OCTOBER 2018 # 47

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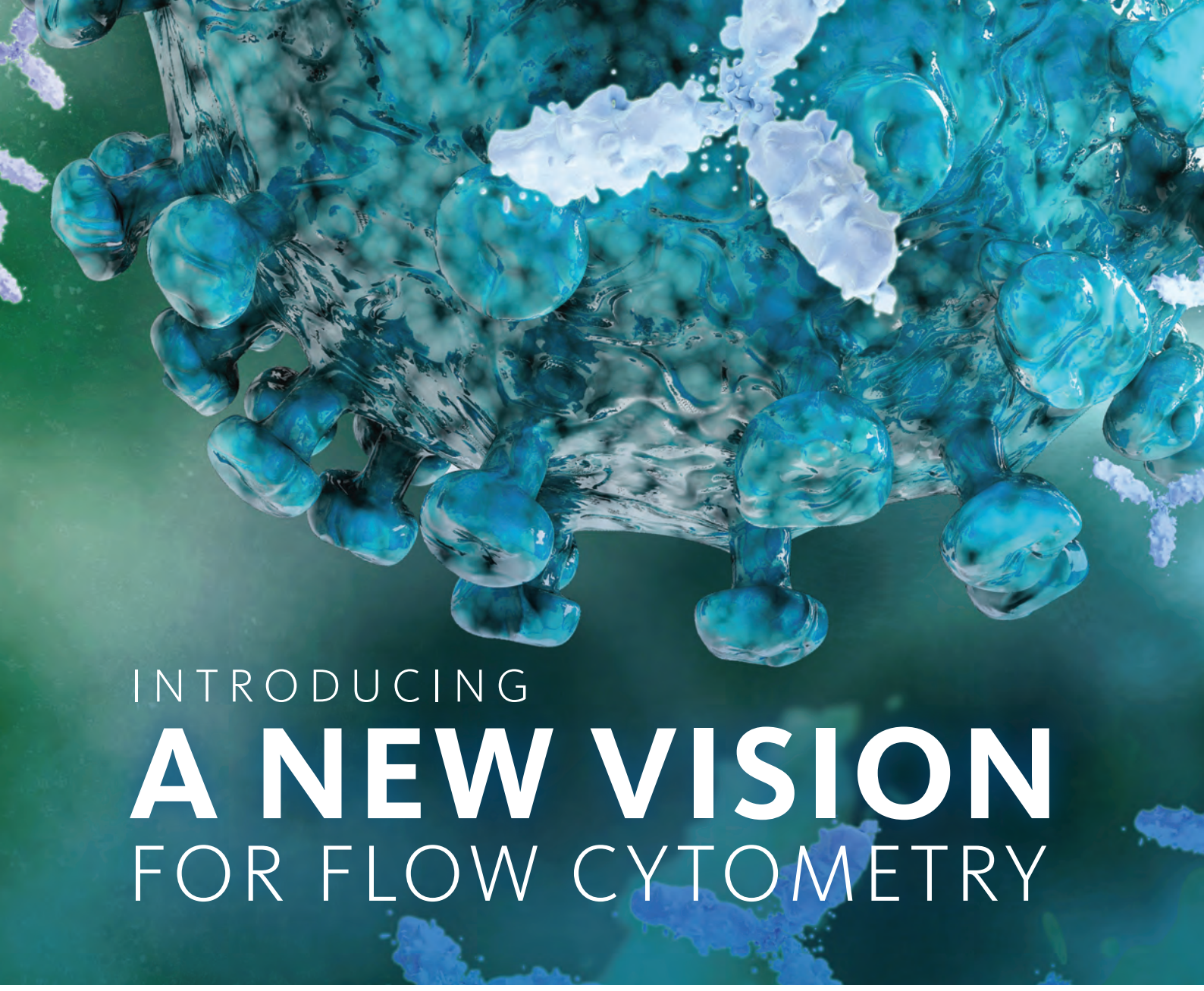

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Case of the Month

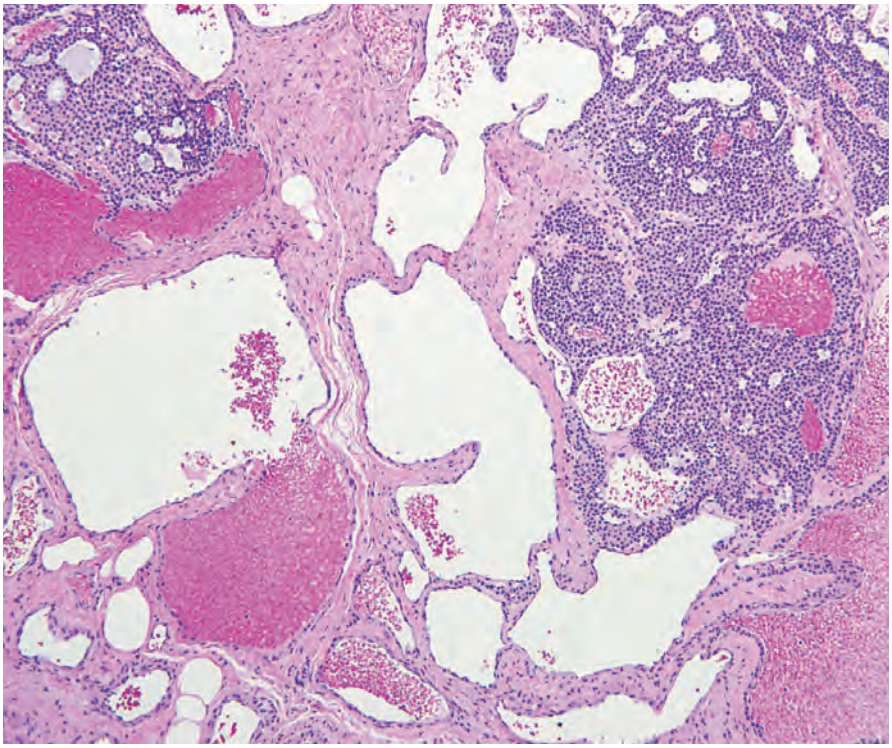
A painful subungual tumor measuring 0.8 cm was removed from the finger of a 29-year-old man. What is the diagnosis?

A. Eccrine spiradenoma

B. Eccrine poroma

C. Glomangioma

D. Arteriovenous malformation



To register your guess, please go to http://tp.txp.to/1018/case-of-the-month
We will reveal the answer in next month's issue!

Answer to last issue's Case of the Month…

B. Angiolymphoid hyperplasia with eosinophilia

This condition is common in middle-aged men. It usually affects the subcutaneous and dermal layers of the skin. There is significant proliferation of the vascular channels lined by plump endothelial cells. Surrounding these vessels is an abundant mixture of inflammatory cells, predominantly eosinophils (1).

Reference

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Submitted by Seoparjoo Azmel bin Mohd Isa, Pensyarah Perubatan & Pakar Patologi (Patologi Anatomik), Jabatan Patologi, Pusat Pengajian Sains Perubatan, Universiti Sains Malaysia, Kelantan, Malaysia.

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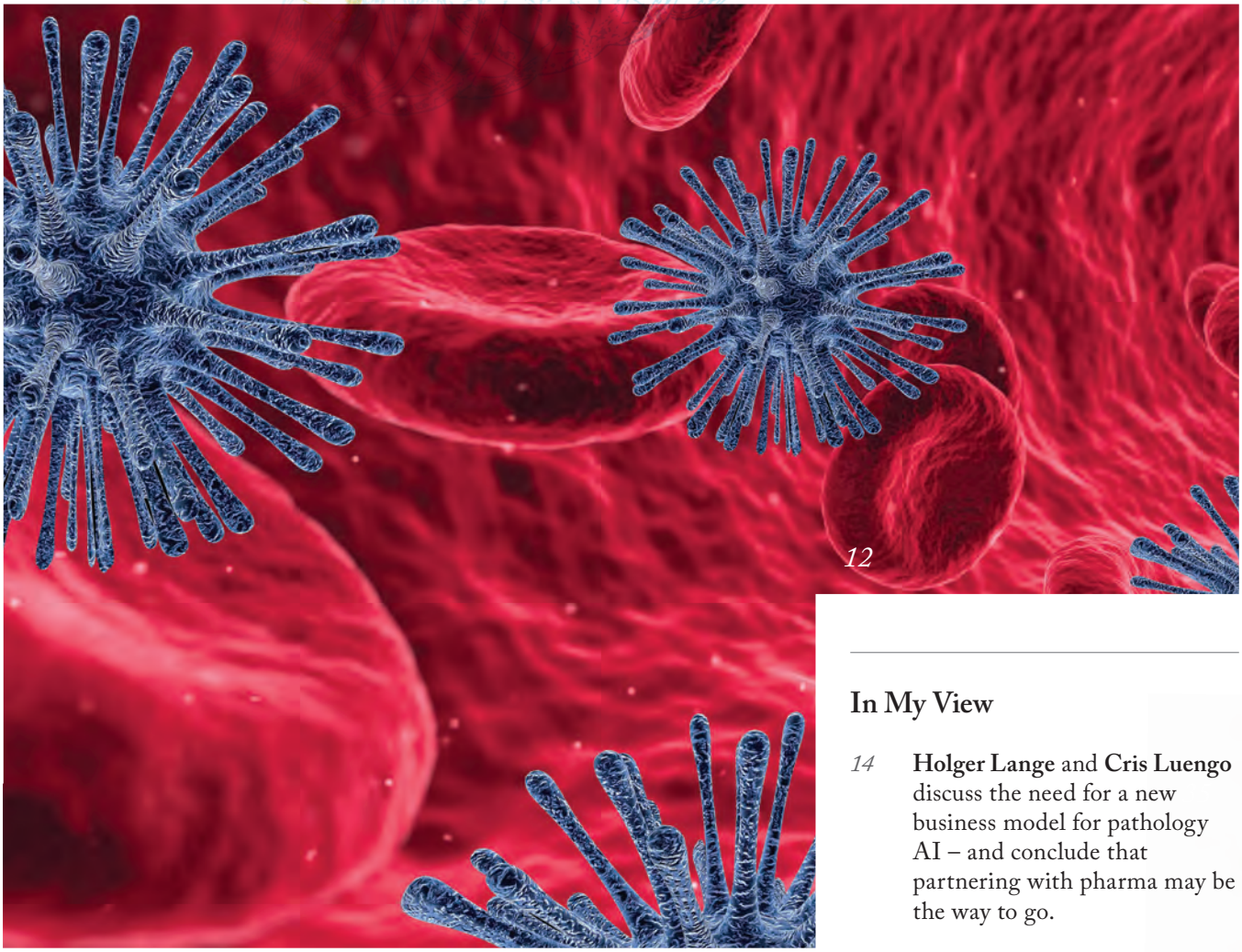

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On The Cover

Frank Dicksee's "Vikings Heading For Land," overlaid with imagery representing both paleopathology and modern pathology.

In Practice

NextGen

Report

Feature

Profession

Sitting Down With

the Pathologist

ISSUE 47 – OCTOBER 2018

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A Community of Equals

In laboratory medicine, each and every one of you has a voice

This past week, I had the honor and pleasure of seeing many familiar faces at the American Society for Clinical Pathology (ASCP)'s annual meeting. Some of you I had met at previous conferences. Others, I had spoken with by phone or had conversations with via email. Some of you I knew only by your Twitter handles. Still others first crossed my path when they appeared on this year's Power List (1). And some of you were friends of friends, people I had heard mentioned in cases or announced in newsletters or lauded for poster presentations.

Throughout my many interactions, I noticed something quite remarkable: it seemed to make very little difference which group each of you fell into. With everyone at the conference, conversation was easy, educational, and convivial. We discussed key problems facing laboratory medicine; we discussed the education and recruitment pipeline in the field; we even discussed how some of you prefer to make (or not make) your beds.

And, equally remarkable, through all of those conversations, there was a distinct lack of hierarchy. I spoke to medical students, residents, faculty members, chairs, and society presidents – on some occasions, all at once. Each person was listened to with equal respect and importance, regardless of their rank or their years of experience. It was clear to me that, at least among laboratory professionals, everyone has a voice, and every voice deserves to be heard. ASCP CEO E. Blair Holladay says that "it takes a village" to ensure optimal health care (see page 17) – but I've found that laboratory medicine is a special kind of village. It's a warm and welcoming community.

Michael Schubert
Editor

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1. *"The Power List 2018", The Pathologist, 46, 18–40 (2018). Available at: bit.ly/2OEEtv0.*

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?

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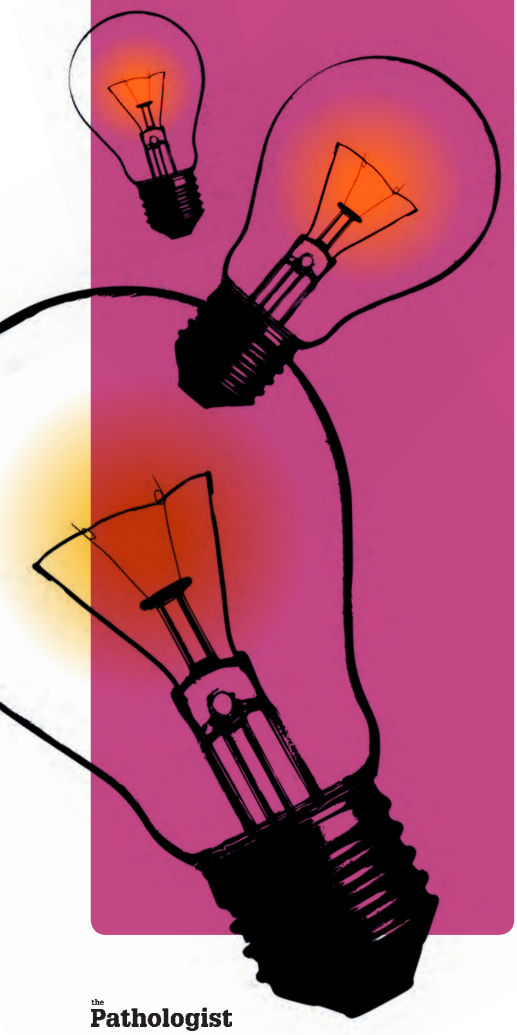
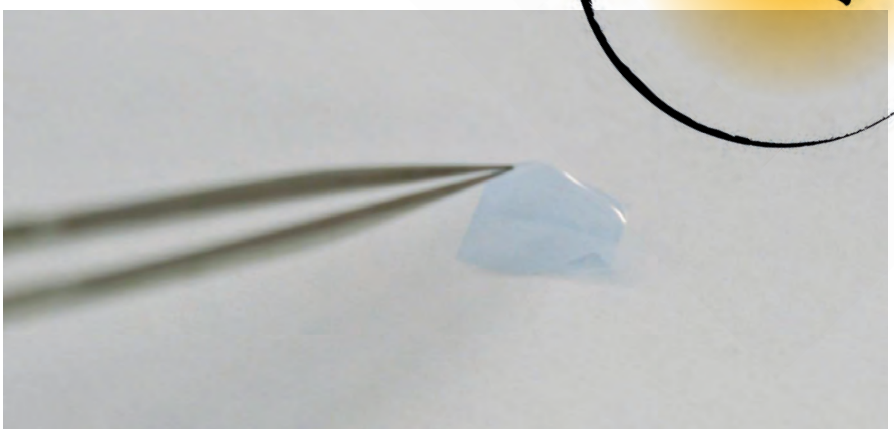




Credit: University of Rochester Medical Center

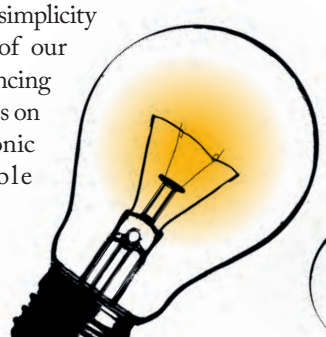
Shining a Brighter Light

Srikanth Singamaneni explains a new approach to enhancing fluorescence-based detection techniques

Fluorescence-based detection and imaging techniques are the cornerstone of modern biomedical optics, with applications ranging from the detection and quantification of biological species to the bioimaging of organelles up to organisms. The main drawback – poor sensitivity – can be enhanced by plasmonic nanostructures, but current plasmon-enhanced fluorescence methods cannot be easily integrated with existing biosensing and bioimaging platforms. To that end, we developed a simple and convenient method to exploit plasmon-enhanced fluorescence in various biosensing and bioimaging methods (1).

There are many ways to increase the sensitivity and signal-to-noise ratio of biodetection of low-abundance species. The key innovation in our approach lies in the extreme simplicity and universality of our fluorescence-enhancing system, which relies on placing a plasmonic patch (a flexible polymer film coated with plasmonic nanostructures) on the fluorophore-labeled surface. The nanostructures on the film act as antennae, concentrating light into a tiny volume around the molecules emitting fluorescence to yield a 100-fold enhancement. In this way, the plasmonic patch is a sort of magnifying glass.

We believe that the patch's preclinical and clinical utility may not be far off. It not only enables the detection and visualization of target biological species at significantly lower concentrations, but it can also be applied to established biodetection procedures without modification. As an add-on method, it can be directly incorporated into existing bioassay workflows to generate immediate enhancement in the signal-to-noise ratio. It could even lead to the development of cheaper, more portable fluorescence readout devices for point-of-care testing in resource-limited areas. The first set of plasmonic patch products tailored for protein microarrays will be available within 12 months – but, in the meantime, we are working to further improve enhancement efficiency, and to apply the patch to DNA/RNA microarrays.



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Fluid Evidence

Liquid biopsies using biomarkers in droplet digital PCR offer a non-invasive method for evaluating immunotherapy efficacy in the most lethal forms of skin and lung cancer

Of the more than 200 different types of cancer we have identified, those that affect the skin and lung are among the most common. Together, they represent about one-fifth of all new cancer diagnoses (1–4.) Immune checkpoint inhibitors, drugs that boost the body's T-cell anti-tumor response by removing the brakes that typically prevent the immune system from killing tumor cells, have greatly improved clinical outcomes for patients with melanoma and non-small cell lung cancer (NSCLC). One commonly targeted molecular brake is programmed cell death protein-1 (PD-1), a receptor found on the surface of T cells. By preventing PD-1 from binding to its target on cancer cells, programmed death ligand-1 (PD-L1) allows T cells to attack the tumor – which is why anti-PD-1 antibodies, such as pembrolizumab and nivolumab, are now approved first-line therapies for patients with advanced melanoma and NSCLC (5,6). Clinical pathologists measure the expression of PD-L1 in tumor tissue to identify patients who score high for PD-L1 expression and therefore might derive the most benefit from immunotherapy.

Using PD-L1 as a predictive biomarker for patient selection is challenging because the immunohistochemistry (IHC) tests used to determine the presence of PD-L1 in tumor biopsies are not standardized – in fact, the four FDA-approved IHC tests for PD-L1 expression use different antibodies, detection systems, scoring systems, and thresholds (7–9). But is there another way? Droplet digital PCR (ddPCR) may help. This form of PCR is highly reproducible across different labs (10), is optimized for rapid, minimally invasive liquid biopsy (11), and allows for both increased sensitivity and precision due to its ability to partition a sample into thousands of droplets (12).

Nevertheless, PD-L1's reliability as a predictive biomarker requires further characterization. Its efficacy as a biomarker may be limited to patients with specific disease characteristics that are not yet well understood. PD-L1 levels may also change over time or as a result of prior treatments, suggesting that a single assessment from a tissue biopsy at diagnosis might be insufficient to inform ongoing therapy. To investigate how well PD-L1 levels correlate with treatment outcomes, researchers from the University of Pisa used ddPCR to measure PD-L1 mRNA levels in liquid biopsies (13). They analyzed plasma-derived exosomes, a source of intact mRNA involved in cancer cell signaling and immunity.

The researchers evaluated changes in PD-L1 expression at baseline and at two months in patients with advanced cancer treated with nivolumab and pembrolizumab. They found that PD-L1 levels correlated significantly with treatment response. Complete and partial responders had the highest levels of PD-L1 expression at baseline and a significant reduction of PD-L1 levels after treatment. Patients with stable disease exhibited lower levels of baseline PD-L1 expression and did not show significant changes in levels after treatment, whereas patients with progressive disease had the lowest baseline levels of PD-L1 and a significant increase after treatment.

It seems clear that patients with elevated levels of PD-L1, decreasing soon after treatment, might derive the most benefit from anti-PD-L1/ PD-1 immunotherapies. By dynamically evaluating PD-L1 mRNA from exosomes via ddPCR, we may be able to obtain useful information on clinical outcomes in cancer patients – information that can be continuously updated as patients undergo treatment.

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Credit: Washington University in St. Louis

A Biomarker for Brain Injury

Two proteins detectable by a simple blood test can help determine whether or not patients require CT scans following traumatic brain injuries

How do we diagnose traumatic brain injury (TBI)? Most people immediately think of patient-reported symptoms, functional neurological testing, or perhaps imaging to spot damage to our most delicate organ. It's unlikely that your first thought was of a blood test – and yet that is precisely the approach approved earlier this year by the US Food and Drug Administration (FDA) and published recently in The Lancet Neurology.

Study author Robert Welch explains, "[Intracranial injury biomarkers] have been a topic of need and development for a long time. Ours was a clinical study that evaluated the new test against a gold standard (CT scan) for detecting traumatic intracranial injury." The goal of the test is to reduce the use of CT scanning, which is costly, resource-intensive, and subjects patients to a dose of radiation equivalent to seven years of natural exposure – but, at the same time, to ensure that there is no increased risk of missing an injury.

The test detects two proteins, ubiquitin C-terminal hydrolase-L1 (UCH-L1) and glial fibrillary acidic protein (GFAP), both of which are naturally present in the brain – but significantly elevated after TBI. The test showed 97.6 percent sensitivity for the detection of intracranial injury, and 100 percent sensitivity for neurosurgically manageable lesions. However, it is not intended to replace CT scans entirely. "It will likely be a screening test that indicates a need for further diagnostic study – similar to D-dimer testing for suspected pulmonary embolism," Welch explains. Patients whose UCH-L1 and GFAP levels indicate the possibility of TBI will continue to be referred for imaging; however, those in whom the test is negative can avoid a scan.

Welch also points out that the test is not intended to be a detailed resource offering continuous values. "Doctors need a yes/no result to make decisions on a patient's need for further testing," he says. "They want an objective test – and this fits the need." But to be fully applicable in the clinic, Welch and his colleagues would like to go one step further. Their ultimate goal? A rapid point-of-care platform so that the initial testing for TBI requires only minimal time and resources.

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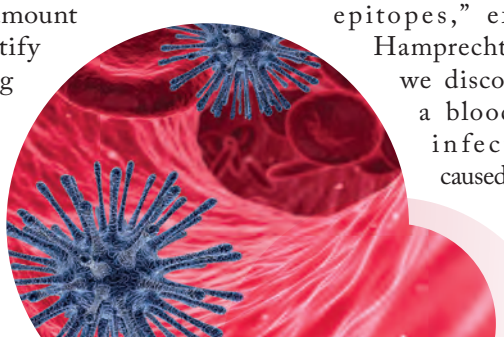
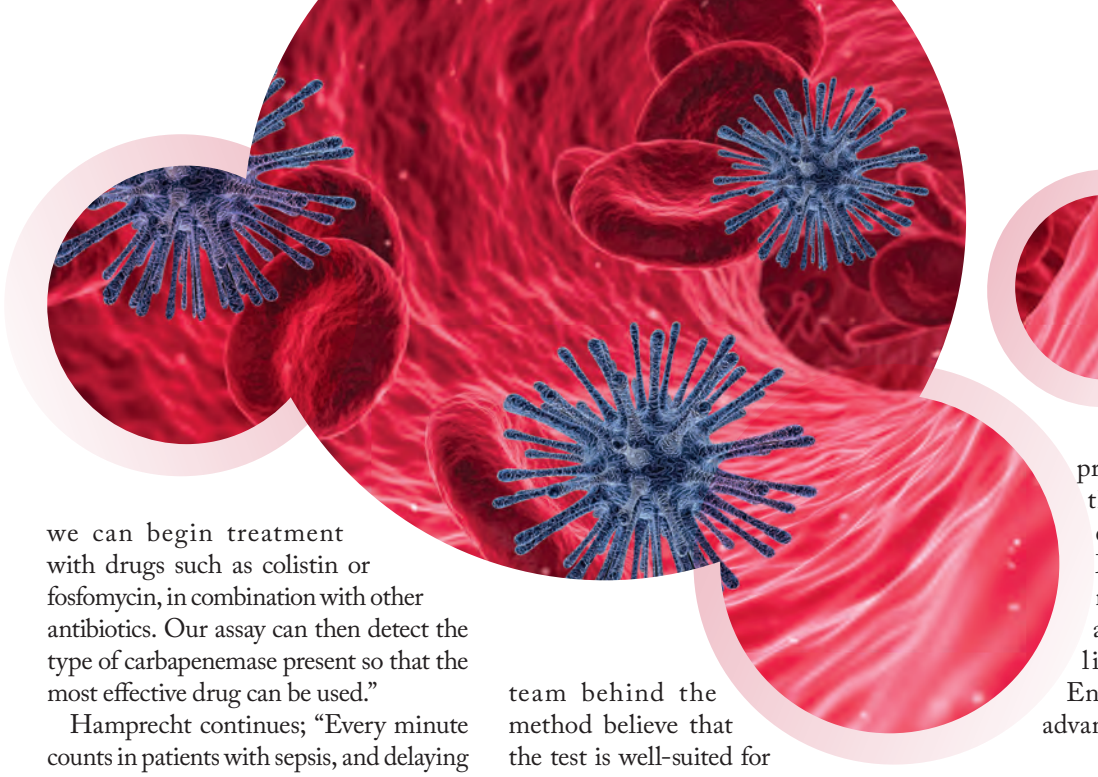
Fighting Resistance in Bloodstream Infections

Can a new immuno-chromatographic test improve the way we treat common bloodstream infections?

Sepsis: a term dreaded by health care professionals everywhere. At best, it heralds urgent care for a severely ill patient, but can result in death in the worst-case scenario. The high mortality rate that accompanies bloodstream infections is exacerbated by an increase in bacterial resistance to carbapenem antibiotics. Bacteria that produce the resistance enzyme carbapenemase can be detected by laboratory tests, but these can take up to 72 hours to complete. A new immunochromatographic test (1) has now been developed that drastically reduces the amount of time needed to identify carbapenemase-producing Enterobacteriaceae (CPE). Axel Hamprecht of the German Centre for Infection Research says that the new test, which he helped create, will optimize the use of antibiotic treatments.

"The incidence of bloodstream infections with CPE is rising and currently there is no method available for its rapid detection. We have developed an immunochromatographic lateral flow assay, whereby carbapenemases are detected by monoclonal antibodies specific for carbapenemase epitopes," explains Hamprecht. "Once we discover that a bloodstream infection is caused by CPE,





we can begin treatment with drugs such as colistin or fosfomycin, in combination with other antibiotics. Our assay can then detect the type of carbapenemase present so that the most effective drug can be used."

Hamprecht continues; "Every minute counts in patients with sepsis, and delaying the administration of effective therapy leads to increased mortality – an increase of 7 percent per hour in severe cases. This method can detect CPE in just 20 to 45 minutes, which is much faster than conventional techniques." The research team behind the method believe that the test is well-suited for clinical laboratories, and are further developing the assays to detect rare types of CPE.

There is a large degree of variation in CPE prevalence around the globe, and in countries such as India, Greece and Italy, over half of *Klebsiella pneumoniae* hospital isolates are carbapenemase producers. Even in the US, they have been found in every state other than Maine and Idaho. This is no minor threat; carbapenems are often used as a last line of defense against Enterobacteriaceae, so every advantage counts.

Reference

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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

Intelligent Pharma Partners

Pathology AI needs a new business model – and partnering with the pharmaceutical industry is an attractive opportunity

By Holger Lange, Chief Technology Officer, and Cris Luengo, Director of Image Analysis at Flagship Biosciences, Westminster, USA

The true barrier to artificial intelligence (AI) in pathology is not the technology; it's the business model. To get pathology AI into clinical laboratories, payers need to provide a value-based model that creates a viable business case.

We estimate the US anatomic pathology market for tissue image analysis, based on the current reimbursement model, to be about US$550 million (about $7–8 per test), even though it is unlikely that the Centers for Medicare and Medicaid Services is going to just add $550 million to their reimbursements. The problem is that the anatomic pathology market is segmented into subspecialties, which correspond to different tissue types, each with a list of different tests that typically correspond to different stains. Indeed, myriad "tissue–stain–clinical outcome"-specific tests each have their own little market segment that we estimate to be on average about $11 million, shared by multiple manufacturers.

Pathology AI is dependent on the adoption of digital pathology, which by itself does not have a tangible business case. Depending on whether or not a laboratory has a scanner, any additional reimbursement for computer assistance may need to fund the purchase of the digital pathology equipment as well. And when you consider the costs associated with building and commercializing a pathology AI system as a medical device, its business case becomes a challenge. Ultimately, though, we believe that pathology AI will drive the adoption of digital pathology, providing it with a return on investment!

Applications that provide the same results as pathologists using a microscope, but with better consistency or requiring less time, make almost no difference in the market to the end user. We have seen this very clearly with the tissue image analysis immunohistochemical (IHC) HER2 test for breast cancer – the poster child for these kinds of applications. Its adoption was very strong between 1998 and 2002, when the additional reimbursement was very high (about an additional $170 per test); by 2002, about 450 ACIS systems (the first commercial product) were placed. The reimbursement dropped to under $60 in 2003, and in 2007 only 250 ACIS systems were still in the market. Today, the additional reimbursement is less than $10 per test.

Interestingly, several additional tissue image analysis IHC medical devices have been developed over the years, all by digital pathology manufacturers who have a completely different business

"Today, immuno-oncology is the 'killer app,' with a massive business case behind it."

case in mind: to introduce their digital pathology equipment into the clinical market. The predicate device, the ACIS system, smoothed their way. But not even devices aimed at rare event detections (such as acid-fast bacilli or mitotic figures), which could save pathologists a lot of time, were able to break into that market. So why would the diagnosis of cancer, the latest application everybody is talking about, be any different? After all, the gold standard is a pathologist using a microscope. Why change – and potentially lose money?

The adoption of pathology AI under the current reimbursement model will only be driven by "microscope-impossible" tests that require the use of AI. Today, immuno-oncology is the "killer app," with a massive business case behind it. There is an extensive need for tissue context data that other modalities, such as next generation sequencing, cannot provide. Analysis of the tissue is far too complex for a pathologist using only a microscope.

Pharmacogenomics allow us to identify the patients who are more likely to respond to particular therapies or who require dose modifications. Stratification of clinical trials, even retrospectively, boosts efficacy and eliminates toxicity. How much is that worth?

Prescribed cancer treatments are effective in only about 25 percent of cancer patients, making them inefficient, expensive and detrimental to patient health. In the US alone, adverse drug reactions account for 100,000 patient deaths and $100 billion in healthcare costs each year. Between 1997 and 2004, 19 drugs were removed from the market because of adverse events.

We believe that the true opportunity for pathology AI lies in personalized medicine with big data. We could run a single test in a clinical laboratory – a standardized panel with multiple markers that provide rich information data for tissue – and use it as a basis for treatment decisions that include the full spectrum of all available and future drugs. New diagnostics, prognostics, and companion diagnostics could be created by clinicians in the field; as the test generates the underlying data, diagnostics, prognostics, and companion diagnostics become just a scoring scheme – a formula that any laboratory professional can develop by correlating existing or emerging health conditions with this database of information. Better characterization of the patient population using rich information data from the test could make drug development faster and cheaper through smarter patient selection. Diagnostics, prognostics, and companion diagnostics based on the test could significantly simplify regulatory pathways. With the generation of rich information data for tissue using a single standardized test, the regulatory pathway can be divided into two steps: first, an easy FDA clearance of the test to provide data (measurements not related to clinical outcome) only; and second, diagnostics, prognostics, and companion diagnostics that are now just simple scoring schemes with much simpler regulatory pathways. For pathologists who want to improve patient care, pharmaceutical companies who want to bring their drugs to market, and payers who want to lower healthcare costs, the combination of AI-assisted pathology, pharmacogenomics, and big data could yield a viable business model – and a bright future for everyone involved.

Automation Inevitable?

Perspectives on artificial intelligence and deep learning in pathology

By Randy Van Ommeren, Department of Laboratory Medicine and Pathobiology; Kevin Faust, Princess Margaret Cancer Centre and Department of Computer Science; and Phedias Diamandis, Princess Margaret Cancer Centre, Department of Laboratory Medicine and Pathobiology, and University Health Network, University of Toronto, Canada

Artificial intelligence (AI), a collective term for a wide variety of machine learning systems, has progressed significantly in recent years with the development and widespread dissemination of deep learning techniques. Deep learning is a specific machine learning approach that uses neural node architectures reminiscent of those found in the human cortex. Neural networks can be trained on large quantities of data, allowing them to develop feature recognition capabilities that permit discrimination between various patterns in a data set. Deep learning approaches have been shown to function at a human – or even superhuman – level in various domains, recently beating a world-class player at the highly complex and intuitive game of GO (1).

The implementation of machine learning approaches for medical diagnostics has long been a topic of interest, but translation to real-world settings has remained limited (2). However, with recent developments in deep learning, the possibility of

sophisticated decision support for clinicians has been aggressively rejuvenated. A flurry of publications in recent years have demonstrated the potential for deep learning applications in such varied fields as dermatology, ophthalmology, oncology, radiology, and pathology. Radiology and pathology, in particular, are considered highly amenable to deep learning-based technologies, given the particular strengths of these algorithms in image analysis (3).

For pathology, deep learning approaches carry significant potential to improve the diagnostic accuracy and daily workflow efficiency of practicing pathologists. Various groups have examined and demonstrated the inter-observer variability present between pathologists who have assessed a single set of cases (4). The introduction of sophisticated algorithms trained on large quantities of data (previously annotated by qualified pathologists) has the potential to improve the consistency of diagnostic decisions. Artificially intelligent systems can be leveraged to not only provide diagnostic outputs, but also examine submitted data sets to identify correlations between patient prognosis and subtle morphologic variants that humans cannot yet recognize. One can further envision the automation of tedious, repetitive tasks: ordering anticipated stains for a submitted section; quantifying features such as mitotic count or percent positivity in immunohistochemically stained sections; populating final diagnostic reports. The concomitant efforts of human and machine diagnosticians may provide an additional layer of quality assurance, reducing the rates of analytical and post-analytical errors present in pathology departments today (5).

Discussions about AI invariably prompt questions and concerns about the possibility of displacing human pathologists from their roles. Evolution of the relationship between man and machine is extremely difficult to predict, as evidenced by the wide range of opinions on the matter. The question is further complicated by the non-intuitive rate of development of novel technologies. Among practicing pathologists today, most believe that these platforms will eventually play a role in diagnostic pathology – but primarily for decision support, rather than clinician-independent analysis.

"Deep learning approaches carry significant potential to improve the diagnostic accuracy and daily workflow efficiency of practicing pathologists."

Perspectives of computer scientists at times diverge from those of clinicians. In radiology, some leading AI researchers have expressed a more dramatic view, proposing that new modalities will likely displace radiologists to some degree. The potential impact on pathology seems to attract less comment – probably due to the reduced visibility of the field, but possibly because some technical aspects of pathology (such as identification of tissue orientation, or the accurate determination of margins and tumor extent) may be less amenable to automation.

In short, AI brings both promise and challenge. Many questions remain unanswered, but will need to be addressed in time – especially considering that, given recent developments, the integration of artificially intelligent tools seems very likely. In the near future, it will be important to develop the technical and intellectual infrastructure necessary to permit smooth and effective uptake of new technologies. Robust involvement by clinicians in the development and implementation of these tools may permit increased control over the process, increasing the chances of effective and productive integration of new approaches.

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It Takes a Village

Each and every link in the chain from sample to patient outcome is indispensable

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

The phlebotomist greets his patient with a smile. He knows people generally dislike getting their blood drawn, so he goes out of his way to make each patient's experience as pleasant as possible. He does his job quickly and efficiently, always putting his current patient at ease. He double-checks the labels on the samples before sending them to the lab for processing.

The laboratory assistant is the first to notice when the laboratory information system (LIS) goes down. She helped write the updated downtime procedures, so she is quite familiar with them. An unscheduled computer downtime can be hectic, but she knows that, if she executes the procedures and communicates well, patients will still receive the correct results in a timely manner.

The bench technologist stretches his back as he dons a new pair of gloves. Today, he's performed preventative maintenance on multiple analyzers, updated several departmental procedures, performed quality control and quality assurance measures to verify all test results, and answered an internist's questions regarding a specific patient's results. It's been a productive day and he leaves the laboratory feeling satisfied about his contributions to patient care.

The pathologist reviews her patient's history in the LIS before peering into a microscope to examine the patient's biopsy. Although it's sobering to diagnose someone with cancer, today it's also gratifying, because she's able to diagnose a Grade 1, minimally invasive breast lesion and also compare it with the molecular profile and circulating tumor cell results rendered from the blood samples drawn earlier. Now, her patient can be effectively treated – and likely cured. Later, she'll speak with her patient's surgeon and offer to meet with the patient if needed. Tomorrow, in addition to her diagnostic duties, she'll review the new immunohistochemistry procedures and explore the possibility of ordering new differential panels before giving a lecture to the new surgical pathology residents.

The laboratory director starts her day by meeting with the managers and supervisors, where she's updated on equipment needs, budget concerns, and personnel issues. Next, she meets with the medical director, where they discuss the timeline for updating testing methodology. That afternoon, she meets with administrators from other departments to discuss a recent hospital-wide inspection; when she's congratulated on the laboratory's perfect marks, she mentions the names of several staff members who worked hard to make it happen. Later, she'll try to find money in the budget to throw the lab a modest "we passed our inspection" party. She sometimes misses working in the heart of the laboratory, but she enjoys being in a position to advance patient care while serving as a leader and rewarding her staff for a job well done.

Every day, laboratory professionals of all backgrounds, educations, and job titles perform their duties with remarkable grace, efficiency, and accuracy. Although in recent years, the laboratory has begun to climb out of the proverbial basement and into the center of health care, it can be hard to appreciate just how integral each and every position is to ensuring uncompromising patient care. For example, for a patient to be appropriately diagnosed with acute lymphocytic leukemia, a phlebotomist must confidently identify the correct patient and draw their blood; a laboratory assistant needs to receive the specimen and send it to the proper department; a medical scientist hematologist must ensure that the instrument is functioning within reproducible parameters before samples are analyzed and is tasked with recognizing when results are abnormal; the pathologist relies on these results as well as the additional samples produced to render her diagnosis; and the laboratory director must ensure that the entire system runs on time and on budget. Removing any step from this complex equation could significantly compromise patient care. The mission of the laboratory community is to provide efficient and unquestionable results so that patients can receive optimal care. Doing so requires commitment – interdependent commitment of the entire laboratory team. And this is why we at ASCP live by the mantra of "Stronger Together."

Antibiotic Test Results – Done Right

In infectious disease, speed and accuracy are key, but pathologists shouldn't have to choose between the two

Rapid treatment... or the right treatment? No pathologist should ever be in a situation where speed and accuracy are an "either/or" choice for laboratory diagnostic decisions. No patient should ever have to sacrifice their degree of certainty about a result to get it faster. But not every infectious disease testing system can offer both at once; the most accurate tests are often slower to return results. Microbiology professionals who aren't willing to compromise must turn to advanced systems that can reduce turnaround times, identify pathogens, and offer broad-ranging resistance detection. Beckman Coulter's DxM MicroScan WalkAway is one such system. We spoke to pathologist Brent Ponder of Poplar Bluff Regional Medical Center to learn about his lab's needs – and where the DxM MicroScan WalkAway fits into the picture.

Could you describe your facility?

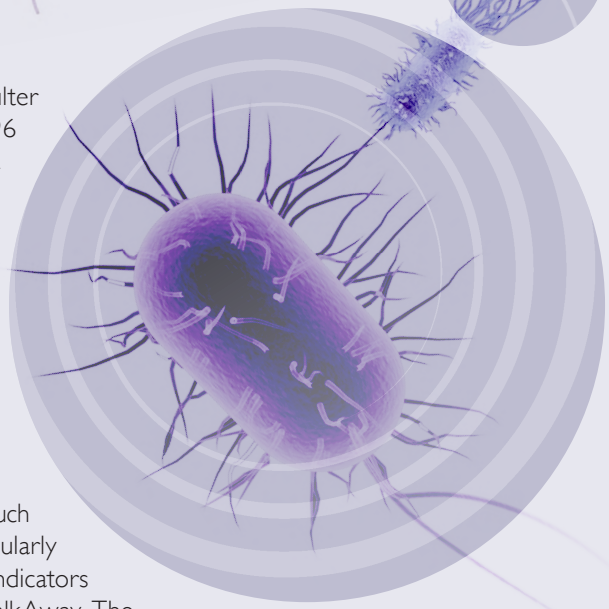
Poplar Bluff Regional Medical Centre is a 250-bed hospital in Poplar Bluff, a town of approximately 17,000 in southeast Missouri. We serve not only the Poplar Bluff area but also surrounding counties, so our microbiology laboratory processes about 30,000 specimens per year. Although I am the hospital's sole pathologist, the other members of my laboratory are equally indispensable. David Crabtree and Glenn Gutterman, the laboratory director and laboratory supervisor, respectively, support three technologists – Carol Baker, Terry West, and Kevin Gordon – who are largely responsible for the microbiology section.

It's clear from the cases we see every day that microbiology, as a field, needs better testing solutions. Technology that can quickly and accurately identify organisms as well as appropriate antimicrobial susceptibility is instrumental in directing appropriate therapy for the patient – not to mention reducing the number of potentially ineffective or even harmful drugs to which the patient might otherwise be exposed. Particularly in our hospital's effort to treat sepsis aggressively and appropriately, such technology is paramount.

Where do current testing methods fall short?

The major shortfall of current standard testing methods is the length of time it takes for organism growth. If we have to wait days for enough microbial growth to identify the disease-causing pathogen, then the patient has to wait equally long for treatment – and, especially in the case of sepsis, not every patient can.

Rapid, accurate organism identification and susceptibility testing doesn't only aid the well-being of the patient, though; it can also result in the reduction of unnecessary health resource expenditure. And that's why we recently decided that we needed to revisit our microbiology needs. At the time, we



were using a Beckman Coulter MicroScan WalkAway 96 plus – which we thought was a great instrument – but we recognized that our laboratory needed a more advanced tool. It didn't take us long to settle on the DxM MicroScan WalkAway as our replacement system – and we haven't looked back since.

Today, our workflow is much faster – and we are particularly impressed by the reagent indicators in the DxM MicroScan WalkAway. The microbiology technologists in our lab find them much easier to read and benefit from the fact that the analyzer does not need to be opened to check reagent levels. The technologist performing the tests can simply glance at the DxM front panel to ensure that the reagents are all set to go before they leave for the day.

How does it work? The microbiology department receives specimens, plates them on appropriate media, and grows them in a CO_2 incubator. Once the culture is ready, they perform Gram staining and any other quick tests they consider appropriate, then prepare dilutions for MicroScan panels to be processed in the DxM instrument. The upgrade hasn't really changed our workflow much other than to decrease our turnaround times – we were able to keep the same protocols and timings we've always used, so the transition to the new system was a smooth one.

To provide quick and effective treatment, pathologists need accurate pathogen identification and resistance detection.

How can other labs follow suit?

When we were ready to upgrade, we explained the benefits the DxM MicroScan WalkAway to our administrators and helped them to understand the need – and they were happy to approve the purchase of a new system. If other laboratories want to go down the same upgrade path, the key is to outline the importance of such advanced systems to optimal patient care. It's also vital to ensure that you'll have ongoing assistance after making a purchasing decision – and I can attest that we have received nothing but outstanding support from the field services, technicians, and everyone else at Beckman Coulter.

Saving Time	*Saving Costs*	*Saving Patients*
• External LED indicators let users check reagent status quickly and easily • Quick bottle release makes reagent maintenance simpler and less time-consuming • Software provides custom options with an easy-to-use interface • Reduced offline testing means faster time to result for more antibiotics	• Fewer confirmatory and repeat tests mean less expense for both materials and labor • Wide range of susceptibility tests on one panel eliminates the need for multiple systems • Efficient software and hardware design streamlines workflow and allows smooth processing of routine samples	• Superior accuracy in detecting antimicrobial resistance – both known and emerging • Automated atypical result detection allows quick recognition and reporting • Fewest clinically significant drug-bug limitations means patients have more treatment options

CONNECTING PAST TO PRESENT

What is paleopathology, and how can it help (and be helped by) modern clinical and research pathology?

By Niels Lynnerup

When diagnosing or studying a particular disease, where do you begin? Perhaps with a patient's self-reported symptoms or their medical and family history. Perhaps with blood and tissue samples. Perhaps with a clinician's report and differential diagnosis. But what if you had none of these things – and what if your patient had lived hundreds or even thousands of years in the past? How would you pursue a disease investigation in an ancient person or population, and what impact could that information have on the modern study of disease?

A brief history of paleopathology

Paleopathology is the study of disease in the past. Most often, of course, disease is studied in human remains – so, when archeologists dig out old skeletons from the Stone Age or look at mummies from ancient Egypt, they might see signs of disease. And that leads to questions. Which diseases hit when? When did they start? How can we trace them? How long has a particular disease been around? It was questions like these that inspired the field; we wanted to provide temporal depth to human diseases as we know them today.

In the beginning, paleopathologists could only study diseases that left morphological traces on human remains, usually bone. As a result, our early colleagues spent most of their time focusing on chronic diseases, such as leprosy, tuberculosis, or syphilis – those that would leave their mark. In recent years, though, we've seen a real revolution. Advances in DNA technology have enabled us to extract ancient DNA from even very old human remains – and that opens up the field to study not just chronic diseases, but also acute infections. We can now extract and analyze human DNA from bones to learn more about ancient diseases and their effects on populations, but it doesn't stop there – we can also look for traces of bacterial DNA to study which pathogens and existed when.

Perhaps even more importantly, we are able to gain much more information about the natural history of the diseases themselves. By looking at how diseases develop alongside humans and other animals, we can gain a much more fine-tuned picture of how diseases evolve, how they co-evolve with humans, and how that process is affected by the huge cultural changes that human populations have undergone throughout even their recent history. An example might be animal husbandry; as soon as a group domesticates animals, they increase their close contact with those animals, which changes the pathogen load to which those humans are exposed – bacteria, viruses, parasites… So now, more than ever, we can look not only at which diseases existed in different past populations, but also how our actions can affect their evolution.

That latter aspect, I think, is very exciting, because it can also give us predictive knowledge. Knowing more about how diseases and pathogens developed in the past may give us ideas about how they might continue to develop. So even as we look at new diseases around the world, we must remember that there is knowledge to be gained by observing the evolution of pathogens from their earliest days to the present.

On a smaller scale, it's also tremendously interesting to know exactly which diseases existed at any given time in a specific past population. What was the level of syphilis in early 16th-century Europe? How prevalent was leprosy in medieval European populations? What degree of malnutrition did various populations suffer? Everything from the close examination of a single skeleton to the study of entire past populations can add to archeologists' interpretation of past society and help them reconstruct the lives of our predecessors.

Mandible with pronounced destruction due to syphilis.

The study of tuberculosis, in particular, has become much richer with the advent of ancient DNA. Suddenly, we're learning about how it may have cross-infected between different species and how *Mycobacterium* species traveled between continents – not just via humans, but also other mammals. My colleague Jane Buikstra (see page 29) has actually published a Nature paper (1) about the advent of tuberculosis in South America (and the Americas as a whole) – a story with a surprising ending! Our ability to use modern DNA techniques to investigate the genomes of ancient *Mycobacterium* strains has given us a better understanding of how tuberculosis was able to travel from the Old World to the New.

And that's just one example in an area where we are rapidly accumulating knowledge. I think it's vitally important to improve our understanding of how tuberculosis spreads, because it is still a global disease and infection rates are actually increasing (in part because we don't practice antibiotic stewardship as well as we should, so strains with antimicrobial resistance are on

"I THINK IT'S VITALLY IMPORTANT TO IMPROVE OUR UNDERSTANDING OF HOW TUBERCULOSIS SPREADS, BECAUSE IT IS STILL A GLOBAL DISEASE AND INFECTION RATES ARE ACTUALLY INCREASING."

the rise). The more we know about how these bacteria react in a "micro-evolutionary" sense, the better we can approach developing new antibiotics to manage tuberculosis.

On the more enigmatic side, we have diseases like leprosy. It doesn't seem like leprosy would be a mystery to us; it's familiar in the sense that it's written about in the Bible. We have lots of skeletons from medieval Europe with leprosy – and, unfortunately, it still exists in some developing countries. But it's not as clear-cut as it seems. For instance, I'm from Denmark, where we have almost no evidence of leprosy before the year 1000, give or take. But then, around the 12th or 13th century, it explodes. Suddenly, there's an abundance of skeletons showing evidence of leprosy, and paleo-epidemiological studies (2) point to almost a quarter of the population carrying the pathogen (*Mycobacterium leprae*). And then, in the 16th century, it disappears again just as suddenly. Why did such a disease, known since Biblical times, abruptly turn up in Europe, have an explosive run through the continent, and then more or less completely vanish, except for certain small areas? We don't know!

Some paleopathologists hypothesize that it's because we began living much closer to cattle, cross-infecting us with tuberculosis – another mycobacterial disease that may have conferred some protection against leprosy. Others have suggested that climate change might indirectly have played a role. For example, there was a warming period in the 12th century, which was followed by the so-called "Little Ice Age" in the 14th century. The Little Ice Age had severe societal repercussions in terms of crop failure and famine, and the widespread poverty may have been a factor in the spread of leprosy in northern Europe. Still others are interested in pockets where the disease remained after its disappearance in most places. In the more remote areas of Norway, for example, they had leprosy right up until the 18th century – much later than anywhere else. The answer is probably a combination of many reasons but, ultimately, no one really knows for sure – at least, not yet. Such questions make this field incredibly exciting.

Digging into disease

We obviously associate very closely with archeologists, so sometimes we actually join excavations to help unearth human remains. On other occasions, when such remains are found on a dig, they're sent to us for further examination. I think our process is somewhat similar to that of pathologists studying living or recently deceased patients and populations. We look at how many individuals were found, whether they were male or female, the age ranges, and so on – and we take note of distinguishing features like healed fractures or signs of malnutrition. Sometimes the signs of disease are subtle, like the skeletal changes associated with syphilis; sometimes less so, like a collapsed vertebral column caused by tuberculosis. So, once all of that information has been tabulated, we can collate it and use it.

One clear difficulty for us that is not faced by clinical pathologists is the human remains themselves. Whichever way you look at it, the remains are always merely a subset of a once-living population. Not everybody dies where they lived; not everybody gets buried where they lived or died; not everybody is located and excavated 5,000 years later by archeologists; and, even if you do happen to be one of the lucky few, so to speak, not everybody is preserved well enough that we can look for signs of disease.

The limited nature of our evidence skews our findings and makes it difficult to answer key questions, For example, what were the demographics of those infected by a particular disease? What was its epidemiology? How many were infected? What was the disease actually like? We can't just take a cross-section of the population

THE PALEOPATHOLOGY ASSOCIATION

The Paleopathology Association, founded in 1973, is a global organization with members from all over the world. We have meetings every year in northern Europe, every second year elsewhere in Europe, and every second year in South America – and we will soon have a meeting in South Korea. The field is attracting a lot of younger researchers, especially with new developments in molecular biology, genetics, proteomics, and similar areas. Everyone is welcome to join, including students, for whom we have a specific group within the association.

For more information or to join the Paleopathology Association, please visit *tp.txp.to/1018-ppa*

Cartilaginous exostoses.

as a modern epidemiologist could; we're always constrained by the skeletal or mummified material.

A changing field

We may suffer a dearth of evidence, but technological advances are helping us get a better handle on it. Previously, many diseases could only be found macroscopically and morphologically, limiting us to long-suffering patients whose bones had developed characteristic changes. (Bone is, after all, a tissue with slow turnover and subject to non-specific changes that could be indicative of a number of diseases and disabilities.)

Now, thanks to the development of specific primers to pathogenic DNA (which medical researchers and clinicians use to develop vaccines, select antibiotics, and so on), we can interrogate ancient DNA for bits and pieces of the genomes of pathogens so that we can find out what infectious agents existed in a given population. It's also possible, of course, for an individual's own DNA to pinpoint heritable diseases that we could not find using skeletal evidence alone. One example is hemochromatosis – a genetic disease that leads to excessive uptake of dietary iron, which accumulates in the liver and ultimately leads to cirrhosis and liver failure. It turns out that, based on ancient DNA analysis, hemochromatosis is more pronounced in northern Europe – it's even been called the Celtic or Viking disease because of its high frequency in Scandinavia, parts of England, and northern France.

The theory is that the genetic defect causing hemochromatosis arose in the Bronze Age or early Iron Age in northern Europe. It's possible that it survived and was passed down through generations because it might have been a beneficial mutation; if you are infested with parasites and intestinal worms (common in those times) and losing a lot of iron, it is hazardous to your health – especially if you are vulnerable for other reasons, such as in the case of pregnant women. Today, it's no longer beneficial – we get plenty of iron and we are unlikely to be infested with all kinds of parasites. We just haven't lost the mutation.

We've seen a similar evolution in the Mediterranean area with thalassemia. If you have mild thalassemia, like many people of Mediterranean descent, it doesn't result in a problematic degree of anemia – but it does confer some protection against malaria. In an era before prophylactic treatment, it would have been a valuable trait to possess.

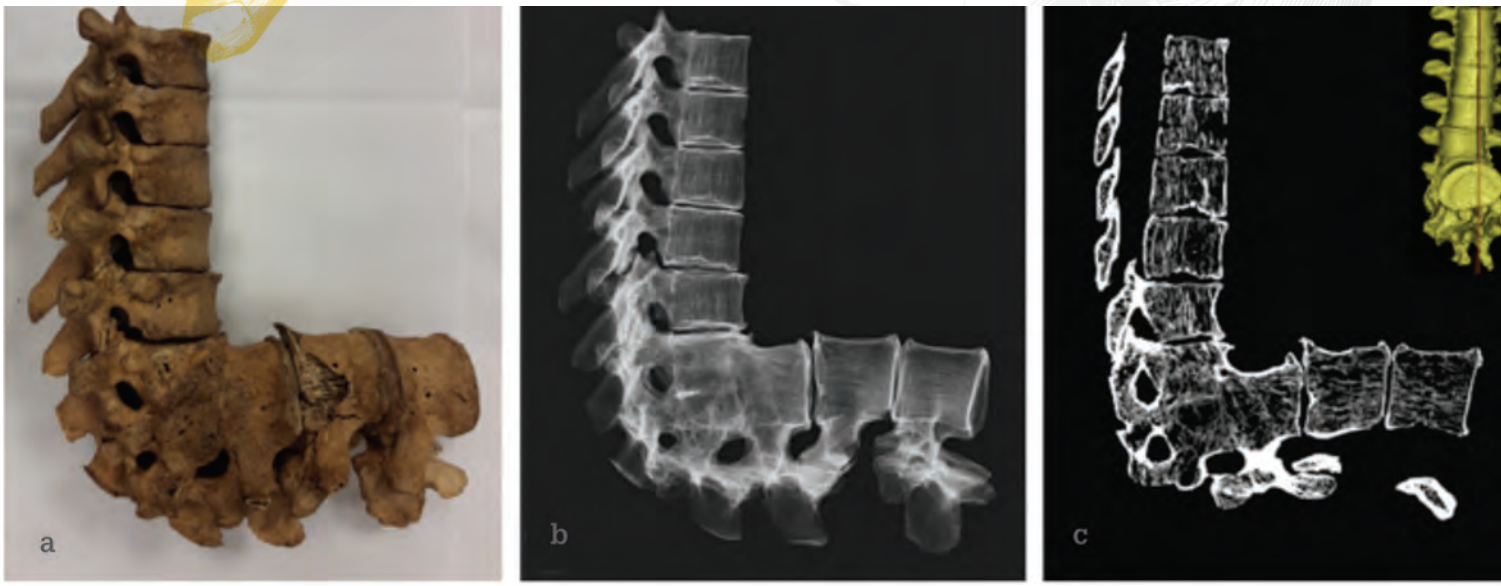
These two examples show what fascinating data we can obtain by studying ancient DNA – what gene variants are common, which variants are correlated with disease, how many carriers there may have been (and who they were), and so on. DNA analysis really has opened up new and exciting areas of exploration for paleopathology!

"I THINK IT'S CLEAR THAT PALEOPATHOLOGY HAS REAL RELEVANCE TO THE UNDERSTANDING (AND DIAGNOSIS) OF MODERN-DAY DISEASE."

Clinical contributions

Clinical advances often drive the forward progress of paleopathology because the disciplines are so closely linked. And I think this shared evolution is very important, because it lets us correlate past presentations of disease with current ones. Here, again, leprosy is a good example. Much of the key research in the paleopathology of leprosy was performed in the 1950s and 1960s by Vilhelm Møller-Christensen, who was not a specialist, but an ordinary general practitioner in Denmark. He began assisting archeologists with the excavation of medieval cemeteries where he lived by examining the bones. In fact, that's how the study of leprosy in medieval human remains began – with Møller-Christensen discovering so many skeletal changes related to the disease. Eventually, he started visiting the Philippines, Thailand, Nepal, and areas of Africa where leprosy was prevalent, because he wanted to parallelize his osteological findings with the present-day development of the disease.

I think it's clear that paleopathology has real relevance to the understanding (and diagnosis) of modern-day disease. It's not just about the horrible diseases people suffered from in days of yore. It's a discipline that is constantly changing and evolving, and one that exists alongside clinical medicine with mutual benefits. The vast array of tests available in clinical laboratories can be useful to us, and our long time perspective can be useful to research and clinical pathologists.



Vertebrae with tuberculosis (Pott´s spine): a) photograph; b) radiograph; c) coronal CT scan.

Becoming a paleopathologist

I originally started training as a forensic pathologist. I wanted to improve my ability to identify human remains in a forensic context but, in Denmark, we (fortunately) don't have many cases that would give me such opportunities. Looking at thousands of skeletons from the past offers the closest possible experience, so I started investigating the remains of Viking Norse from Greenland. As you can imagine, I found it fascinating, so I started studying Greenland mummies, performing CT scans, and delving ever deeper into the world of ancient remains. Combine that with my medical training, and it's obvious why I found paleopathology so intriguing.

Currently, I'm head of the University of Copenhagen's forensic medicine department, but a lot of my research is in the area of paleopathology. My colleagues in the Paleopathology Association have diverse backgrounds; some are medically trained, some come from anthropology, and some are experts in archeology or other related disciplines. I think that's what makes our association so interesting – we have a great mix of people; not just doctors and anthropologists, but also biologists, geneticists, and other experts from all sorts of fields. The cross-disciplinary nature of our group – and our work – means we have truly creative discussions at our meetings.

If you're interested in paleopathology, I would recommend contacting people who work in the field. Ideally, find someone local who does the type of work that interests you, perhaps at a university or a museum – and then get involved! Most of the people I know in this field got here by simply pursuing a personal interest. A good example is the late, well-known paleopathologist Art Aufderheide, a clinical pathologist working in the United States who was asked to look at some tissue specimens from Egyptian mummies. The work captured his imagination to the point where he drove a great deal of research in paleopathology, developing methods to rehydrate and stain burial tissue and carrying out a lot of diagnoses on ancient tissues. His story also shows that you don't necessarily have to leave the clinic to participate. We often go to clinical pathologists for help with our work – for instance, developing better stains to look at histological specimens, or using tissue microscopy to better examine preserved soft tissue in mummies. No matter what your field of pathology or your particular research interests, there is a place for you in paleopathology.

Niels Lynnerup is Head of the Department of Forensic Medicine at the University of Copenhagen, Denmark.

Reference

1. *KI Bos et al., "Pre-Columbian mycobacterial genomes reveal seals as a source of New World human tuberculosis", Nature, 514, 494–497 (2014). PMID: 25141181.*
2. *JL Boldsen, "Leprosy in Medieval Denmark--osteological and epidemiological analyses", Anthropol Anz, 67, 407–425 (2009). PMID: 20440960.*

BIOARCHEOLOGY: PEOPLING THE PAST

Jane Buikstra discusses the past and future of paleopathology and why collaboration – especially with clinical pathology – is vital

What drew you to paleopathology?

I wish there were an easy answer to that question!

My dad was a doctor, so I always had an interest in health and disease. My mother spurred my interest in history and past cultures; she often spoke about how she felt that the Native Americans had been given a rough deal. I thought I could marry the two interests by studying archeology – but, when I was in training, I found that people talked a lot more about material culture than they did about people. As a result, I've always been intrigued by "peopling the past," which is what I call "bioarcheology." I have the dubious distinction of having coined that term (as it is currently used) in the 1970s.

A key aspect of investigating the people of the past is studying health and disease. In paleopathology, we look at the issue in two ways: some people focus more on community health, whereas others focus on the history of specific diseases and their co-evolution with humans and the environment. We've had a real revolution on both sides with the advent of molecular approaches that enable us to investigate previously intractable questions about certain diseases. An example close to my own heart is tuberculosis. In graduate school, I began looking at this peculiar American tuberculosis that we find prior to first contact by Christopher Columbus in the era of exploration. How did such a disease get to the Americas in the absence of transatlantic human interaction? Nobody knew – but I wanted to find out.

My colleagues and I played a key role in identifying the molecular signatures of that disease, which helped us to differentiate it from other strains. Then, we discovered that it wasn't brought over the Bering Strait by humans, as we originally believed – instead, it was brought to South America by pinnipeds, such as seals and sea lions! And that's what I love about my work; there are always surprises. As a result of this particular surprise, we're now trying to chart the spread of tuberculosis through the Americas from its point of origin.

What role does paleopathology play in the clinic?

I have colleagues who work in evolutionary medicine, and they have been shocked to find that, when they explain their work to other medical professionals, they sometimes have trouble getting the "evolutionary" part across. I'm delighted to hear of the broadening of perspective in pathology training. Paleopathologists are usually the "history of medicine" people – relegated to the far corner – but our input in medical training is becoming increasingly valuable as science becomes more and more interdisciplinary; anthropologists, social scientists, and others have an important role to play. If we're really going to have a discipline called paleopathology, what kind of training (or, at least, core knowledge) should its practitioners have from each relevant field? The interdisciplinary angle is one we can't ignore, because the diagnosis of a disease in the past, however exquisite, can be wrong if it's not interpreted in the archeological or historical context.

Naturally, one identifies disease based on one's experience, but I think something that paleopathologists bring to the diagnostic table is a knowledge of the history of disease and the possibilities each symptom cluster contains. When I first started work at Northwestern University, I spoke to one of my clinical colleagues about our differential diagnoses for tuberculosis, and specifically the fact that the disease could mimic blastomycosis. He told me flat-out that blastomycosis had never been diagnosed in the

Osteomyelitis on a left femur.

Midwest – but I knew that some of the earliest cases were from the Chicago area, because I had read the literature and knew the history. That was a practicing pathologist – so if a patient with blastomycosis had come into his clinic, he might have missed the diagnosis simply because he didn't know the history of the disease. That's just one example of how a broader perspective can help in the clinic.

How are new advances shaping paleopathology?

Molecular approaches are giving us a new perspective on a wide range of diseases. To stay abreast of the newest tests and technologies, we have a strong interface with research and clinical biology. The clinic affects our work in other ways, too; for example, we have to be wary of the clinical picture since the antibiotic era, because administering treatments has changed the incidence, prevalence, course, and effects of infectious diseases – and changed the pathogens themselves, of course. If we're going to model peak time for an infection, though, we certainly benefit from the clinical perspective!

In my opinion, the next breakthroughs are going to be i) looking at the immune system, ii) working more effectively in oncology, and iii) greater appreciation for the role of non-human hosts in the origins and evolution of infectious diseases. We're starting to deal more with genetics and the development of various cancers in the past, so I'm excited to see where that takes us in the future. I think paleopathology gives all pathologists a deeper appreciation for the changing patterns of disease and how they reflect our natural and human environments. In terms of health delivery, I think we draw in elements that illustrate the need for every step of the disease control process. The ability to cure a disease is, of course, essential, as is the ability to identify it. But unless you have healthcare delivery, you still have an issue. It's no use knowing what the disease is and how to treat it unless you can actually act on that knowledge! And that depends on how the diagnosis and treatment are delivered – which, in turn, depends on (among other things) cultural context.

What I find particularly striking right now is the degree to which health and healthcare involve the interactions between humans and their environment. I'm currently looking into the species-jumping ability of some pathogens – something that affects not only animal health and conservation, but also human health. For example, in India, where troops of monkeys inhabit temples that are visited by tourists, researchers have documented the spread of pathogens from tourists to monkeys and back again. Such interactions have clear implications for healthcare and epidemiology now and in the future; paleopathology can make its biggest contributions to the clinic by improving understanding in this area.

What's next for the field?

I'm in charge of a large project in Greece, where I'm pushing for large-scale screening of skeletons from the Archaic Period site of Phaleron for both primary tumors and secondary metastases. People generally don't do such systematic screening because it's expensive and time-consuming, but it's the only way we're really going to get a picture of cancer prevalence in the past. From there, we can start looking at the genetics of the oncologic changes we see. Sometimes, you need to look back to see the way forward!

As Editor-in-chief, my developmental goal for the International Journal of Paleopathology is to bring together three historically distinct branches: human paleopathology, animal paleopathology (which tends to develop through archeofaunal analysis and has a separate intellectual history to the other branches), and then the "mummy folks," who tend to be clinicians focusing on specific diseases in the developing field of mummy science. Trying to draw those three together and give them a venue to publish and to interact is certainly a work in progress, but I think there's some really interesting potential, if we all work together. When it comes to important questions, collaboration is the name of the game.

Have you encountered any misconceptions about paleopathology?

The two most common misconceptions are that we deal with dry bones and isolated cases. As to the first, we study not only skeletons, but also mummified remains – and all within archaeological and historical contexts. And as to the second, although we do investigate isolated cases of disease – which can be important when they're linked to a specific evolutionary or cultural question – we spend more of our time painting a broad picture of disease in humankind in the past.

But, to me, the worst misconception is the idea that we have nothing to say to modern practitioners of medicine. Paleopathology is, of course, the study of ancient disease – but we study it so that we can contribute to a better understanding of what's going on today. Again, it's about collaboration – we can be useful to clinicians dealing with modern-day health and disease, and they can be useful to us. All we need is communication.

Jane Buikstra is Regents' Professor of Bioarcheology and Director of the Center for Bioarcheological Research at Arizona State University, USA, and Editor-in-Chief of the International Journal of Paleopathology.

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[1]*Kalorama United States Market for In Vitro Diagnostic Tests*, 2017, pg. 878.

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†References available upon request.

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What's in a Brain?

A guide to identifying common adult intracranial neoplasms for anatomic pathologists

By Jason Karamchandani

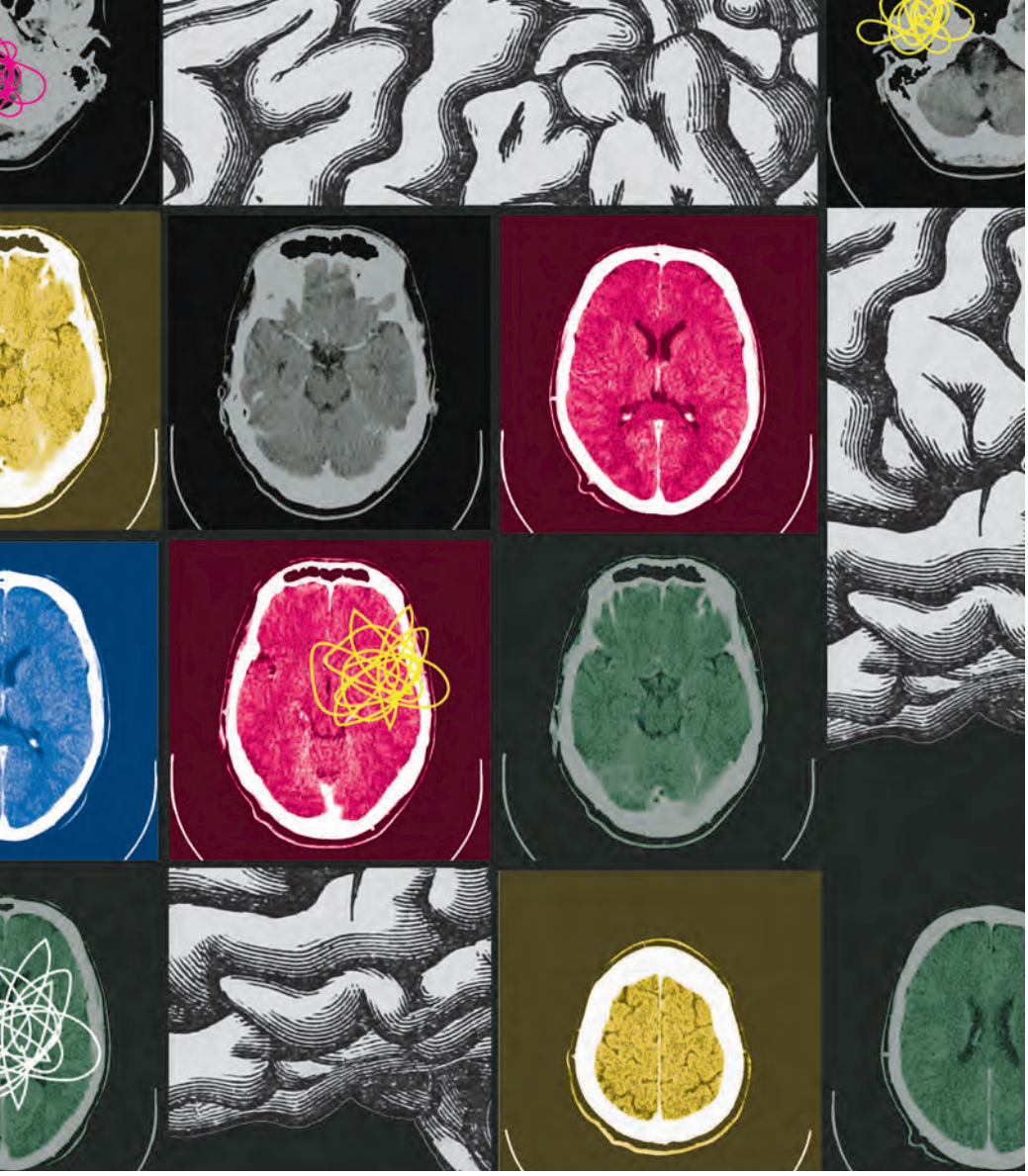
As diagnostic experts, pathologists are routinely faced with challenging tissue samples. But, for many, none are so intimidating as those that originate from the brain. Although there are many areas of the brain that are particularly eloquent, there is no true way to resect brain tissue without impact to the patient. With so much at stake, it can be hard to confidently render a diagnosis – and, indeed, many consider central nervous system (CNS) tumors among the most intimidating, particularly in terms of intraoperative assessment. In reality, these tumors are no more intimidating than any other, and a few handy tips, tricks, and algorithms can help any pathologist tackle common intracranial neoplasms.

At a Glance

- *Intracranial neoplasms present a diagnostic challenge, but a few simple algorithms can assist in the process*
- *The most common intracranial tumors in adults are metastases; only consider primary CNS neoplasms after ruling out this possibility*
- *Meningiomas are the most common primary intracranial neoplasms of the central nervous system and its coverings and are more common than primary glial tumors*
- *When facing a glial tumor, distinguishing between astrocytoma, oligodendroglioma, and ependymoma can have significant effects on prognosis and treatment decision-making*

Many pathologists will be familiar with the concept of integrated diagnosis. Hematopathologists, for instance, have been working in an integrated fashion for well over a decade. But it's a far more recent phenomenon in soft tissue pathology, where morphology and histology have long been the definitive gold standard for interpretation. Many specialties within pathology now use a synthesis of histology and ancillary testing – including, in many cases, molecular testing. Integration is key; no one type of information dominates over any other. One of my favorite examples lies in the comparison of angiomatoid fibrous histiocytoma and clear cell sarcoma. The two have exactly the same translocation *(EWSR1/ATF1)*, but angiomatoid fibrous histiocytoma has a typically benign prognosis, whereas clear cell sarcoma kills about half the patients who receive the diagnosis. So the same monogenetic event, with a different site and a different histology, yields a wildly different outcome.

The same applies to brain tumors. A nice example of this pathology is ganglioglioma – a WHO grade 1 tumor frequently associated with the classic *BRAF* V600E mutation. These tumors typically have a benign course, with many patients enjoying a normal lifespan following curative surgery. Nonetheless, the same mutation appears in epithelioid



"The same monogenetic event, with a different site and a different histology, yields a wildly different outcome."

glioblastoma, a WHO grade 4 tumor with an abysmal prognosis. You can't just put tumor tissue in a blender, fish for genetic changes, and assume that this will yield a diagnosis. You have to examine the histology, decide what testing would contribute to the diagnosis, and interpret the test results in the context of morphology. No one test alone is enough; it's the combination that holds the diagnostic key.

The intraoperative assessment

Many anatomic pathologists are responsible for intraoperative assessments for neuropathologic specimens (some consider these to be the most challenging frozen sections they face). Depending on the surgical procedure and clinical situation, a frozen may play a vital role… or may be deferred with no consequence for the patient whatsoever. The key is to know which situation you're in.

When dealing with a biopsy – particularly a stereotactic biopsy – pathology is absolutely essential. One of the classic indications for a stereotactic biopsy would be distinguishing between a high-grade glioma and a lymphoma – this is a high-stakes scenario in the brain, as the safely resectable enhancing tumor will be removed, whereas a diagnosis of lymphoma does not indicate surgical intervention, giving us a classic "cut it out or not" scenario. If, however, the surgeon intends to resect a space-occupying mass, the stakes are somewhat lower. The surgeon is already planning to cut out as much grossly abnormal tissue as possible and is unlikely to change that plan based on the pathology.

Tip

If the procedure is a biopsy, the pathologist must let the surgeon know if the tissue is diagnostic, as well as if the pathology does not indicate further surgical intervention (for instance, in the case of lymphoma or infection).

In the background, the pathologist has to keep in mind the neuroanatomy of the biopsy site. By way of example, the cerebellum has a granular neuron layer which, when examining a smear or frozen section, may (falsely) appear to be hypercellular and set in a fibrillary background; granular neurons can resemble lymphocytes on a smear preparation. It's always a good idea to know what part of the brain you're examining.

Some pathologists prefer to read the radiology report prior to assessing the histology; others – like me – prefer to review it after seeing the histology to confirm (or contest) their independent assessment. An absence of concordance

"You can't just put tumor tissue in a blender, fish for genetic changes, and assume that this will yield a diagnosis."

between the radiology and histology prompts closer examination and re-evaluation of the tissue.

Common intracranial pathologies

What's the most common intracranial lesion in adults? If you answered with any primary CNS lesion, think again. The most common intracranial lesion in adults is a metastasis – and we're seeing increasing numbers of them as we get better at treating stage IV cancer and identifying situations in which resection carries symptomatic (or even survival!) benefit. There are some diseases – like breast or lung cancer – in which the surgical and oncology teams can achieve systemic control that, as long as the brain metastases are resected and treated with postoperative radiosurgery, can achieve near-curative outcomes in metastatic cancer.

Tip

When examining tumor samples from the brain, remember to consider the possibility of metastasis before diagnosing a primary CNS neoplasm.

I have noticed that, sometimes, my residents (who would have no trouble recognizing cancers occurring in their native organs) neglect to consider metastatic pathologies when examining tumor samples from the brain. Breast cancer and melanoma are good examples of lesions that can have abundant eosinophilic cytoplasm. Frozen sections are not always perfect representations of the morphology of a tumor, so if you see a homogenous pink "thing" with atypical nuclei, you may be tempted to diagnose a primary glial neoplasm. If you are comfortable with neuropathological smear samples, it's advisable to look for convincing evidence of glial differentiation; for instance, cytoplasm that is drawn out into long, slender, hair-like processes.

It's also not uncommon for a brain metastasis to be detected before the primary. Melanoma and small cell carcinomas are two common examples. In the case of melanoma, the primary may go unnoticed, especially if it doesn't arise on visible skin, or the cutaneous melanoma may have regressed. Lung cancer is another disease family in which brain tumors may be diagnosed either first or simultaneously with the disease in the lung. Interestingly, in cases where the brain metastasis is symptomatic, the CNS material will be used to assess the molecular profile of the tumor – especially if the primary tumor can't be resected.

For every sample I encounter in the frozen section room, I ask myself:

- Is this normal or abnormal? That is, does any native brain tissue look like the sample? If not, then I proceed down the abnormal branch.
- Is it neoplastic or reactive/inflammatory? We're often so quick to jump to tumors that we forget that diseases like progressive multifocal leukoencephalopathy, organizing infarcts, or demyelinating disease can all have features reminiscent of a tumor – but they are not neoplastic. That's a key step; never skip that question.
- Is this of the CNS and/or its coverings? Including the meninges, is this a brain or meningothelial tumor? If the answer is no, it's time to consider metastasis.

Tip

To diagnose a primary glial neoplasm, look for evidence so clear that a resident would unequivocally call a glial process; otherwise, you may be seeing artifacts of the smear process.

In fact, glioma isn't even the second most common intracranial pathology in adults. That honor falls to meningioma – which is an easier diagnostic entity. Not only can the surgeon tell you whether the tumor is attached to or arising from the dura, but the radiology is fairly typical; meningiomas are extra-axial (outside the brain parenchyma) and attached to the dura mater. One of the unfortunate challenges of meningioma smears is that meningothelial cells have abundant "diaphanous" cytoplasm (usually semi-translucent and white or pink) and form tight junctions with their neighbors with innumerable interdigitating filaments – so when these are smeared out, they can mimic glial processes.

But there's one key way to spot a meningioma: the whorls. Almost every meningioma features true whorl formation somewhere. One nice trick is to perform a touch prep instead of a smear. You may see less overall, but you'll be able to identify the whorls, as well as some other common features such as psammoma bodies. Meningiomas are more common than gliomas!

Tip

A combination of cytologic preparations and frozen sections, along with radiology and history, can help you diagnose meningioma.

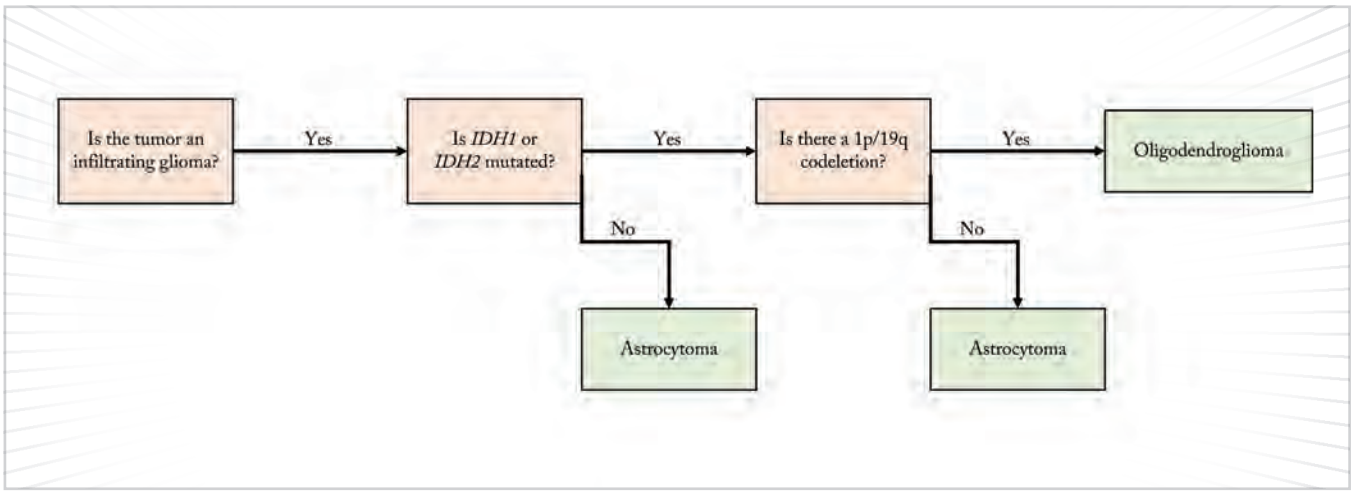
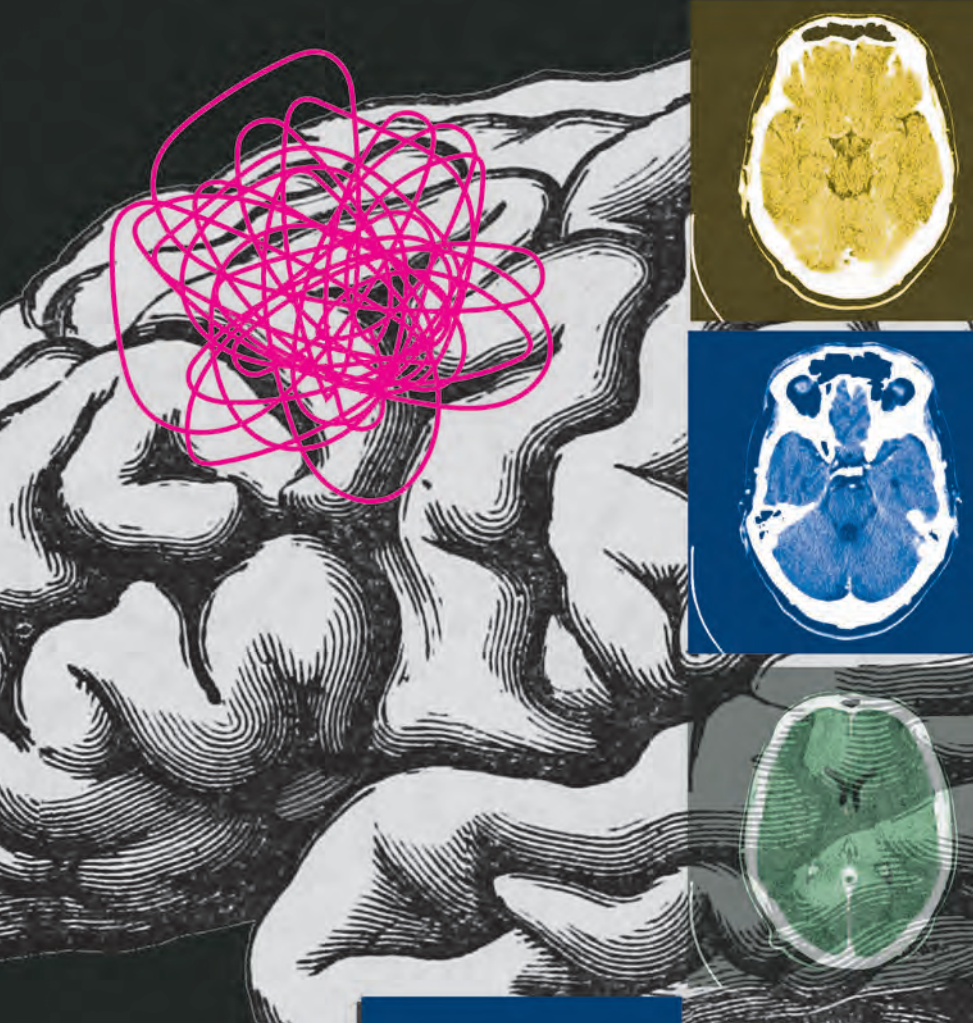


Figure 1. Diagnostic algorithm for primary glial tumors.



"Must you always make a diagnosis of glioblastoma in the intraoperative arena? Not necessarily."

The third most common intracranial neoplasm in adults is a primary glial tumor – specifically glioblastoma. This WHO grade 4 tumor is by far the most common glioma in adults. When you perform your smear, you may see eosinophilic glial processes; you may see a fair degree of pleomorphism; you may see mitotic activity. The defining characteristic, though, is the presence of microvascular proliferation and/or necrosis.

Must you always make a diagnosis of glioblastoma in the intraoperative arena? Not necessarily. Identifying a glial tumor should be enough to guide the surgeon, who will integrate your intraoperative assessment with the radiology and the gross appearance under the dissecting microscope. Because these tumors are so infiltrative, it's impossible to truly resect them in their entirety. The surgeon's role in the treatment of glioblastoma is to maximally remove the enhancing component of the tumor – and if they are successful, it's considered a gross total resection. Glioblastoma shares many characteristics with other glial tumors, such as oligodendrogliomas, and differentiating between the diagnoses often requires not just histological, but also molecular, investigation.

Tip

Diagnosing a glial tumor intraoperatively is often enough to provide adequate surgical guidance; identifying the particular type and grade of tumor can wait for molecular testing.

The glial tumors

There are three main types of glial tumor seen in adults: astrocytoma, oligodendroglioma, and ependymoma (in order of incidence).

Ependymomas are unusual in that they are non-infiltrating – which means that they can be cured by surgical resection. The classic histologic feature is the perivascular pseudorosettes, and the ancillary immunohistochemical test is epithelial membrane antigen (EMA). If you see perinuclear, dot-like positivity on EMA testing, you can confidently diagnose ependymoma.

The world of infiltrating glioma is more complicated. Essentially, you have two choices: astrocytoma or oligodendroglioma. A helpful diagnostic algorithm (see Figure 1) can allow you to distinguish between the two.

Tip

Oligoastrocytoma is an unhelpful diagnosis for neuro-oncologists – and many neuropathologists don't believe it is a true molecular entity.

The most important molecular alteration in infiltrating gliomas is mutation in one of the isocitrate dehydrogenase genes. The most common, which accounts for 90 percent of *IDH* mutations in gliomas, is the *IDH1* R132H mutation. Fortunately, we have mutation-specific immunohistochemical testing to identify this alteration, which we perform on all infiltrating gliomas.

If that test is negative and either the morphology looks like oligodendroglioma or the patient is under 65, we proceed to secondary *IDH* testing. Here in Montreal, we use three different tests: immunohistochemistry, Sanger

sequencing, and SNaPshot sequencing. SNaPshot tests for the most common mutations in both *IDH1* and *IDH2,* and it's quite satisfying how many times the tumor resembles an oligodendroglioma, but the immunohistochemistry is negative – and then we find either an unusual *IDH1* or, more commonly, an *IDH2* mutation.

Tip

If a tumor resembles an oligodendroglioma, but immunohistochemistry is negative, test for less common mutations in both IDH1 *and* IDH2 *before making a final diagnosis.*

If neither *IDH* gene is mutated, you can safely diagnose astrocytoma. If *IDH1* or *IDH2* is mutated, the next question is the status of 1p/19q co-deletion, a large cytogenetic alteration required to diagnose oligodendroglioma. Many centers test this by fluorescence in situ hybridization, but some use loss of heterozygosity studies or next generation sequencing for copy number alteration. Regardless of your testing platform, if the tumor shows *IDH* mutations and 1p/19q co-deletion, you can unequivocally diagnose oligodendroglioma.

Grading a glioma

Astrocytomas come in three grades: WHO grade 2, 3, or 4. As soon as you have hypercellularity and nuclear atypia, you know an infiltrating astrocytoma is at least grade 2. The addition of mitotic activity should prompt an upgrade to anaplastic (grade 3) astrocytoma.

Tip

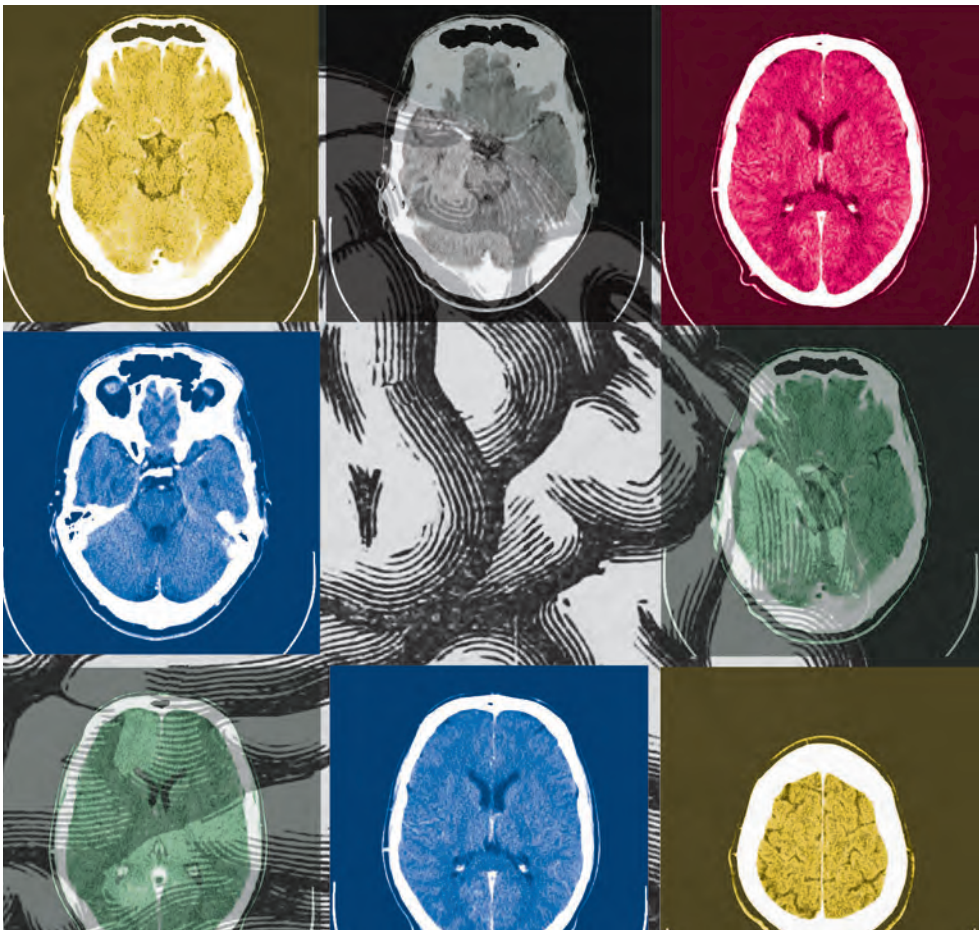
Evaluation of mitotic activity can be somewhat subjective, even one mitotic figure on a needle biopsy or in a small amount of tissue is enough to increase the tumor grade.

If, on top of those characteristics, you also see palisading necrosis and/or microvascular proliferation, you can diagnose a glioblastoma (grade 4) tumor. A nice trick for spotting microvascular proliferation is so-called "endothelial duplication." In normal brain tissue, the endothelial cells of the blood vessels are flat and elongated, with eccentric nuclei, and they almost never line up. In microvascular proliferation, you can often find two endothelial cells sitting on top of one another other on the same side of the lumen – endothelial duplication. If you see that, you are likely dealing with microvascular proliferation, indicating a diagnosis of glioblastoma multiforme.

Unlike astrocytomas, oligodendrogliomas only come in two grades: WHO grade 2 or 3. If you see only oligodendroglial proliferation, you have a grade 2 tumor; if you see a microvascular proliferation or necrosis, you should upgrade the diagnosis to anaplastic (grade 3) oligodendroglioma. Many neuropathologists also factor in mitotic activity, although this is less reproducible.

Ultimately, why is the correct diagnosis and grade so vital? Because the survival difference between an astrocytoma and an oligodendroglioma can be well over a decade. An *IDH*-mutated tumor, even a glioblastoma, has a much better prognosis than an *IDH* wild-type tumor. Furthermore, strong evidence suggests that patients with oligodendrogliomas benefit from postoperative chemo- and radiotherapy.

Jason Karamchandani is Associate Professor in McGill University's Department of Pathology, and a practicing neuropathologist at The Montreal Neurological Institute and Hospital, Montreal, Canada.



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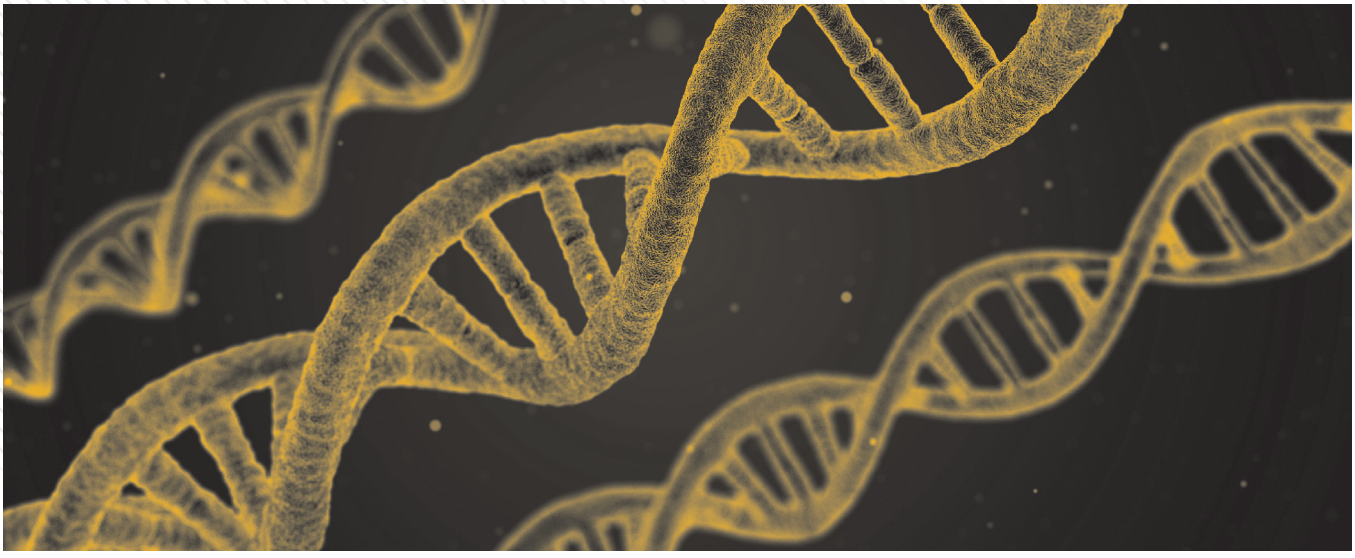

Principles and considerations for Tumor Mutational Burden (TMB) testing

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The identification of biomarkers for the safe and effective use of targeted therapies is emerging as a key part of a cancer patient's journey. With an increasing number of targeted therapies available, oncologists need comprehensive genomic tools to identify which drugs should be given to a specific patient.

In this webinar, Albrecht Stenzinger will discuss the principles of using next-generation sequencing (NGS) to identify the number of genetic alterations in a tumor (called tumor mutational burden or TMB). As an early adopter for using TMB in translational cancer research, Dr. Stenzinger brings valuable insights and considerations for laboratories interested in implementing TMB measurement using NGS.

Learning Objectives of Webinar

- Gain understanding of the value of Tumor Mutational Burden (TMB) in tailoring precision medicine.
- Learn about key requirements for a robust NGS panel to measure TMB.
- Hear first-hand insights from a clinical researcher using genomics in translational cancer research

Tuesday 27 November 2018 at 17.00 CEST

Speaker
Albrecht Stenzinger, M.D.
Head, Center for Molecular Pathology (CMP)
Head, Section for Biomarker Development and Molecular Diagnostics
Institute of Pathology Heidelberg (IPH), University Hospital Heidelberg

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Searching Is Intelligence

Image retrieval – the next revolution in pathology

By Hamid Tizhoosh

The human brain is the result of millions of years of evolution – and, as such, it's an extremely capable recognition machine. Every time we see somebody we know, we effortlessly recognize their face, an astonishing ability that we perceive as trivial thanks to our visual cortex (responsible for processing images). For machines, however, this has – until recently – been an impossible task.

Almost eighty billion neurons (each one connected to approximately ten thousand others, on average) serve our innate thinking and recognition abilities, so mimicking it is far from easy. Many details of image recognition in the central nervous system are still unknown, yet we may justifiably deduct that at least some, if not most, of our impressive cognitive capabilities are literally based on "re-cognition." We re-identify an image that we have previously seen and, depending on the depth of the memory in which that image is stored, recognize it instantly (or after a short while, with some mental effort – for instance, when encountering someone we don't know well or have not seen for many years). Image information, in whatever format it may be stored in our brain, is certainly subject to sophisticated comparisons and inferences for the purpose of identification. Neuroscience will continue to amaze us with more discoveries and conclusions that we can hopefully translate into more capable algorithms for computer vision.

At a Glance

- *Artificial intelligence is increasingly advancing on pathology – but has yet to be implemented in the most practical ways*
- *One useful application of AI is image search and retrieval – a task that computers can perform much faster than humans*
- *New approaches using artificial neural networks can help overcome challenges with computer-based image recognition*
- *Content-based image retrieval may rely on AI, but it's a pathologist-centric application that cannot function without a human element*

"Seeing" pathology

In medical image analysis, we have a large collection of computer algorithms that perform different operations on digital images: quality enhancement, filtering, registration, and segmentation, to mention just a few. The latter has been the focus of extensive research to quantify cell nucleus morphology and distribution. As important as these measurements may be, they have not been able to bring about a disruptive change in diagnostic imaging. Why? Chiefly because conventional quantification is often fed into a "smart" algorithm to output a "classification" – a category of some sort, generally either a yes/no decision or some type of disease grading. As valuable as these quantifications may be, they have not fundamentally altered the diagnostic process, perhaps because such computer algorithms do not reduce uncertainty to increase pathologists' confidence in a diagnosis. More importantly, classification-oriented computer algorithms have not been able to truly assist pathologists because they provide no clues for writing the pathology report. And so the pathology community has instead turned to well-organized second opinions through telepathology to reduce inter-observer variability (an apparent manifestation of diagnostic error).

Image search, as an alternative approach to medical image analysis, offers the historical chance to perform "virtual telepathology," consulting other pathologists by accessing their knowledge

without requiring their physical presence to examine specimens. It also allows us to consult not just one pathologist but as many as we would like within a given healthcare institution or network. Image search lets us access the expertise of multiple pathologists in a very short time and at much lower costs than doing so in person, or even via real-time telepathology. And it can establish a reliable framework to move toward quality control through computational consensus-building.

But why do we assign such immense expectations to image search? Although synaptic connections (with their binary states of excitatory and inhibitory) are the building blocks of the human brain, the actual inference is granular, fuzzy, implicit, and qualitative – as opposed to specific, certain, explicit, and quantitative – characteristics that seem to enable us to process highly complex, ambiguous information like variable tissue patterns and the intricacies of polymorphism. The diagnostic process commonly ends in writing a report, an activity we can describe as "computing with words," The contradiction is that we – both the computer vision community and the artificial intelligence (AI) community – understand "computing" to mean merely crunching and producing numbers. We may ignore what algorithms do internally, but what they output could be decisive if it helps pathologists write better reports or have more confidence in their conclusions.

Given a large archive of diagnosed patients with corresponding data (images and reports on treatment and monitoring), we should be able to identify and retrieve images that are anatomically or pathologically similar to the biopsy sample of the patient being examined – as well as the annotated data for each case. The reports contain the medical knowledge of many other pathologists for similar cases, making them a treasure trove of high-quality diagnostic information. Next generation computer software may make

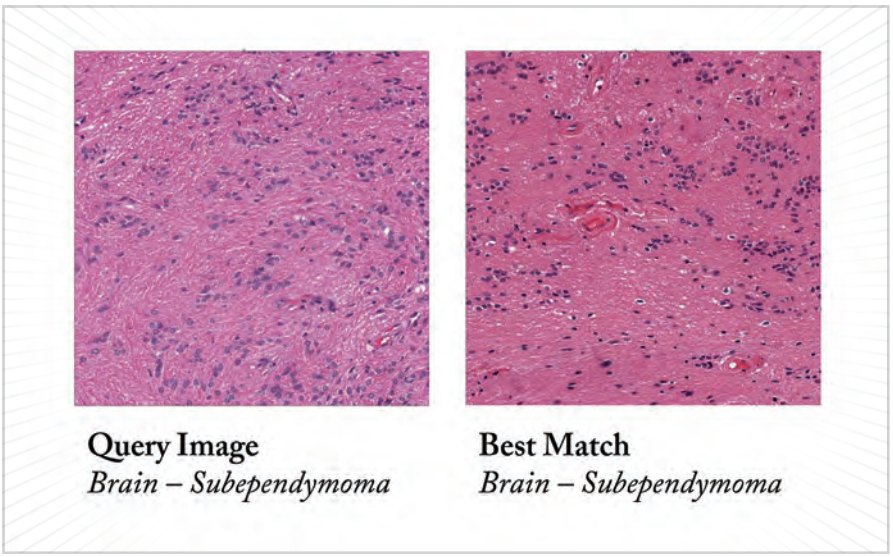

Figure 1. When given a query image (left), image search can find similar ones (right). This search was conducted among 2,000,000 patches extracted from scans of 300 patients with more than 85 conditions.

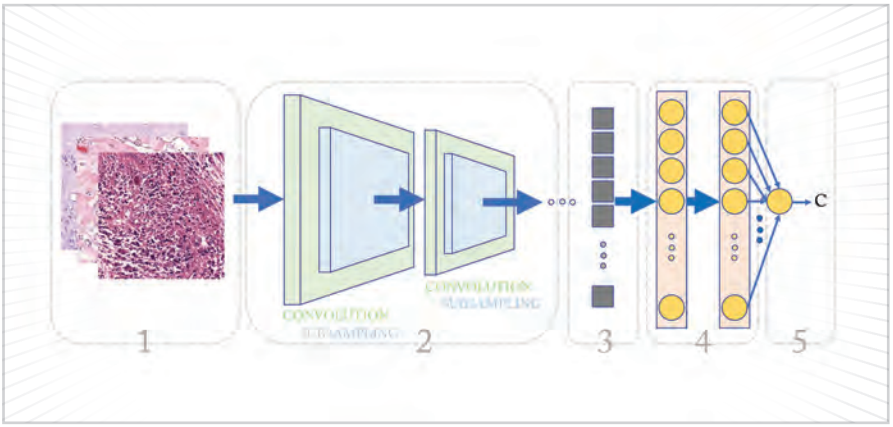

Figure 2. Schematic illustration of a deep convolutional neural network. 1) Many labeled – often meaning benign vs. malignant – images are used for training; 2) images go through many series of convolutions (image filtering) and subsamplings (image downsizing); 3) the end result of many convolutional layers is a large number of small image sections that capture significant information such as edges and corners; 4) all small image sections now go through "traditional" layers of artificial neurons; 5) one or more classification categories are assigned to each image.

the raw information directly available to the pathologist (showing retrieved images along with corresponding reports), or it may fuse the key information in retrieved reports to provide "auto-captioning" of whole slide images. The latter would even allow triaging and prioritization in real-time as glass slides go through digital scanners. The world of AI-based image search opens up a vast range of options for advancing and optimizing the laboratory workflow.

Content-based image retrieval

Research into content-based image retrieval (CBIR) has been happening for almost three decades. So if our above expectations are justified, then why hasn't

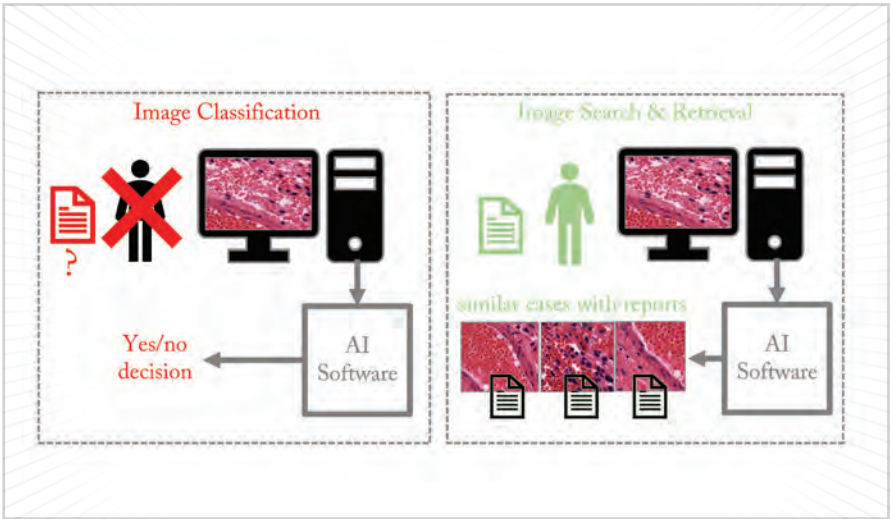

Figure 3. Left: AI-driven image classification makes decisions on behalf of the pathologist; it is not clear who should write the pathology report if an AI entity is in charge of diagnosis. Right: Image search strengthens the pathologist by providing similar images and their corresponding reports from archives.

"Content-based image retrieval is going through a renaissance with the promise of a revolution."

CBIR delivered on these promises?

The most important reasons, from an engineering perspective, are computational and accuracy challenges. The former refers to the difficulty of performing image matching in large archives in real time; the latter is about matching images properly so that the identified images are actually similar to the query image (see Figure 1). But from a digital pathology perspective, the obstacles are slightly different. To us, the main reason CBIR systems haven't made it to the daily laboratory workflow is most likely the so-called "semantic gap." Image representations in computer vision are numerical and objective, whereas human pathologists use verbal and subjective representations that often can't be modeled or analyzed. The resulting gap between computers and human experts does not permit an unambiguous definition of similarity. Indeed, the semantic gap is arguably the paramount challenge in adopting CBIR into the laboratory workflow; the results of CBIR have not thus far been acceptable to pathologists. The path to the retrieved images is irrelevant if the pathologist doesn't agree that the matched images are truly similar to the query image – a wrong answer is wrong, no matter how it was reached. But, in recent years, this has started to change; CBIR is going through a renaissance with the promise of a revolution.

AI is a general term used for a class of computer algorithms capable of instructional and sample-based learning. From its birth 70 years ago with some simple abstractions of the way a neuron operates in the human brain, AI has become an indispensable tool for computer vision applications. Most notably, artificial neural networks (ANNs) have gained great popularity due to their impressive recognition capability when implemented with many layers of artificial neurons (processing units that can perform simple aggregation of incoming synaptic values originating from other units). These "deep" ANNs recognize the content of a digital image by learning a compact representation of the image – an elegant encoding that we can assume to be a primal, but functioning, computational model for what happens to a retinal image when it travels through the optic nerve to reach the visual cortex in the human brain.

Convolutional neural networks (CNNs) are among the most successful such solutions to extract relevant features from digital images (see Figure 2). A typical example is to learn 1,024 deep features to represent a face or an object depicted in a 240x240 image, reducing the information to less than 2 percent of its original size. To create such compact representations, deep networks usually adjust several hundred thousand artificial synapses to achieve their learning goal, a training process dominated by trial and error in the design phase and many hours or even days of actual training. Countless papers and articles report high recognition accuracies for face and object recognition using deep networks. Many papers have also begun to report similar findings for medical imaging in general, and for digital pathology in particular. Most, however, use deep features for the purpose of classification (that is, to tell us whether or not an image depicts a malignancy). Image search solutions in medical CBIR refrain from this approach.

Spotlight on the pathologist

Medical CBIR is fundamentally pathologist-centric, in contrast to classification-based AI, which essentially attempts to make decisions on behalf of the pathologist. You may be understandably opposed to the latter – but the former makes valuable use of AI solutions. Instead of letting CNNs and other deep ANNs use the extracted image representations (deep features) as a basis for a "yes/no" cancer classification (see Figure 3), we can use them to index and retrieve whole slide images, which draws upon several advantages. First, the image recognition capabilities of deep networks have empirically shown that the semantic gap between computer and human perceptions can be closed. Second, AI offers a multitude of versatile techniques for recognition, indexing and search. And third, advances in software and hardware have made it possible to perform millions of image comparisons in a fraction of a second. The fact that we are currently undergoing a transition from microscopy to digital pathology is just an amazing coincidence that further benefits computer vision adoption in pathology.

Despite the obvious opportunities, there are, of course, still many hurdles to overcome if we want to bring CBIR systems to pathology laboratories – not least the need for thorough and comprehensive validation of image search for different purposes in pathology. Unlike image classification, which can be validated in the engineering lab, image search cannot be validated without the presence and intensive involvement of pathologists. But there's a silver lining to this cloud: the technology places the focus on human pathologists, rather than seeking to replace them. CBIR systems exist to help pathologists – and they cannot be designed and validated without our direct involvement. Moreover, once in use, they cannot continue to learn without pathologists at the heart of the process.

The design, validation, and regulatory clearance of image search solutions will certainly not happen overnight. In the meantime, we can identify practical use cases for image search that demonstrate how it can propel us toward computational consensus-building. With the recent success of AI in a multitude of computer vision applications and the rapid growth of digital pathology, we're moving ever closer to the horizon of pathologist-computer partnerships.

Hamid Tizhoosh is the director of Kimia Lab (Laboratory for Knowledge Inference in Medical Image Analysis) in the Faculty of Engineering at University of Waterloo. He is also a member of the Waterloo AI Institute, and a faculty affiliate to the Vector Institute. As part of his commercial activities, he is presently the AI advisor of Huron Digital Pathology, St. Jacobs, Canada.

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A Question of Cancers

How the International Collaboration on Cancer Reporting is standardizing cancer pathology reporting worldwide

By John Srigley

Who diagnoses cancer? Members of the public are likely to respond "oncologists" or simply "doctors." Patients may have a somewhat clearer idea. But medical professionals will know that, most of the time, it is the pathologist who makes the diagnosis. In fact, for many of us, cancer is such a significant part of our work that I refer to us as "diagnostic oncologists" – those responsible for naming and guiding the treatment of our patients' cancers.

But what are the characteristics that define a specific type of cancer? And, beyond that, what is the particular stage or grade of tumor? The answer may differ from region to region, or even between institutions. Obviously, such differences can impede patient care – especially as changing economies and technologies make our patient populations more globally mobile than ever. The solution? A set of cancer diagnostic and prognostic reporting guidelines that are consistent around the world – and that is precisely the goal of the International Collaboration on Cancer Reporting (ICCR).

At a Glance

- *Different diagnostic and reporting guidelines mean that patients in different locations may not receive consistent cancer diagnoses*
- *To standardize these guidelines, we need international collaboration, guided by a single entity such as the ICCR*
- *The ICCR works with the WHO and professional pathology organizations worldwide to establish diagnostic datasets for each type of cancer*
- *Success requires resources – not just financial, but also in terms of contributions from as many subject matter experts as possible*

A history of the ICCR

The fundamental mission of the ICCR is to produce standardized and internationally harmonized protocols – known as datasets – for the structured reporting of cancer worldwide. The reason this was such a compelling mission lies in the history of the ICCR itself.

David Ellis and I conceptualized the ICCR together nearly a decade ago. I had been leading the synoptic cancer pathology program in Cancer Care Ontario for the past five years, and we had adopted the College of American Pathology as our protocol standard for cancer pathology reporting. At the same time, Ellis and the Royal College of Pathologists of Australasia had embarked upon a similar program referred to as "structured pathology reporting," in which they were developing their own cancer datasets. When I went on sabbatical to New Zealand to work on urological cancers, I worked with a friend of Ellis' who told him about my work in Ontario; it led to an invitation to Sydney to give a talk to their structured pathology group. Eventually, we thought, "Wouldn't it be nice to have one approved, internationally harmonized dataset to reduce the burden of protocol development worldwide? We could make it readily available, especially to low- and middle-income countries without the resources to develop datasets locally." And that's how it all started.

By 2011, we had a quadripartite group together: the College of American Pathologists, the Royal College of Pathologists (in the United Kingdom), the Royal College of Pathologists of Australasia, and the Canadian Association of Pathologists in conjunction with the Canadian Partnership Against Cancer. At that point, we had developed four trial datasets, one led by each country: lung, endometrial, melanoma, and prostate cancer. During that process, we established a protocol for dataset development that allowed us to work quickly (finishing all four datasets in six months) and efficiently (reducing the number of elements in each dataset by including only those with a solid evidence base).

"The fundamental mission of the ICCR is to produce standardized and internationally harmonized protocols – known as datasets – for the structured reporting of cancer worldwide."

One noticeable advantage to working across international borders is what we call the "international paradox." We found that we were able to attract the world's best domain experts and develop consensus far more readily at the international level than locally or nationally. This was partly because there was more international respect, and partly because lower-level politics were less obvious in a big, global group. In fact,

on the basis of our four initial datasets, we were able to bring the European Society of Pathology into the group – and then we were further joined by the American Society for Clinical Pathology (ASCP) and the Faculty of Pathology at the Royal College of Physicians of Ireland for a grand total of seven sponsoring entities.

Global expansion

We've also built an important alliance with the International Agency for Research on Cancer (IARC), part of the World Health Organization. Currently, we are working very closely with Ian Cree to develop datasets corresponding to each volume of the fifth series of the Blue Books. We started that work three or four years ago in conjunction with the fourth series, so we have coordinated datasets for the thoracic volume, the genitourinary volume, the head and neck volume, and – still in progress – the endocrine and skin volumes. It's a great collaboration because the Blue Books produce the actual classification system with the morphology, markers, and molecular data, whereas the datasets include staging, predictive, and prognostic information as well.

We plan to continue creating these datasets in conjunction with the fifth series of Blue Books, but that's not all we're doing. At the moment, we are trialing the translation of our datasets into other languages. The ASCP has been very interested in improving cancer diagnostics in low- and middle-income countries through a project spearheaded by the Union for International Cancer Control, so they have supported the translation of our initial 20 datasets into Spanish, French, and Portuguese. I think that, as we move forward, all of our datasets will be translated into multiple languages. We are currently in discussion with an organization called the China Anti-Cancer Association, whose oncopathology committee is interested in working with the ICCR to translate datasets into Chinese languages, which would be amazing. There are so many different cancer treatment centers in China that standardization is an invaluable step forward.

The problem with translating the Blue Books themselves is that it would require more resources than are currently available, and that it's hard to ensure that the content is properly reflected in the translation. As a compromise, IARC is happy to have the ICCR datasets available in multiple languages, so that at least the diagnostic information is accessible to people all around the world regardless of income, resources, or preferred language.

We're also collaborating with SNOMED International. The ICCR datasets can be implemented in different formats – paper-based, via word processor, or in sophisticated software setups. We use a classification system for cancer pathology reporting that goes from Levels 1–6. Level 1 is pure narrative reporting without standardized content, whereas Level 6 is "the ultimate report" – structured data based on standards like the ones we're establishing at the ICCR. Some of the CAP and ICCR datasets have

been structured in a format based on the SNOMED CT concept, with each element linked with the corresponding SNOMED CT terms – and there's an international group whose priority is to complete the remaining datasets over the next few years. The ultimate implementation of the dataset is that Level 6 format with links to the SNOMED CT terminology, because it gives them true international interoperability. The terminology is the same no matter what country you're in or what system you're using. The idea has been a success so far, and I'm looking forward to the next few years.

Toward structured pathology

What does a non-structured, or Level 1, report look like? Most are narrative reports that pathologists simply type or dictate. They contain no structured areas and follow no external standards. A Level 3 report consists of discrete elements – procedure, organs and systems involved, size and appearance of the tumor, histological characteristics, tumor grade and stage, predictive and prognostic biomarkers, and so on. A Level 6 report contains all of those discrete elements within a defined structure and uses standardized terminology; it's also saved in an appropriate transmission format and linked by numerical codes for retrospective analysis.

My Ontario jurisdiction was the first in the world to fully implement structured cancer pathology at Level 6 across the whole province (about 110 hospitals and 450 pathologists serving 13.5 million people). Every day, we produce hundreds of cancer pathology resection reports – thousands of data elements. What we've done is take that data and develop quality indicators that we can compare across hospitals and regions to evaluate performance. So not only is pathology data used for patient care at individual institutions, but at a population level via the Cancer Care Ontario registry. We can look at data such as the distribution of cancer types, grades, or tumor stages, and we can provide feedback on quality to hospitals or individuals so that they can improve their practices. The project was fully implemented in 2012, so at this point we have a phenomenal amount of data relating to cancer pathology in the province – and it will only continue to grow.

The Level 6 structured synoptic cancer pathology reporting program has now been implemented in five other Canadian provinces, and they're now starting to roll out quality indicators as well. In the next five years, we hope to have the remaining provinces up and running – and I know similar work has been done in California, the Netherlands, and Switzerland. Pathologists here, there, and around the world play a vital role not only as diagnostic oncologists, but also in cancer control, which is why this population-level information is so important. It allows us to do appropriate healthcare planning and resource allocation, develop quality metrics, and conduct pathology research. I think many pathologists don't understand that they have a huge role outside of individual cancer care within their regions or countries: describing

the burden of cancer on the population, breaking down the information, ensuring its accuracy, and using it to improve future healthcare and cancer control. Structured reporting is a foundational step toward making cancer care better at every level.

Developing a dataset

What makes a dataset? In each one, we include clinical notes, macroscopic examination (the gross features of the tumor), and microscopic data related to the diagnosis, staging, and predictive and prognostic information. When we begin developing a dataset, we identify a series champion who advises the steering committee on the selection of chairs for individual dataset committees and helps us locate the best domain experts from around the world.

The process itself begins with a project manager who combines and updates existing datasets into a draft document outlining the proposed elements; committee members vote and discuss to determine which are selected, and which are core (absolutely required for clinical practice and treatment) versus non-core (desirable and useful, but perhaps lacking a fulsome evidentiary base). At the end of the day, we end up with a final draft document that comes back to the dataset steering committee for input and then goes out for wide international consultation. That's a key part of the development cycle; we send the data to a huge list of pathology and oncology organizations for their feedback, then incorporate it into the final product. Ultimately, the dataset is published on our website and in academic journals.

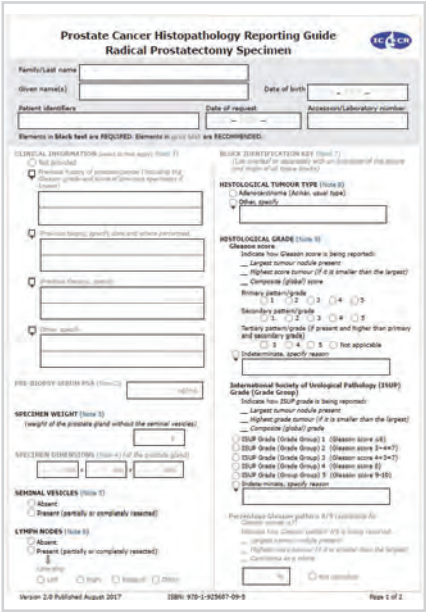
Extending the remit

Over the past few years, we've made huge strides in biomarker research and applications. Many classification systems are moving in a molecular direction – for instance, the central nervous system (CNS) tumor dataset. The brain tumor puzzle includes a lot of molecular pieces, so the next evolution of that dataset includes both immunohistochemical and molecular biomarkers.

Our CNS tumor dataset is unique in that it is layered. The first layer includes the key morphological aspects; the second incorporates biomarkers; the third integrates both. We took that approach because most low- and middle-income countries don't have the resources to do complex biomarker testing. We wanted pathologists in those countries to have standardized morphological guidelines to use in structured reporting, while those with more resources can apply the molecular and integrated layers. That's now spreading to other datasets – for instance, in lung cancer. The pipeline for new datasets looks promising!

We're also expanding our relationships with professional organizations related to individual tumor types. Urological and gynecological pathology are two good examples; both the International Society of Urological Pathology and the International Society of Gynecological Pathologists have done a lot of work in standardizing cancer reporting, so we've approached them for the names of experts who can help develop our datasets. We are currently approaching patient groups for various tumors, to help support our initiative, although we haven't seen much success in that arena yet. Hopefully, as we continue to expand our remit and our relationships, that will change.

Those who wish to join our mission can do so in a number of ways. Individual pathologists, pathology groups, and professional organizations can all take part – but for groups who want to make the biggest difference, I recommend becoming a sustaining member. That provides a seat on the ICCR board of directors and one on the dataset steering committee. Sustaining members can also recommend pathologists for the dataset operating committees, and we make


Prostate Cancer Histopathology Reporting Guide
Radical Prostatectomy Specimen

An image of the ICCR dataset for prostate cancer reporting.

sure that each operating committee includes at least one such recommended individual. That helps us ensure broad representation and lets pathologists at every level give input into the dataset development process. It also improves our sustainability – a critical issue, because although pathologists donate their time and effort to the cause, there are other significant project management costs. Financial issues aside, it's an absolute necessity that we continue to standardize diagnosis, prognosis, and treatment for our patients worldwide. So for any pathologist or group with an interest in improving global diagnostics, I invite you to take advantage of our existing datasets – and perhaps even work with us to improve them!

John Srigley is President of the International Collaboration on Cancer Reporting, Professor of Laboratory Medicine and Pathobiology at University of Toronto, and Consultant Pathologist at Trillium Health Partners, Toronto, Canada.

From Bench to Bedside and Back Again

Sitting Down With... James Wilson, Rose H. Weiss Professor and Director, Orphan Disease Center, Professor of Medicine and Pediatrics, University of Pennsylvania, USA

What inspired you to study medicine – and what drew you to genetics?

As an undergraduate, I was interested in the physical sciences, and had planned on attending graduate school to do chemistry. However, my father and grandfather were both physicians, and I made the decision that if I was going to have a career in science, I wanted the results of my research to be closely connected to improving outcomes for patients. So I decided to enter a combined MD/PhD program at the University of Michigan.

My interest in genetics derived from my work as a young scientist and physician – my training really set the stage for my entire career. My motivation came from the interactions I had with patients during my research, as well as in my clinical rotations in pediatrics. I got to know three different patients who had really awful genetic diseases – a young man with Lesch–Nyhan syndrome, and one who had metachromatic leukodystrophy. The third patient – one who left a lasting impression on me – was a young boy with a severe form of epidermolysis bullosa.

How close – or far – are we from treating such genetic conditions?

I began my career studying genetic diseases and made the decision, literally on the spot, that I was going to focus on gene therapy. Of course, I didn't realize at the time how complicated that would be, or how long it would take to get to a point where we were having an impact on patients! It's been a 30-year journey, and now we're at the point where we're seeing gene therapies being approved for patients with rare diseases.

The fact is that we're only at the beginning, and I have to remind myself – and those who are affected by what we do – that this still experimental science. But we're at the stage where the translational investigator can play a key role. We're taking our discoveries from the bench to the bedside, but the most important step in the entire process is learning the potential and limitations of our technology in the clinic, and bringing it back to the bench. The future is bright, and there will be successes, but there will also be failures. One thing is certain: we need to continue to innovate.

"My dream since I was a young student has been to change the course for patients with genetic disease."

Your work sounds challenging – but also rewarding...

One thing that I enjoy about my job is the challenge of integrating medicine and science on a daily basis. I find it helpful to view myself as a bit of a generalist, both in terms of clinical practice and research. I try not to stay confined to the disciplines I've trained in. I've also been able to benefit greatly from the input of the incredibly bright and talented young scientists and trainees in my lab, who help me to expand my horizons.

A critical factor for success is the ability to appreciate the other aspects of translational medicine that you need to move into the clinic – the ones that are not necessarily related to the science. You need to figure out what they are, learn about them, and take as much control over them as you can. For example, interfacing with the biopharmaceutical industry, and the various aspects of technology transfer. I often see scientists defer these important parts of the process to others. Learning what these issues are and getting involved has given me more influence and control over the trajectory of my work, and that has been pivotal to my success.

What advice would you give to young translational researchers?

There are three areas to consider. The first is to establish a goal, and do whatever you need to do to achieve it. Also you must realize that you may be forced to become knowledgeable about (or even a master in) areas of science or medicine that you previously had no direct experience of.

Secondly – and crucially – place yourself in an environment that is truly committed to translational research. I see the word translation virtually everywhere, but very few institutions really support the development of careers in translational research, or support bench to bedside and first-in-human studies, which is where our impact can be. Find that institution, and get there.

Finally, our field is complicated, and involves many different stakeholders and contributors. As a translational scientist, you can be the glue that brings them all together – the "missing link." So you have to be interested in networking and building teams. You need to be a leader, and pull together many diverse individuals, many of whom don't report to you. It's a real skill, but essential for your success.

What is your career highlight?

I still think I'm waiting for the true highlight. My dream since I was a young student has been to change the course for patients with genetic disease, and I think we're getting closer and closer. These families had no hope, but now I think we're providing a little. We want to go further by providing real solutions.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