing a race plan (even when it begins to fall apart), and the well-earned celebratory beer at the finish line. In 2019, I participated in Yukon Quest (a 1,000-mile race between Whitehorse, in Canada's Yukon Territory, and Fairbanks, Alaska) for the first time. I had always wanted to run it and, at my age, it was now or never. Although the Quest is arguably tougher than the Iditarod, I jokingly stated in a speech at the banquet before the start, "The Iditarod was getting too tough for me, so I decided I should try an easier race!"

Surprisingly, there are a few parallels between pathology and sled dog racing, mainly in that both involve medical care. My knowledge of medicine, pathology, and physiology has enabled me to evaluate and treat canine health issues, sometimes in conjunction with a veterinarian. The same applies to nutrition and conditioning. And then there's my own body, which is a museum of dog musher pathology in itself: fractures, prosthetic joints, tendinitis, hemorrhoids, dog bites, lacerations, and amputations. The last is memorialized with a mummified big toe dressed in a tuxedo and lying in a coffin with the accompanying text of a eulogy. Both pathology and sled dog racing involve observation, diagnosis, and analysis – take stock of what happened, establish what worked well and what didn't, determine how to fix it, and resolve to do it better or at least differently next time.

How do you motivate yourself to carry on?

There are many times when I came close to giving up but, in these moments, I drew on experience. I knew that, no matter how bleak it seemed, things would get better – so I hung on. Despite this, there are times when I have had to retire. I have successfully completed 16 of my 20 Iditarod races; four ended in disappointing circumstances. One of these was due to a ruptured Achilles tendon, another a fractured clavicle, and yet another because I developed pneumonia. The fourth came in the 2018 Iditarod when, 40 miles from the finish line, I was blown out to sea in a fierce storm and had to be rescued.

As for motivation, I remind myself that I'm out there in a predicament of my own making and that I am supposedly enjoying it. Alternatively, motivation can come from an inspirational cause. In one race – dubbed a "Mush-a-thon" for a new thermal unit at my hospital – people pledged money for each mile I completed, so I was compelled to reach the finish line in Nome. I raised US$14,000 for the unit – and was then immediately admitted to it myself for frostbite suffered during the race!

What is the most valuable thing you've learned throughout your career – as a pathologist or as a sled dog racer?

Things will get better. But that doesn't mean you should simply wait; if you take action, things will get better sooner. Tend to the injury, mend the broken sled, hydrate the dehydrated, form your alternate plan – and the same is true for crises in medicine. Believe it or not, my medical training prepared me well for sled dog races, especially the 1,000-mile events. During these long races, sleep comes in one- to two-hour increments – at most twice each day. Over the entire race period of more than 10 days, that leaves you with just 15 to 20 hours' sleep. It's grueling and things get pretty fuzzy, but you must continue to make decisions and take action. Being on call and taking care of patients for entire nights before working the next day helped prepare me for the races to come.

What advice would you give to those at the start of their medical careers?

These are the good old days. Life is great and so is your chosen profession, so make the most of it! And, importantly, make room for other things. In my case, that has meant music, mushing, and family, with a little commercial fishing on the side. For many years, after I had finished my day at the lab, I would hook up my team of dogs to go for a run after midnight and then get up the next morning to do it all over again. How did I manage it? Younger and dumber, I guess…

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