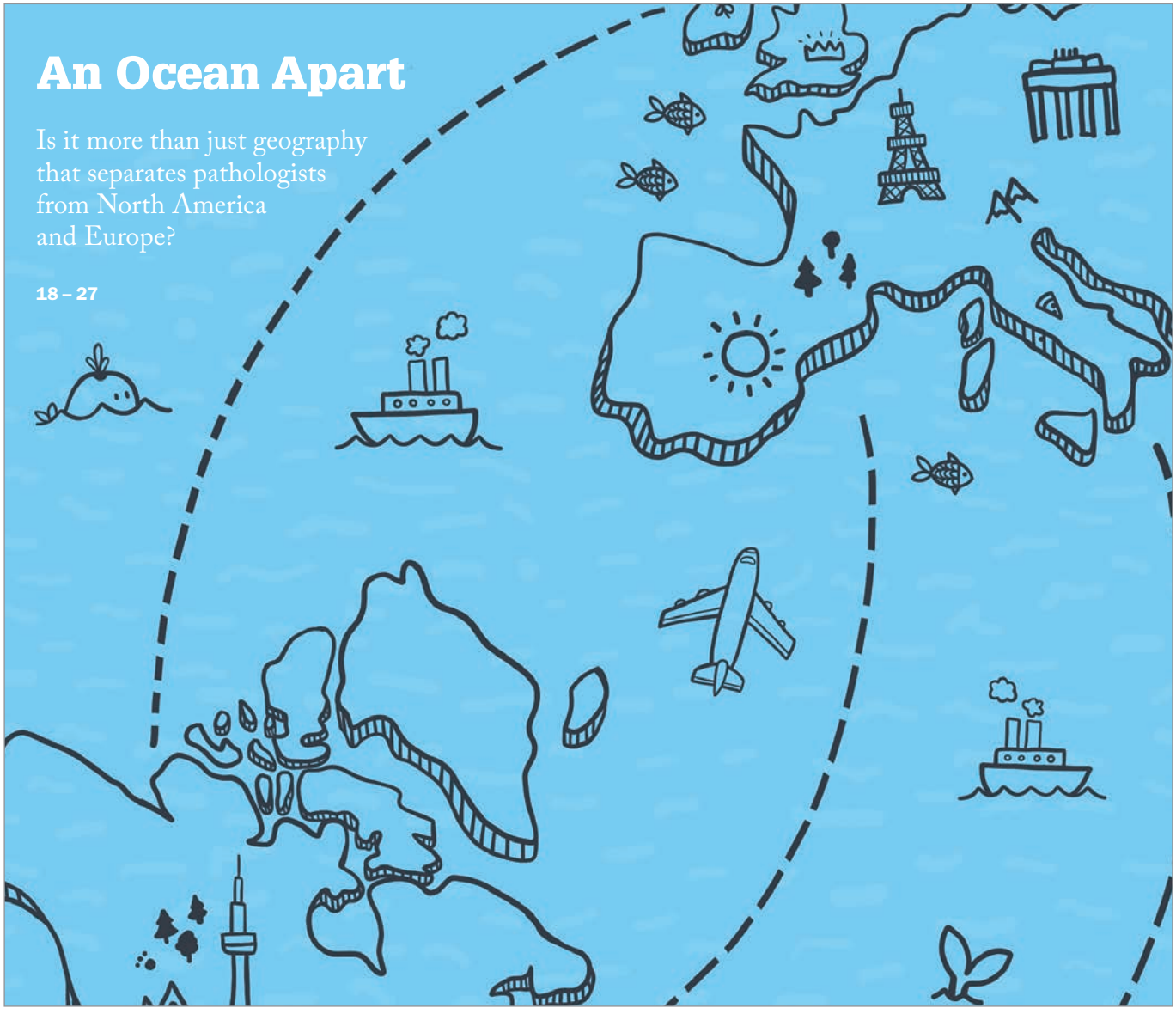
JANUARY 2017 # 26

the Pathologist

An Ocean Apart

Is it more than just geography that separates pathologists from North America and Europe?

18 – 27



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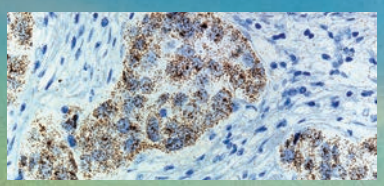

HER2 expression in human breast cancer FFPE tissue using RNAscope® 2.0 HD Reagent Kit-BROWN

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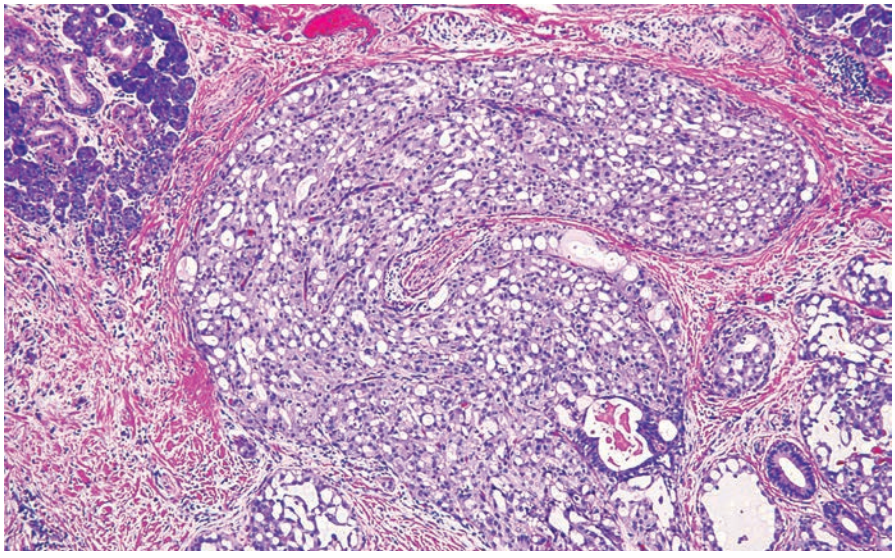
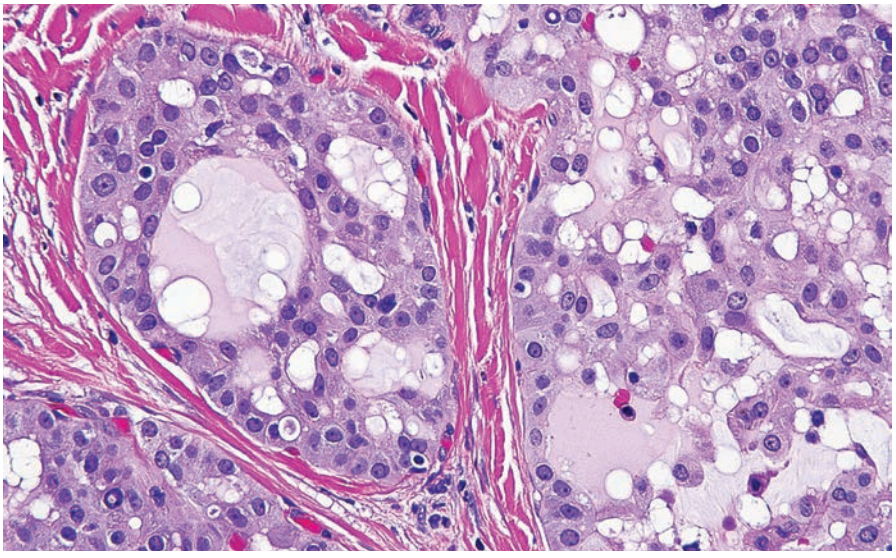
Case of the Month





Salivary gland tumor

The tumor shown was resected from the parotid gland of a 52-year-old woman. What is the most likely diagnosis?

- *A* Acinic cell carcinoma
- *B* Adenoid cystic carcinoma
- *C* Mucoepidermoid carcinoma
- *D* Ductal carcinoma
- *E* Mammary analog secretory carcinoma

Do you think you have a good case of the month? Email it to edit@thepathologist.com

To register your guess, please go to http://tp.txp.to/0117/case-of-the-month
We will reveal the answer in next month's issue!

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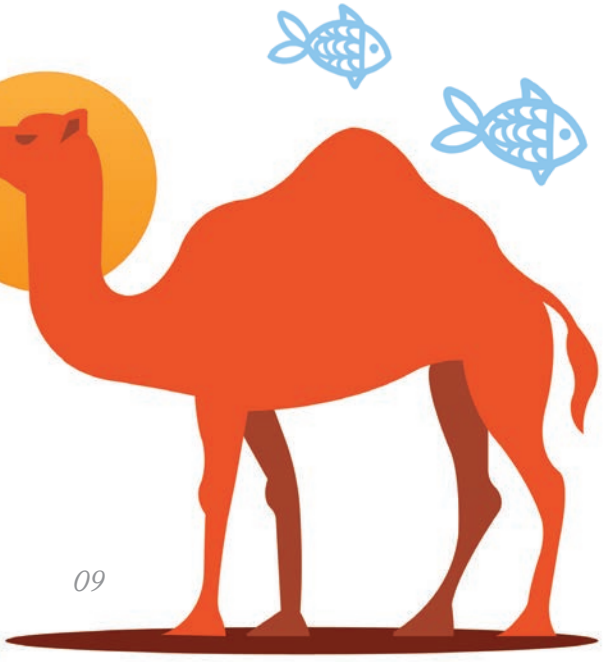

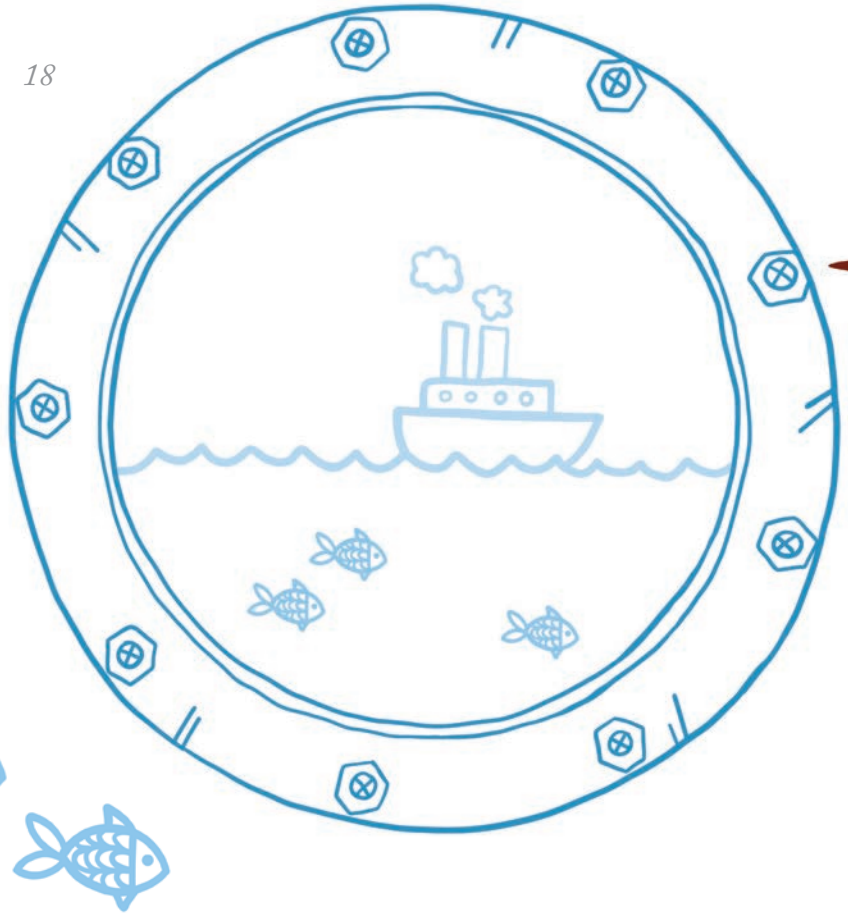

On The Cover

Bespoke illustration depicting the oceanic divide between North America and Europe.

In Practice

NextGen

Profession

Sitting Down With

the Pathologist

ISSUE 26 - JANUARY 2017

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We listened, and here's our answer...

It gives me great pleasure to say: Hello, North America! We've always had a loyal online following, but this month marks the launch of our first monthly print edition in the US and Canada. And I couldn't be happier. We've received a lot of support and positive feedback from our North American colleagues since we launched The Pathologist some years back, and this is our way of continuing to show our commitment to you. "We need you in the States," I was told by a global thought leader in pathology last year. "You need to read this magazine and you need to get behind it. This is going to help us improve our profession," announced a Society President to a packed room at a Canadian congress last Summer. Let me pause there and note that I don't want to come across as arrogant; I can assure you, I'm not. What I am is very proud...

When we launched The Pathologist, I knew there was a risk – we had no idea how pathologists and laboratory specialists would react, because there was nothing else like it out there. We wanted to create a publication that would push boundaries, address controversies that nobody else would, and to "tell it like it is" – all while inspiring our readers to come together to push for a better future for the profession. Not only am I proud of my colleagues' commitment to this cause, but I'm overwhelmed by the dedication and enthusiasm of our readers to join us in this quest.

We need more of you to share what you love about your job, why others should want to do it too, and to shout about the exciting research you're involved in and the concerns that you have. You can email any ideas for articles to edit@thepathologist.com any time; we want you to feel part of The Pathologist community. To that end, I would like to announce another launch: a new section that I really hope you'll engage with called "Case of the Month." Every month, on page 3, we will feature an unusual diagnostic case that has been supplied by a reader. We will then invite you to tell us what you think it is online, and we'll reveal the answer the following month. I would like to offer my personal thanks to our good friend Ivan Damjanov for inspiring this new and exciting section, and invite you all to get involved and submit any case that demands the attention of the wider community!

Finally, I would like to thank you for working with us to exceed all of the goals that I initially set for The Pathologist. It was created for you and is made possible because of you. Here's to a 2017 of positive change!

Fedra Pavlou
Editor

Upfront

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

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

Email: edit@thepathologist.com

Only Tau Will Tell...

Could tau be a useful biomarker of concussion?

With a bestselling novel and a Hollywood film to its credit (1), the subject of sports-related cranial trauma is finally receiving some long-overdue attention. American football is notorious for repeated concussion, and with the combined worth of National Football League teams being nearly $75 billion (2), safety of its stars – and protecting them from the probability of long-term neurological symptoms – is of great interest. To that end, researchers at the National Institutes of Health (NIH) have been investigating diagnostic markers to not only detect cases of concussion, but also to provide insight into prognosis and recovery (3).

Tau proteins have previously been linked to axonal damage after traumatic brain injuries (4) and, therefore, have potential as biomarkers of concussion. Indeed, the NIH team discovered that higher levels of tau observed six hours after a sport-related concussion correlate with an extended recovery period – findings that may eventually play a vital part in determining when an athlete can resume play.

There is a complicating factor, though; athletes generally have higher tau concentrations than non-sport playing controls, which must be taken into account. The researchers suggest that the elevated base level of tau may be caused by the general physical exertion of sports in conjunction with the increased blood-brain barrier permeability that occurs during sports-related activities. Although this natural elevation seems benign, it remains an important factor to consider – both for research into the association between tau and brain injury, and for any eventual diagnostic use. *WA*

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2. *Forbes, "2016 NFL Valuations" (2016). Available at: http://bit.ly/2jH65ms. Accessed January 20, 2017.*
3. *J Gill et al., "Acute plasma tau relates to prolonged return to play after concussion", Neurology, [Epub ahead of print] (2017). PMID: 28062722.*
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Number One Mystery

How solving a riddle about pungent camel urine could lead to potential diagnostics or treatments for African sleeping sickness

Sleeping sickness, also known as African trypanosomiasis, is a parasitic disease perpetuated by *Trypanosoma brucei*, and mainly affects sub-Saharan Africa – resulting in approximately 9,000 deaths a year. Researchers from Trinity College Dublin have found a new potential tool for early diagnosis – or even treatment – of the disease by solving an old riddle: why do camels infected with *T. brucei* excrete pungent red-brown urine? (1).

According to Anne McGettrick, Senior Research Fellow at Trinity College Dublin and lead author of the paper, it all started in a pub, over a pint of cold Guinness…

"Luke O'Neill, Professor of inflammation at Trinity College Dublin, had just published a paper in Nature showing that the metabolite, succinate, acted as an immune modulator," says McGettrick. "And he was chatting in the pub one evening with Derek Nolan, a molecular parasitologist at Trinity, who mentioned that *T. Brucei* produces high levels of certain metabolites in the bloodstream of infected patients – and camels."

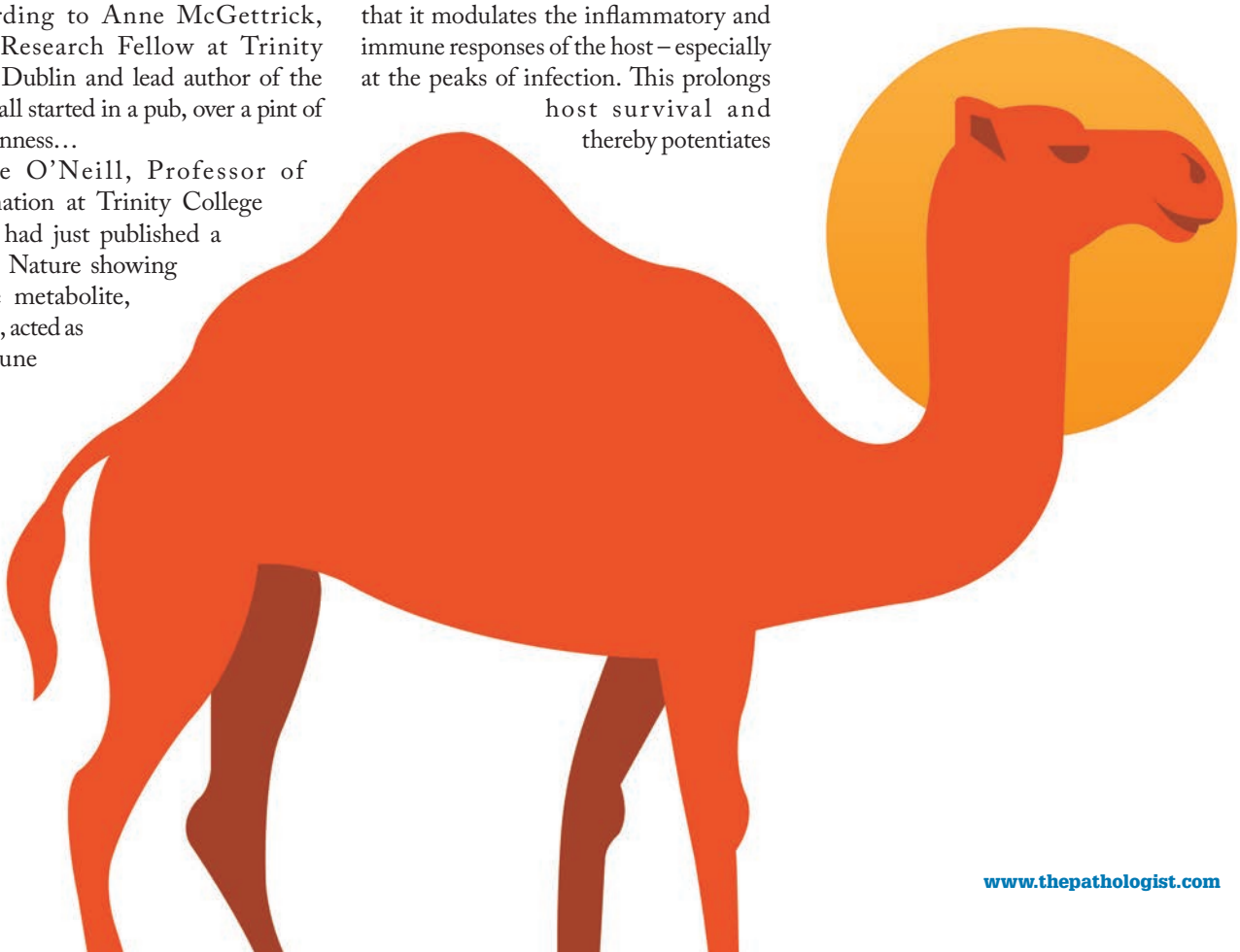
Researchers had always thought that the metabolites were simply a by-product of their metabolism, but Nolan wondered if they might play a role in the ability of these parasites to evade the immune response. "O'Neill agreed to test some of these metabolites to see if they had any effect on the innate immune response of cells in the laboratory," says McGettrick.

The testing unearthed a metabolic by-product of *T.Brucei* activity known as indolepyruvate, which alters the composition of the camel urine – affecting its color and odor. "The advantage of the parasite excreting indolepyruvate is that it modulates the inflammatory and immune responses of the host – especially at the peaks of infection. This prolongs host survival and thereby potentiates transmission of the parasite to the tsetse fly, which ensures it can complete its life cycle," says McGettrick. "This is the first demonstration of a metabolite, produced by a parasite, interfering with the host immune response."

The researchers hope their work will open the door to new tests for early diagnosis and treatments for sleeping sickness – with indolepyruvate as a potential target. In addition, McGettrick believes the research could open up the possibility that other metabolites, produced by invading pathogens, could modulate the immune response. *JS*

Reference

1. *AF McGettrick et al., "Trypanosoma brucei metabolite indolepyruvate decreases HIF-1α and glycolysis in macrophages as a mechanism of innate immune evasion", Proc Natl Acad Sci USA, 113, 48 (2016).*



Instant Raman

A fiber-optic spectroscopic tool probes IBD – in real-time and in vivo

Approximately one in every 200 people have inflammatory bowel disease (IBD) (1). For sufferers, it's not just the pain and indignity of some of the disease's characteristic symptoms (abdominal pain, weight loss, diarrhea), there is also an increased risk of gastrointestinal cancer – so appropriate disease management is key.

To effectively treat the condition, it's important to correctly diagnose the subtype – ulcerative colitis (UC) or Crohn's disease (CD) – but an overlap in symptoms makes the task difficult. In fact, there is only one (significantly invasive) way to avoid diagnostic uncertainty: colon biopsy (2).

In the past, researchers have investigated less invasive techniques such as laser endomicroscopy or MRI. Unfortunately, these methods focus on structural tissue changes, which are caused by IBD rather than being a symptom of it, making disease diagnosis less accurate.

Could Raman spectroscopy offer an effective in vivo alternative? A team of researchers led by Anita Mahadevan-Jansen decided that it was worth a shot (2). By coupling the technique with a fiber-optic probe, they created a real-time, minimally invasive tool to characterize the spectral signatures of IBD, reaching 90 percent sensitivity and 75 specificity to CD. The method was also able to determine the severity of the disease.

By striking a balance between diagnostic accuracy and patient safety and comfort, the new tool could be an important first step toward a minimally-invasive, real-time clinical diagnostic for IBD. *WA*

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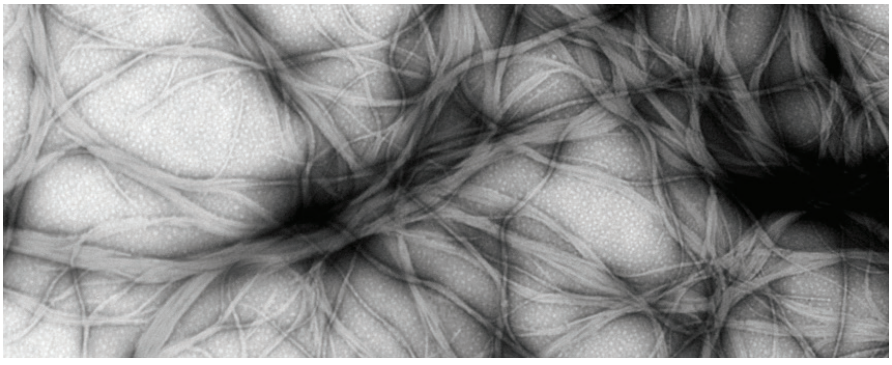
Prion Pursuit

A new diagnostic emerges for vCJD in blood



Credit: Flickr user NIAID

The pathology of prion-based diseases remains elusive, especially because, despite their highly infectious nature, it is still difficult to identify prions pre-mortem.

In 2014, Claudio Soto, Professor in the Department of Neurology at the University of Texas, led a team to develop protein misfolding cyclic amplification (PMCA) – an assay able to detect variant Creutzfeldt-Jakob disease (vCJD) in urine samples (1). Similar to PCR amplification of DNA, PMCA forces prion replication in a cyclic manner to produce enough misfolded proteins to detect.

Soto has now built upon those initial findings to create a blood-based diagnostic for the disease (2). vCJD is the human form of bovine spongiform encephalopathy, the prion infection colloquially known as "mad cow disease." The significance of this new diagnostic is twofold. First, there have been cases of iatrogenic vCJD (through blood transfusions or dural grafts). Second, although the well-publicized vCJD outbreak of the 1990s has passed, the disease can lie dormant for years in asymptomatic carriers before re-emerging (3).

The team analyzed the blood of 14 vCJD patients and 153 controls (including some patients affected with sporadic CJD) and demonstrated that the new assay had 100 percent sensitivity and specificity. The researchers note that more studies are needed to further validate the technique, but that the initial results show promise for the noninvasive diagnosis of this lethal disease with no known cure. *WA*

References

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The Power of Pyrin

Researchers describe a new diagnostic tool for identifying familial Mediterranean fever

Inflammation, fever, and severe pain – a combination of these symptoms that could be ascribed to a wide range of conditions, which is why patients with familial Mediterranean fever (FMF) can remain undiagnosed for years. But despite the difficulty in identifying it, FMF remains the most common monogenic autoinflammatory disease in the world. That's why scientists at VIB Leuven and Ghent University have collaborated to create a diagnostic tool to detect it (1). To find out more about the test, we spoke with Mohammed Lamkanfi, lead investigator and Professor at Ghent University.

What prompted you to investigate familial Mediterranean fever?

My lab has a longstanding interest in the mechanisms of inflammation, and in pathologies associated with defective innate immune signaling – particularly with regards to the inflammasomes. Pyrin, the protein mutated in FMF, triggers assembly of the inflammasomes and drives abnormal production of highly fever-inducing molecules (interleukins) that also cause tissue damage.

The causal gene of FMF has been known for almost 20 years, but it remained unclear how over 300 known causative mutations in the pyrin gene MEFV could trigger disease. Our studies clarified the molecular mechanism and led us to define an immunodiagnostic method that has been validated in 13 FMF patients so far.

How will the diagnostic affect patients?

The immunoassay requires a limited amount of blood, no sophisticated equipment, and gives results in a couple of hours. We think it will help reduce the current FMF diagnostic time – which I believe to be around five years – drastically, preventing unnecessary suffering, emergency care visits, and surgical procedures.

Timely diagnosis allows faster initiation of therapy – colchicine and anti-IL-1 drugs have proven efficacy in the condition – helping to prevent serious long-term complications like kidney failure.

How far are you from clinical trials – and what's next?

The assay was tested in healthy controls as well as in patients suffering from FMF and two other unrelated autoinflammatory diseases. Our test specifically identified the FMF patients in those studies.

We are currently organizing a follow-up study involving larger cohorts of FMF patients and those suffering from other autoinflammatory diseases to validate the sensitivity and selectivity of the assay. If all goes well, we hope the test can be implemented in clinical diagnostic routines around the world in a year or so.

We will also continue studying the fundamental scientific mechanisms of inflammation responses in diseases with evidence of deregulated inflammasome signaling. Our ultimate goal is to advance understanding of the pathological mechanisms and to identify new targets that can be applied in diagnosis and therapy, so that as many patients can benefit as possible.

Reference

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Troponin at the Heart of it

Are cardiac troponin plasma levels the statin-therapy trackers of the future?

"It is well established that high-sensitivity cardiac troponin concentrations can predict cardiovascular events, but it is not clear to clinicians how we can use this information to guide patient care," says Nicholas Mills, Chair of Cardiology at The University of Edinburgh. Eager to seek out the full benefit of the metric's clinical potential, Mills acquired funding from the British Heart Foundation to lead an investigation to determine whether cardiac troponin I (cTnI) concentrations could predict cardiovascular risk or identify those healthy individuals who would benefit most from statin therapy.

In the study, Mills and his colleagues used novel, highly sensitive assays to measure cTnI levels in patients' plasma and found that increased concentration suggested an elevated risk of coronary heart disease (1) – but that's not all. The team also discovered that the protein may be a better indicator of statin therapy effects than standard cholesterol measurements. "Perhaps our most important observation was that troponin concentrations are reduced by statin therapy," Mills says. "And individuals who have the greatest reduction in troponin have the lowest risk of coronary heart disease." According to Mills, the absolute reduction in risk with statin therapy was threefold greater in men with hs-cTnI concentrations over 5 ng/L than in those below 5 ng/L. "In clinical practice we repeatedly measure cholesterol after initiating treatment. But our observations suggest that we should be tracking response to treatments for the prevention of coronary heart disease with high-sensitivity cardiac troponin I measurements," says Mills.

In fact, he believes that cardiac troponin concentration has the potential to become the gold standard for predicting heart disease risk – and for tracking statin effectiveness, but notes that more work needs to be done: "We need to determine whether similar changes occur in women and in populations with coronary heart disease, and to determine whether a risk stratification threshold of 5 ng/L can also be applied to these populations." *WA*

Reference

1. *I Ford et al., "High-sensitivity cardiac troponin, statin therapy, and risk of coronary heart disease", J Am Coll Cardiol, 68, 2719-2728 (2016). PMID: 28007133.*

Credit: Flickr user Hey Paul Studios

A Simple Solution?

Uterine saline lavage may be the key to endometrial cancer screening

There is currently no screening method for pre-malignant or early-stage endometrial cancer, but with an estimated 60,000 new cases and 10,000 deaths each year in the US (1), a great need exists. Now, researchers from Icahn School of Medicine at Mount Sinai, Swift Biosciences, and Jefferson School of Medicine think they've found a method that could provide a simple solution: next-generation sequencing (NGS) and genomic analysis of uterine saline lavage fluid (2). If detected early enough, survival rates of endometrial cancer patients improve – five-year survival rates are 95 percent for localized endometrial cancer and under 20 percent when metastasized (3). Given the simplicity and accessibility of the lavage method, which can even be performed in a physician's office, the work may represent the first positive signs of a new gynecological screening method.

The investigators note that post-menopausal women are the highest risk group for endometrial cancer, and though diagnostic sampling isn't as successful as hoped, they found that their screening method works equally effectively in pre- and post-menopausal women.

Right now, the NGS-based method only indicates whether the endometrial cancer-associated gene mutations are present rather than pinpointing patients with cancer, so more understanding of cancer development is needed. Indeed, the investigators note that their "ultra-deep sequencing" approach could offer insight in that area, by digging into the development and clonal expansion of somatic cancer-driver mutations in tissue that appears to be healthy. *WA*

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In My View

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

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

Contact the editors at edit@thepathologist.com

The Real Cost of NGS

NGS isn't as cost-effective as many would consider, but resource and cost constraints can be minimized with careful planning

By Linnea Baudhuin, Associate Professor of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, Minnesota, USA

With next generation sequencing (NGS), we are now able to provide genetic tests that are more comprehensive, faster, and less expensive per base than ever before. But, this doesn't mean that NGS is low-cost. As laboratories get into the NGS game, they quickly realize that the technology is expensive, there are multiple new complexities encountered, and there may be issues surrounding reimbursement and regulations. These factors may cause many to question if it's worth offering this type of testing at all. The short answer is: maybe!

Before setting up an NGS testing program, laboratories should consider which types of tests would provide value to their internal and external clients, and balance this with an awareness of the resource-heavy nature of NGS.

There are several different clinical uses for NGS with much of the testing falling into three major categories: gene panels for oncology (somatic), gene panels for inherited disorders (germline), and whole exome/genome sequencing (WES/WGS) for diagnostic odyssey/rare disorders. The latter two are not as dependent on rapid turnaround time (with the exception of rapid genome sequencing for critically ill newborns), and therefore they may not be as critical to implement for in-house testing purposes. However, somatic panels usually require quick turnaround and may be a good choice for laboratories that want to service their internal practice for this clinical need. It is important to keep in mind that a timely orthogonal method for confirming reportable somatic testing results may need to be factored in, and could involve NGS sample processing in parallel.

"There are multiple new complexities encountered, and there may be issues surrounding reimbursement and regulations."

For many oncology and inherited disorder gene panel tests, there is a race between laboratories to provide the most comprehensive test. Laboratories and clinicians, however, need to realize that more is not always better. Labs need to be shrewd about their gene panel design, evaluating the clinical utility of each gene and including only those genes with a strong evidence base. Why is this important? Because the more genes that are included, the more variants are detected (including variants of uncertain significance [VUSs]), and, consequently, more variant interpretation and categorization will need to be carried out. All of this translates to resources spent by the laboratory, time spent by the clinician

trying to understand and explain the results, a higher potential for incorrect interpretation of the report by clinician/patient, and potentially unnecessary follow-up testing on VUSs. So, careful upfront gene panel design with multiple iterations between genetic counselors, clinicians, and laboratory directors is time well spent.

Notwithstanding all of the care that has gone into designing the gene panel, many laboratories will need to update their panel to add new genes every six to 12 months. There are two main reasons for this: first, clinician demand for a very specific panel (often a subpanel of a larger panel, especially in the cases of somatic testing); and, second, the discovery of new genes that may have clinical utility. Laboratories will find, however, that upgrading NGS tests is difficult; each panel needs to be redeveloped and revalidated as genes are added. Therefore, laboratories may want to think about upfront development and validation of a very large gene panel reagent (containing as many genes as could possibly be needed; perhaps even the exome or an enhanced medical exome reagent) and implementing sub-panels from it. This approach could prevent some of the later redevelopment and revalidation of tests, and would help to streamline validation efforts and workflows by having one large reagent with many sub-panel tests.

Personnel can be another resource constraint. With the introduction of NGS comes the hiring of bioinformaticians. Because bioinformaticians are generally new to the clinical laboratory workspace, effort is required to thoroughly validate the bioinformatics pipeline and provide full training to ensure competency of bioinformaticians with respect to the clinical testing environment. This is unchartered territory for many labs, and there may be a steep learning curve initially. In addition, implementing NGS tests also dictates the need to increase genetic counselor capacity. Because of the increased demands on genetic counselors, and the general shortage of them, laboratories will need to implement creative solutions to offload some of their work without compromising the integrity of the test.

While NGS testing can prove costly, there is a definite clinical need and benefit that is pushing many laboratories towards implementing it. My tips for minimizing resource constraints include thoughtful gene panel design; streamlining development, validation, and workflows through a maximized test reagent; preparedness in terms of assessing employee competence; and consideration of employee workload demands. Careful upfront thought and planning, though, will really help to prevent downstream unnecessary expenses as laboratories embark on their journey of NGS clinical testing.

Classifying the Unclassifiable

Mimiviruses don't really fit into any known group of living things – let's be brave and come up with a new domain, lest we stifle progress

By Didier Raoult, Microbiologist, Director of Research Unit in Infectious and Tropical Emerging Diseases, Marseille, France.

About 20 years ago, I was investigating amoeba and the *Legionella* bacteria living within them, in a collection from Timothy Rowbotham. We identified five new species of *Legionella* and also made a surprising discovery – Gram-positive chlamydia-like bacteria living in amoeba. We tried and tried to amplify the newly discovered microbe, but all our attempts came to nothing, until eventually we started to question if it was a bacterium at all. We inspected the amoeba under an electronic microscope before and after extraction, and saw something that wasn't bacteria-like at all, but instead looked very much like a virus. What we originally thought was a *Legionella*-like bacteria turned out to be mimivirus, a giant 0.4–0.8 µm virus with a 1.2 megabase genome.

Mimivirus is a very unusual virus. In fact, it's debatable whether it is a virus at all. It bears more resemblance to bacteria, archaea, and eukarya. When we investigated mimivirus further, we found that the structural motif of its DNA and RNA polymerases are very old – we suspect that their origins may date back to before the operation of ribosomes. Mimiviruses can also be infected by viruses (virophages) themselves.

A recently published study from my lab showed once more that mimiviruses don't adhere to the typical properties of a virus (1). In this study, we discovered that mimiviruses have a defense mechanism against virophages, which we called MIMIVIRE, and it operates similarly to the CRISPR–Cas system in bacteria, representing a nucleic-acid-based immunity.

I believe that there should be a fourth branch to accommodate microbes such as mimivirus. The classification system needs to shift and adapt to new discoveries just as the rest of the scientific field does. Right now, I'm arbitrarily referring to this fourth

"The classification system needs to shift and adapt to new discoveries."

branch as "truc" which means "thing" in French. I'm not the only one with this belief about classification – there are other scientists who agree that it's time to update our system (2), and I think if we keep relying on this outdated classification standard then we'll miss out on so many discoveries, just like my collaborators and I almost missed out on discovering mimivirus.

Going forward, whether the classification system changes or not, we need to encourage young, upcoming researchers to think outside the box and to treat theories as theories, not the ultimate truth. They have to be prepared to break theories apart and find out the truth for themselves. If we want future scientists to discover new things, we need to teach them how to fish. I often tell young scientists that they need to try something new – they can either use a new type of fishing rod (new tools) or fish where nobody else is fishing (new theories).

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How Serious Are You About Quality?

Fewer and fewer microbiologists are based in satellite laboratories, causing the accuracy of Gram stains to sometimes suffer. Telemicroscopy could be the solution to this worrying consequence...

By Linda Zuchowski, Midwest Regional Microbiology Manager, Quest Diagnostics Laboratories, USA

Danish physician Hans Christian Gram first experimented with alkaline dyes to differentiate bacteria in 1884, and his staining method remains a valuable tool in microbiology labs today. Highly accurate, clinically relevant Gram stain results can quickly support or change an infectious disease diagnosis and lead to effective therapeutic decisions. But, physicians need confidence in Gram stain quality – "anything less than accurate, clinically relevant results is below the community standard of care" (1). Therefore, the lab must make every effort to provide high quality, timely Gram stain results to enable an acceptable standard of care for our patients. For some labs, telemicroscopy may be a key component of the solution.

In my view, providing highly accurate Gram stain results is not always easy. In our evolving healthcare climate, labs are consolidating and forming core microbiology labs, leaving many satellite lab locations without a microbiologist onsite. General technologists with little microbiology experience are then responsible for preparing and interpreting Gram stains in these satellite labs, which is far from ideal. Some struggle with maintaining proficiency with this high complexity skill; they may have trouble making adequately stained slides, ending up with Gram-variable staining and vague results. Or, they may have difficulty identifying the bacterial morphology and thus hesitate to report the probable genus (2–5).

"Without a robust training and competency system in place to help support these generalists, Gram stain accuracy can be less then 90 percent relative to culture results."

Without a robust training and competency system in place to help support these generalists, Gram stain accuracy can be less than 90 percent relative to culture results. Needless to say, inaccurate interpretation is not without its consequences: revised reports, incorrect diagnoses or treatments, and ultimately, a poor outcome for the patient. Much effort is therefore needed to improve Gram stain proficiency in satellite

"Use of telemicroscopy to maximize the accuracy of Gram stain results is an effective way to achieve our mutual goals."

labs and to provide continual monitoring as part of an ongoing quality assurance program. As difficult a task as it may sound, it is not impossible. In 2011, we successfully initiated a performance improvement plan using telemicroscopy in a satellite hospital lab; Gram stain accuracy was boosted to 97 percent and it has been sustained for the past four years!

However, according to a poll at the 2015 annual American Society for Microbiology meeting in New Orleans, very few labs are actually using telemicroscopy. In my opinion, they are missing the many advantages of this progressive technology:

- easy and cost-effective consultation 24/7
- real-time slide review with microbiology experts across vast lab networks
- increased confidence and competency among less experienced technologists
- improved accuracy and patient outcomes
- confidential sharing of images using Windows IP configuration (no special software required)
- digital image library that can be used in training programs
- strengthened partnerships between core microbiology labs (or reference labs) and satellite labs
- application to any lab department using microscopy (hematology, parasitology, urinalysis)
- enhanced collaboration with public health officials during outbreaks and within bioterrorism preparedness programs.

The cost of implementing a telemicroscopy system is minimal, especially when compared with the cost of revised reports or negative patient outcomes. With improvements in telemicroscopy and the advent of virtual Gram stain proficiency testing, this is absolutely the perfect time to incorporate digital technology into the microbiology lab. We all want to support the generalists in our satellite labs, share our expertise, and provide high quality, clinically relevant results for optimal patient outcome. Use of telemicroscopy to maximize the accuracy of Gram stain results is an effective way to achieve our mutual goals.

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An Ocean Apart

How pathology differs on either side of the Atlantic – and how it doesn't

By Michael Schubert

What exactly is a boot? Or a biscuit? Or a chip? If you pictured part of a car, a sweet treat, and a French fry, you may be from Great Britain – but if you thought of footwear, savory baked goods, and a crunchy snack, you may be from North America. The two are often described as "two countries divided by a common language," and it's easy to see how difficulties in communication might arise. But are these quirks of language the only challenge pathologists face when trying to relate European to North American practice? The simple answer is: no. While there are striking similarities between the art of pathology on each side of the Atlantic, there are surprising differences, too. So if you're considering a move, or simply wondering how your international colleagues see things, read on – our five experts from the United States, Canada, the United Kingdom and continental Europe share their perspectives on everything from training to technology.

An outside look

How do other medical professionals view pathology? In this, at least, the countries see eye-to-eye. Rather than being determined by location, the respect pathologists are given by their colleagues seems to depend on how much day-to-day interaction the disciplines have.

"It's variable," says Michael Prystowsky, Chair of the Department of Pathology at New York's Albert Einstein College of Medicine. "The working relationship between pathologists and oncologists, for example, is great. Everyone involved in cancer care understands what pathologists do, and we all work together very well." But he cautions that other specialties, who have less contact with pathology, may not understand its role equally well. "Pathologists see themselves as professionals and experts in diagnostic medicine, and not all physicians appreciate that perspective. They may see diagnostic

testing as a commodity – just order a test and deal with the results, and that can impact their professional interactions with pathologists."

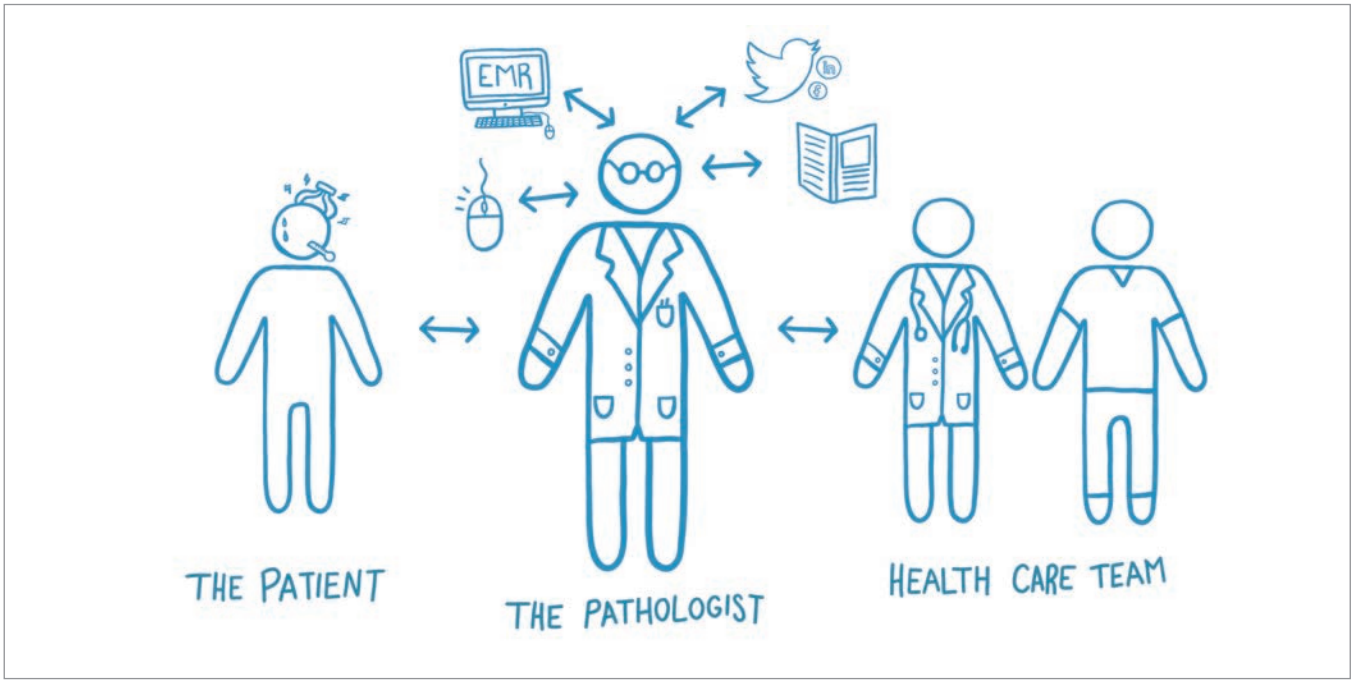
European pathologists agree. "I encounter many medical professionals who feel that pathology is very important for patient management," says European Society of Pathology past President Han van Krieken. "But obviously, the ideas are mixed. It depends very much on the level and quality of interaction."

Suzy Lishman, President of the United Kingdom's Royal College of Pathologists, goes one step further and highlights one likely reason for the disparity. "We know that today's new doctors qualify with less of an understanding of basic pathological principles than their predecessors," she says, "particularly in universities where dedicated pathology teaching has been dropped from the curriculum. Not only does this mean that they are less able to understand what is happening to their patients, but also that they are less equipped to select appropriate pathology tests and to interpret the results when they receive them."

The problem, it seems, begins early. A poor introduction to the discipline in medical school means that fewer students enter pathology – and also that those who choose other fields have a much less comprehensive understanding of who pathologists are and how they fit into patient care. "I don't think trainees are exposed to pathology as much as they were in the past," says Victor Tron, President of the Canadian Association of Pathologists. "There's less pathology in medical curricula now, so we're a bit mysterious to students. We're trying to change that, but we're fighting an uphill battle."

"Most students enter medical school to diagnose and treat sick people," says American Society for Clinical Pathology President William Schreiber. "The satisfaction, excitement, and human drama of dealing with living patients is hard to resist. By comparison, pathologists may seem introverted or antisocial, because our days are spent analyzing tissues and fluids from those patients. Many physicians move around the hospital during the day with an entourage of residents and students in their wake. Most pathologists spend the bulk of their time in labs or offices, available for consultation but not out on the front lines – and the difference in visibility makes an impression on students."

Prystowsky sees an opportunity to make a difference. "As medical school curricula are changing, it's important for pathologists to get involved when it comes to our professional activities – after all, we are the experts in diagnostic medicine." And this is one thing van Krieken perceives as a distinct strength of European pathology.



Credit: Academic Pathology

Figure 1. The pathologist, as an integral member of the health care team, advises on test selection, evaluates results, and explains outcomes both to the rest of the team and to patients directly. Adapted from (6).

Conversations with clinicians

Van Krieken, who is very familiar with US pathology practice, explains, "Large pathology departments interact with many hospitals, mainly through reporting. There is very little interaction by phone or face-to-face, because of distance or a lack of time." He points out that, in difficult cases, it's vital for the entire multidisciplinary team (MDT) – including the pathologist – to discuss the available options. "You can't expect everyone on the team to know everything. It's too much for one person. A team works best when each member performs their own specialized role and communicates well with the others."

He offers an example from his own experience (1). "I received what I was told was a biopsy from a patient's neck metastasis. It looked like adenocarcinoma with no special features, so I performed immunohistochemical staining to track down the primary tumor. I found prostate-specific antigen (PSA) positivity, so I reported that it was most likely metastatic prostate cancer, and the patient was given hormone therapy.

"But at the MDT meeting a week later, they showed more images and I realized that the tumor was actually extending from the floor of the mouth, rather than a lymph node in the neck. Perhaps it wasn't really a metastasis at all. After studying a series of cases, I discovered that there is a special type of primary salivary gland tumor that exhibits PSA positivity – something we had never previously known. The patient didn't have metastatic disease after all, but the primary tumor responded to hormone therapy anyway – and that's now the standard treatment. Sometimes, you can only discover these things through the information that's brought together in MDT meetings!"

And North America is eager to learn. Prystowsky says, "I see the pathologist as an integral member of the healthcare team (see Figure 1). They're actively engaged, providing diagnostic medicine expertise – which tests to use, how to perform them efficiently, how to explain the results to patients and care providers, and how to reach the right diagnosis in a timely manner and decide on the appropriate treatment.

"We need to focus on the pre- and post-analytical components by assisting our clinical colleagues on diagnostic ordering and interpretation," agrees Tron. "Those two bookends are going to become increasingly important – and we can't do that alone; we have to work with clinicians. They're the ones out there treating patients, so we have to make them a part of this venture." Tron's workplace, St. Michael's Hospital in Toronto, Canada, holds workshops to discuss bridging the communication gap between pathologists and treating clinicians, with the aim of understanding each other's needs and frustrations – and generating ideas. Perhaps there's a leaf to be taken out of the European pathology book...

"We possess unique skills that other physicians need and, in most cases, they appreciate our expertise in helping them to diagnose and manage their patients. Without a pathology department, hospitals simply could not function. Both administrators and medical staff know this!" – William Schreiber

"Pathology must be recognized as a vital part of almost all patient pathways and worthy of investment, not seen as a back-office function and an easy target for cuts." – Suzy Lishman

"It is important that we are recognized by our clinician colleagues, and that they see that we need resources to achieve results." – Han van Krieken

"I've tried to focus on improving not just the public's, but also medical students' and trainees' perception of pathology. We've tried to develop some leadership amongst our junior people, and we're working on the best way to transition in the next phase of leaders." – Victor Tron

Patients and the public

Although interaction with clinicians may vary widely depending on which side of the Atlantic you practice on, both sides agree that communication with patients and the public needs to improve. "My goal is to see pathologists talking more to patients," says Schreiber. "There are opportunities to discuss what we do, explain diagnoses, and provide our medical opinions to the patients we serve. It's the best way to demystify the profession and raise our public profile." And demystification is certainly needed. "Whenever someone asks me what I do for a living, I say that I'm a doctor," he shares. "They ask my specialty. After saying that I'm a pathologist, I allow a few seconds for them to respond, gurgle, or otherwise react. 'That's dead people, right?' is a typical comeback."

"I don't think the public largely knows what pathologists do," concurs Prystowsky. "It's our responsibility to get out from behind the microscope, get out of the laboratory, and solidify our place as part of the healthcare team."

On the other side of the ocean, the aim is the same. "One of the Royal College's priorities is to highlight the central role that pathology plays in healthcare," says Lishman. "Thousands of events have been held over the last few years to increase public understanding. There is still some way to go to dispel the myths, but I hope that high-profile pathology role models will help portray a more realistic and engaging side of the specialty."

Lishman's mission for many years has been to engage non-pathologists of all stripes, hoping not only to improve public awareness, but also to ensure that the best and brightest young students see pathology for what it is: a fascinating specialty worthy of their time and attention.

The numbers game

Unfortunately, all of the engagement in the world won't help if the discipline can't solve one critical problem – the shortage of pathologists worldwide. Although there are notable exceptions to this rule (for instance in the Netherlands, where there's actually a surplus of trained laboratory medicine professionals), most pathologists agree that there are simply not enough of them to maintain standards of care. "There's a pending shortage of pathologists," says Schreiber, "as well as a current shortage of medical technologists." He cites ASCP Vacancy Survey (2) statistics that reveal increased vacancy rates in all specialties except cytology and cytogenetics, along with the US Bureau of Labor Statistics' estimation that the need for lab services will grow as much as 16 percent over the next decade (3).

But can supply keep up with demand? "We're in a retirement cliff for pathologists in the United States," says Prystowsky. "We're an aging population, and we haven't increased the number of trainees, so we're heading for a deficit in the number

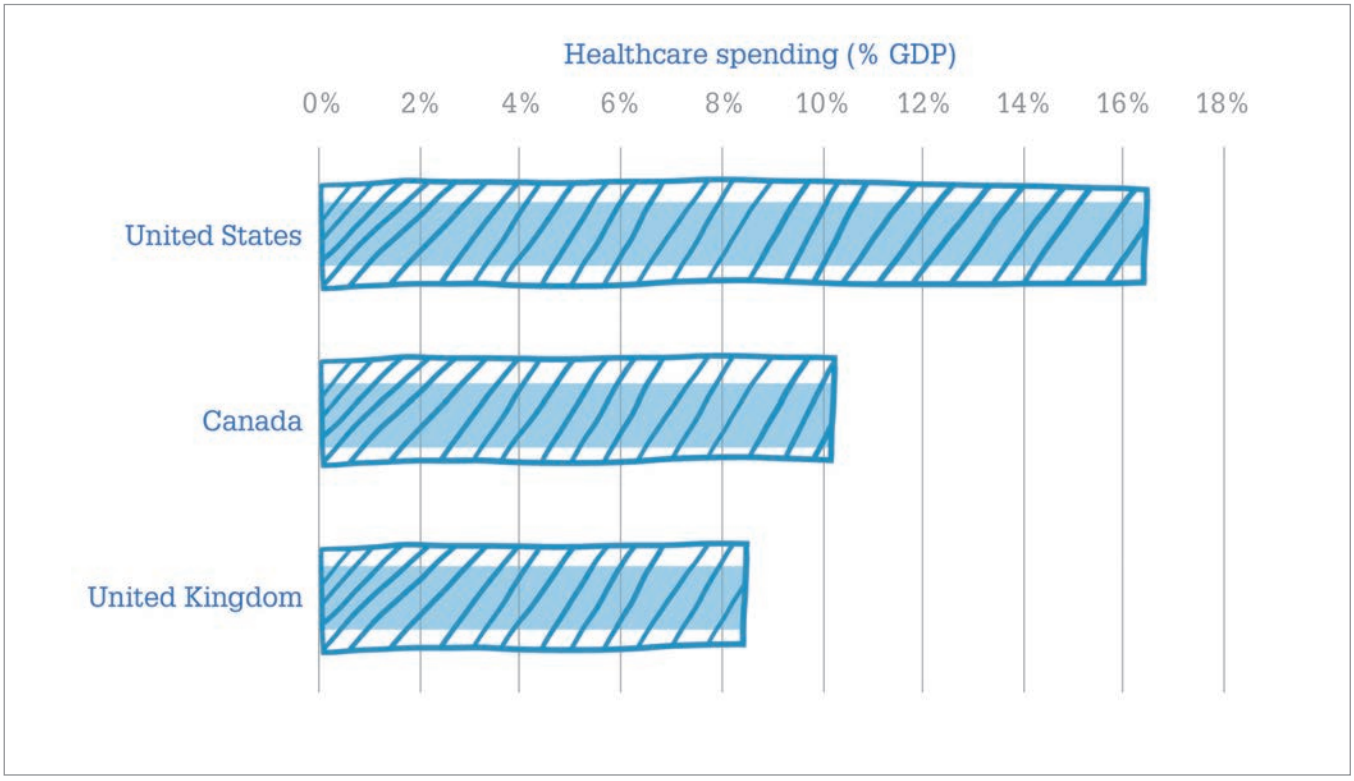


Figure 2. Comparative healthcare spending (as percentage of gross domestic product) between the United States (which ranks 1st in healthcare spending worldwide), Canada (10th), and the United Kingdom (25th).

of pathologists." Everyone agrees that more candidates need to be recruited – but that's much easier said than done.

"When I talk to people around Canada, there's always the sense that they're understaffed and workloads are becoming more complex," says Tron. "It's an uphill battle trying to convince the people with the money that additional positions are needed."

The outlook for most of Europe is little better. "A recent report by Cancer Research UK (4) described pathology services as being 'at tipping point,'" says Lishman. "Many services are overstretched and understaffed at a time when demand is increasing. We know that many pathologists plan to retire over the next few years and in some disciplines there are too few trainees coming through to replace them." Not only that, but many trainees opt for part-time work or shy away from smaller or less popular departments because so many are being closed or consolidated.

Some areas of Europe have an additional obstacle to overcome: the lack of available funding even when there are enough pathologists. Van Krieken highlights differences in the way pathology is perceived – and resourced – in different countries: "In Poland and the Czech Republic, there are very good molecular laboratories. But in places like Greece, Spain, Portugal or much of Eastern Europe, pathologists are often quite low-paid and low-ranked. So although they excel in areas like classical morphology, it can be very difficult to get access to new equipment and technology; they simply don't have the resources."

With shortages like this, though, come creative solutions. "In anatomic pathology, increasing workloads may require the help of technologists trained to screen tissue specimens," suggests Schreiber. It's a model that already works well in cytopathology and is ripe for expansion. He also proposes the use of telepathology to cover areas that lack local pathologists. Both solutions are ones that are gaining popularity in Europe as well.

"With increasing volume and complexity of work and a diminishing number of medically qualified pathologists, I believe that the roles of biomedical and clinical scientists will be further extended in coming years," says Lishman. "The Royal College, working with the Institute of Biomedical Science, has recently developed a training program for biomedical

"We should embrace cross-disciplinary and cross-professional roles, particularly in relation to molecular pathology. As 'guardians of the tissue,' pathologists are ideally placed to coordinate testing and integration of results and provide advice to clinical teams." – Suzy Lishman

"Pathologists used to be those people in the basements of hospitals who gave you results and whom you didn't often see." – Han van Krieken

"I think that we are the definitive opinions when it comes to cancer diagnosis. I always say that radiologists provide a differential diagnosis and we provide *the* diagnosis. It gives me a lot of comfort to think that we make such a great impact." – Victor Tron

"The pathologist needs to be central in the diagnostic testing, helping the team to choose the right tests and give the right analyses for each patient – but also to do study cohorts of patients longitudinally to improve treatment." – Michael Prystowsky

scientists to learn how to dissect and report a limited number of surgical specimens. The first few scientists are nearing the end of their training and will soon be reporting cases independently. I hope that, as they start contributing to their department's workload, they will be accepted and supported by their medical colleagues."

No matter where one practices, it seems that pathologists are increasingly facing the challenges of limited staffing and resource availability. But as digital pathology gains followers, the world is shrinking – so it's possible that pathologists on either side of the Atlantic Ocean will soon be able to turn to one another for help in surmounting those challenges.

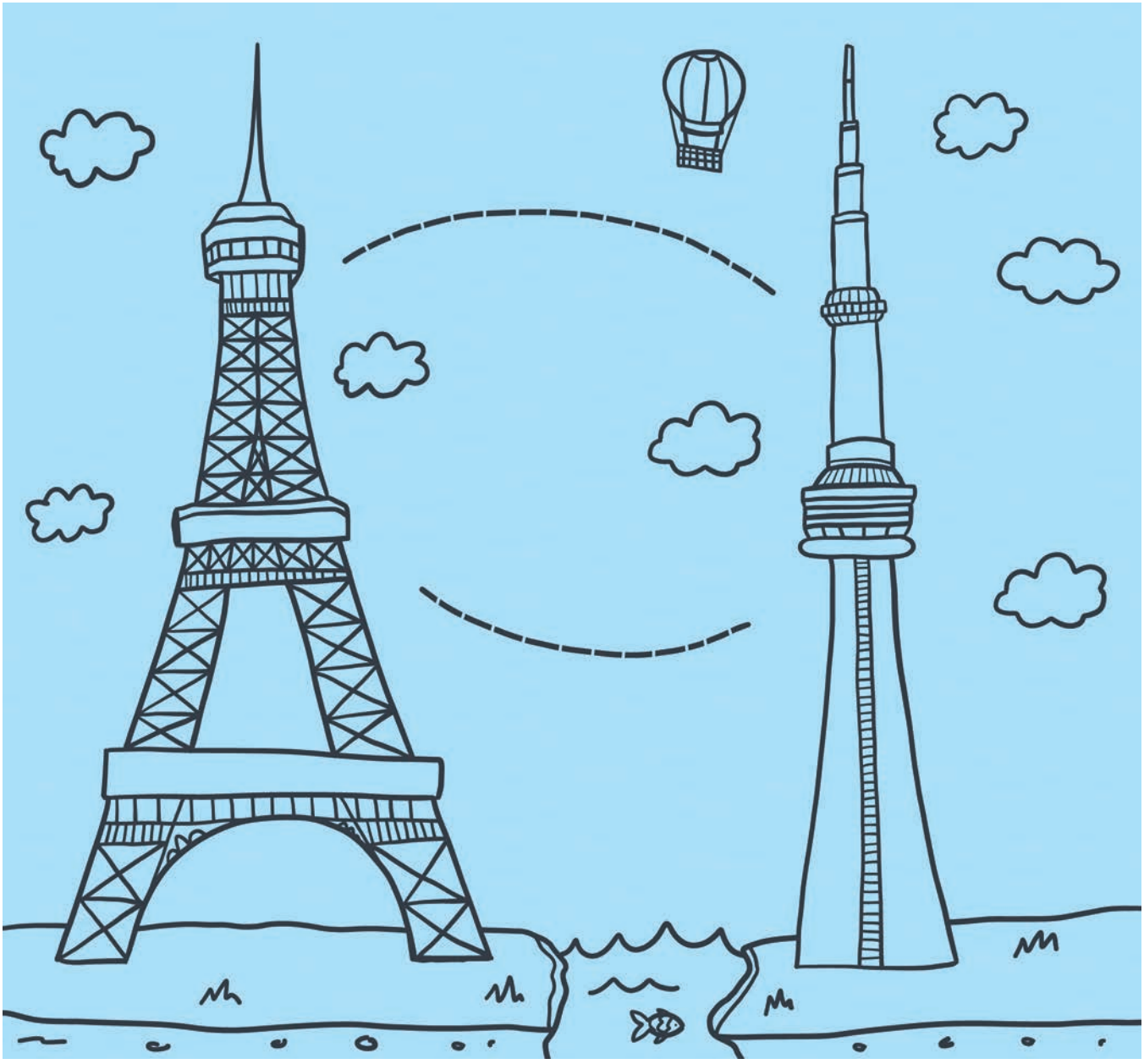
Hey, big spender

Speaking of difficulties specific to the United States and Canada, Schreiber says, "One major challenge is the sustainability of the two countries' healthcare systems (see Figure 2)." Why such a great disparity in healthcare spending? "The introduction of new technologies – some of unproven value – is driving a portion of these costs. In the future, it will be necessary to justify the use of newer and more expensive tests. The American Board of Internal Medicine (ABIM) Foundation's Choosing Wisely campaign identifies practices considered to be wasteful and unnecessary; to date, ASCP's participation has resulted in 15 recommendations (5) that, if followed, will reduce the cost of laboratory services."

But how are these services funded in the first place? This is possibly the area of greatest difference from one country to the next – and, even now, it's in flux. "The changes in the payment model are a challenge facing all of US medicine," says Prystowsky. "We don't know how that's going to impact us. That's why the pathologist has to be seen as an integral professional member of the healthcare team to improve time to diagnosis and enable implementation of an optimal treatment plan."

Schreiber agrees. "At the level of public policy, pathologists need to demonstrate their involvement in promoting good patient outcomes. Reimbursement from governmental sources in the US will be increasingly tied to evidence of quality indicators. Because our services are part of a larger picture, it can be difficult to show how our practice directly affects patients – but we may be required to do so."

Canada has the added complication that each province administers its own healthcare system. "The federal government really provides some general direction, but provinces run things day-to-day," explains Tron. "Trying to coordinate things across the country also raises unique challenges. CAP-ACP tries to advocate for resources, but no two provinces have the same needs." Although he'd like to see the country more united, he



says it's difficult to encourage the provincial governments to relinquish control. "I don't think we are achieving the goal of having appropriate numbers of pathologists doing the work. I wish it were a bit more coordinated."

Even in countries under a unified healthcare system, limited funding still poses a problem. "Most pathologists in the United Kingdom work within the National Health Service (NHS)," says Lishman. "Resources in the NHS are limited and the government's priority is to maximize the efficiency of pathology services. Unfortunately, pathology is often seen as a 'back-office' function rather than an integral part of clinical pathways. One of my challenges is to persuade policymakers that investment in pathology can save far more money elsewhere along the patient pathway – by making timely diagnoses, detecting disease earlier, or even preventing it from developing at all." Is there anything pathologists can do to help? "I suspect we're in for tough times and further cuts before the value of investing in pathology services is recognized. It's becoming increasingly

"Patients who have spoken with a pathologist involved in their care are usually quite grateful. They say that the pathologist took time to explain their diagnosis and may have saved their life. Direct patient contact makes a big difference in how our profession is perceived, and it's an area where we can do better." – William Schreiber

"The general public is basically unaware of what pathologists do, unless they have had to interact with one because they have a disease that needs to be explained. But once people have had that kind of experience, they become great advocates of pathology." – Michael Prystowsky

"Many laypeople don't have a good idea of what pathologists do. But in the end, for me, it's not important to be recognized by the laypeople. As long as they get good diagnoses through the clinicians, I am fine with that." – Han van Krieken

difficult for pathologists to take time away from service delivery to contribute to national work – so if policymakers want expert input, they will have to consider how experienced pathologists can be released from other commitments," she adds.

An imperfect split

For North Americans, the fragmentation of pathology also makes advancement and advocacy difficult. "Pathologists represent only two percent of all doctors in the US and Canadian systems, yet there are more than 30 organizations focused on pathology and laboratory medicine. The profession needs a collective voice to speak on policy and practice issues to government, our medical colleagues, and the public," warns Schreiber. "Otherwise, we risk diluting ourselves until none of our voices are heard."

Van Krieken has recognized the same phenomenon and sees integration as one of Europe's strengths. "Very early on, we adopted molecular pathology as an integral part of pathology – and programs throughout Europe are pretty good. In the United States, they have the Association of Molecular Pathology, which is separate from the United States and Canadian Academy of Pathology. They work together, but they have separate meetings. I'm a strong believer in combining the two – so for me, that's already a sign that the interaction is not optimal."

In terms of training, though, the reverse may be true. Prystowsky emphasizes a significant difference in how pathologists are educated in North America and elsewhere. "Pathology has two major disciplines: anatomic pathology and clinical pathology (or laboratory medicine). In the United States, most of our pathologists are trained to do both; we view pathology as diagnostic medicine and both aspects are integrated." He points out that in hematopathology, for instance, it's vitally important to be able to make a morphologic diagnosis, use laboratory techniques, and apply molecular tests – all three are necessary for a comprehensive diagnosis and treatment plan (6). "That's where we think pathology should be for all areas of diagnostic medicine. In Europe, there appears to be more of a split between training in anatomic pathology and laboratory medicine."

In Canada, training is even more diversified. "Clinical pathology is broken into three distinct disciplines – hematopathology, medical microbiology, and medical biochemistry," says Schreiber. "These clinical subspecialists tend to practice in large hospitals or private laboratories, where there is a need for full-time expertise in each area."

Learning Lessons

Whichever training method one adopts, Europe – which has so much to teach North America about integrating pathology into diagnostics – knows it has a lot to learn about pathology education. "I think what we can learn from the

United States is their rigorous education tools," van Krieken says enthusiastically. "They are much more advanced than ours." And with the rapid adoption of digital pathology, the transition to computer-based examinations, and even the use of simulations and virtual reality in teaching and training, it's certainly true that North American institutions are moving ahead by leaps and bounds in the way that they educate the next generation of pathologists.

The next challenge? Pathologists from both continents agree that, with ever-increasing amounts of information to be crammed into a single residency, both curricula and teaching methods will need to change, if young pathologists are to keep up with their chosen discipline.

So is it true that North America and Europe are "two continents divided by a common practice?" In some ways, certainly – but in others, not so much. Despite differences in training, funding and even professional respect, pathologists around the globe are united by increasing workloads, staffing shortages, and the slow but steady shift from a traditional to a digital world. Most of all, though, what connects all pathologists is the same desire that drives any doctor: the goal to see every patient diagnosed, treated, and cured. And in that respect, it pays to reach out – because North American and European laboratory medicine professionals still have a lot to learn from one another.

Suzy Lishman is President of the Royal College of Pathologists. She is Head of the Department of Cellular Pathology at Peterborough City Hospital, Peterborough, UK.

Michael Prystowsky is Professor and University Chairman of Pathology at Montefiore Medical Center and Albert Einstein College of Medicine, New York, USA. He is a board member for the College of American Pathologists and Councilor for the Association of Pathology Chairs.

William Schreiber is President of the American Society for Clinical Pathology, consultant pathologist at Vancouver General Hospital, and Professor in the Department of Pathology and Laboratory Medicine at the University of British Columbia, Vancouver, Canada.

Victor Tron is President of the Canadian Association of Pathologists, as well as Chief of the Department of Laboratory Medicine at St. Michael's Hospital, Toronto, Canada.

Han van Krieken is past President of the European Society of Pathology, Rector Magnificus of Radboud University, and past Chair of Pathology at Radboud University Medical Center, Nijmegen, Netherlands.

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Under Pressure

What our smartphones taught us about transporting blood samples through pneumatic tube systems

By Garrett Mullins, James Harrison and David Bruns

When looking out for laboratory error, one of our most powerful resources is the curiosity of the astute clinicians who receive and interpret test results. Clinicians are in the pivotal role of comparing a patient's laboratory results and clinical status – which often makes them the "first reporters" of laboratory errors not detected by routine quality assurance protocols. We recently dealt with just such a report informing us of unexpected increases in plasma lactate dehydrogenase (LD) concentrations in several of our patients. Samples from the location in question are analyzed in one of two laboratories:

At a Glance

- *When identifying and addressing laboratory error, the sharp eyes and curiosity of clinicians interpreting test results is a powerful asset*
- *Clinicians alerted us to unexpected results from numerous blood tests, which led us to identify a potential problem with pneumatic tube system (PTS) transport*
- *Using smartphone accelerometers to examine PTS transport, we learned that samples were subject to shock forces and turbulence, making some samples prone to preanalytical error*
- *We have shown that any medical center with a PTS can monitor and adjust it easily and affordably with the aid of smartphone accelerometers*

Figure 1. Preparing a sample for pneumatic tube system (PTS) transport.

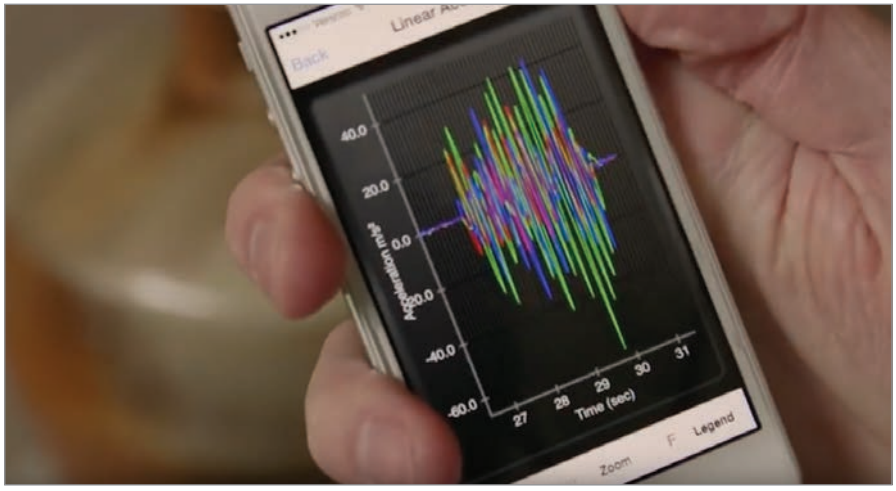

Figure 2. A plot of acceleration vs. time on the data-logger app.

an onsite satellite laboratory for routine chemistry and hematology analyses or, alternatively, a core laboratory half a kilometer away that handles more comprehensive testing. Initial investigation of the unexpected results included quality control review, instrument-to-instrument comparisons, clinical correlations, and even centrifuge testing in both labs… but none of these revealed the reason behind the high plasma LD. What did we notice? That the unexplained high results were reported from the distant core laboratory, whereas the lower results came from the onsite laboratory.

An unexpected problem

We transport patient samples to our core laboratory through a pneumatic tube system (PTS) – a seemingly ubiquitous means of sample transportation in large medical centers. Although the systems are convenient and efficient, excessive acceleration force and distance traveled have previously been correlated with increased sample hemolysis (1), which can increase plasma LD. That made us curious about the impact of our own PTS on sample hemolysis and plasma LD – so we launched an investigation. We began by transporting replicate

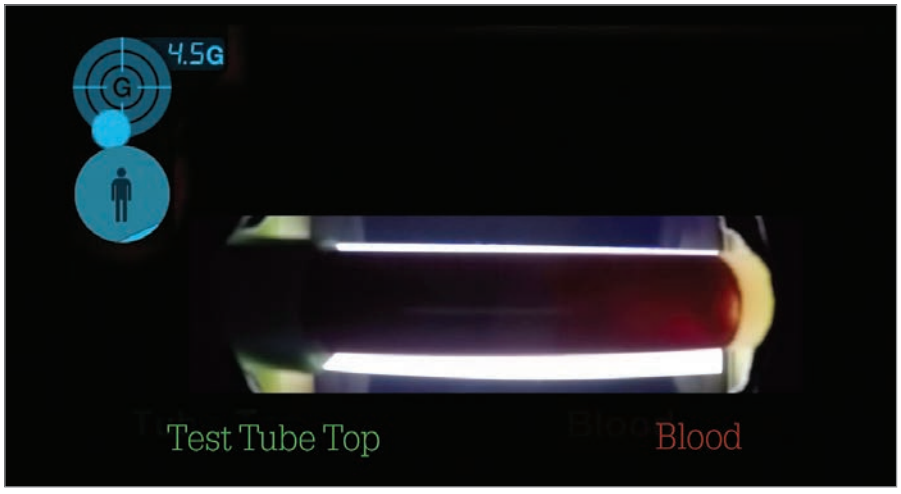

Figure 3. Smartphone image of a blood sample during PTS transport.

blood samples from volunteers, either by walking courier or by one of numerous PTS routes (see Figure 1). We found that samples sent via PTS from our location of interest to the core lab frequently showed increased hemolysis and plasma LD activity compared with samples transported through other PTS routes or carried by courier (2).

Once we had identified the likely cause of the increased plasma LD, we wanted to know why one particular PTS route compromised sample integrity while others had little to no effect. To do that, we needed the right tools. There are accelerometers specifically designed to monitor forces experienced by objects traveling through a PTS – but we couldn't obtain any, so we had to come up with an alternative solution. That's when it occurred to us that modern smartphones are equipped with relatively capable accelerometers of their own. Could we collect PTS acceleration data that way?

A smart solution

We decided to try, using an iPhone 5 with a data-logger app (see Figure 2). Initial tests proved that the phone was capable of providing useful acceleration data – and, fortunately, weren't significantly damaged in transit. Experimenting further revealed that, although samples sent through various PTS routes experience shock forces of similar magnitude, the route of interest imposed 70 percent more shock force than any other (2). Our data suggested what others have also seen: that too many shock forces due to a long PTS route can contribute to preanalytical errors associated with sample hemolysis (3). What makes our study unique is that it's the first time that smartphones have been used to investigate shock forces in a medical center's PTS. And not only that – we also used the audiovisual recording and flashlight capabilities of two phones to actually see the effects of shock forces on blood samples as they travel through the PTS (see Figure 3). The resulting recording showed that the blood experienced marked turbulence, resulting in the formation of bubbles and foaming that may contribute to sample hemolysis and increased plasma LD activity (4).

There and back again

Others have already recommended that medical centers regularly monitor and adjust their PTS to ensure sample integrity (3), but we can now suggest a practical way of doing so. Using a smartphone makes this kind of monitoring possible for virtually every medical center with a PTS. We can check new and existing PTS routes for quality assurance purposes, particularly after maintenance, and investigate specific routes that we suspect may be compromising sample integrity (2,4). Since our initial studies, our smartphone technique has identified another PTS route at our medical center that may cause sample hemolysis – and by providing data for us to use in collaboration with our PTS provider, it has helped us work toward a solution as well.

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David Bruns is Professor of Pathology, Director of Clinical Chemistry and Associate Director of Molecular Diagnostics at the University of Virginia.

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Working with the IT Crowd

What exactly is "scientific computing" – and how can researchers and clinicians facilitate the most productive collaborations with computing departments?

By Peter Maccallum

"Scientific computing" is often treated as a catch-all term that means different things to different people. I define it as the application of computers to scientific research, which in a biology laboratory can mean one of three different things:

1. High-performance computing (for mathematics and large-scale data analysis)
2. Advanced data visualization (including 3D modeling)
3. Laboratory data management (sample tracking, data collection and analysis)

All three of these aspects are becoming increasingly commonplace as laboratories move toward digital work. In biomedical research, the volume of sequencing is skyrocketing – and we're doing a lot more image processing, mathematical modeling and analysis of large amounts of data, too. In pathology, as digital imaging and telepathology slowly encroach on traditional onsite methods, the demands for scientific computing are growing ever greater. But even with these advances, many users aren't well-acquainted with scientific computing. So who are we – and how can we best provide resources to the people in the laboratories?

A day in the life

In my department – IT and Scientific Computing for the Cancer Research UK Cambridge Institute – our days are spread across three sets of tasks. Firstly, we are responsible for operating all of the equipment. We have storage arrays; we have power-hungry supercomputers; we have standard and high-end workstations; and, of course, we run all the networks – from high-performance right down to the wireless setup everyone uses. We have to keep everything running smoothly, monitor performance, handle security, and deal with any incidents. If you manage your own home network, you can probably imagine that it fills up a lot of time…

Secondly, in response to what the scientists need, we have to build new systems. That means buying new storage systems, building new servers, replacing the high-performance computing systems… We're always working on large-scale infrastructure and software projects, which is how we not only stay up to date with technological advancements, but build in growth as well.

The third thing that we have to do – because we're not always replacing last year's equipment with this year's version of the same thing – is keep abreast of the latest developments in high-performance computing, networking and software, in particular. Most of our customers are biomedical scientists, and the techniques they use change very rapidly. We have to make sure that we provide the right systems to support those techniques. So we spend quite a lot of our time looking one step ahead, whether it's investigating graphics processing unit (GPU) computing for visualization or considering low-energy computing to grow our data center. We study any area with significant change, so that we can bring that knowledge back to the Institute.

What do we compute?

Most of our high-performance computing resources support the handling of large DNA sequencing datasets – of which there are many. All sequence data has to be aligned to reference genomes and then interpreted, which takes up the bulk of our CPU hours. Less common are the mathematical tasks we undertake, including Bayesian modeling, systems biology, and data visualization at the single-cell level. The latter is key because it helps us better understand diseases like cancer. We have new imaging platforms that allow us to unpick the real-time behavior of single cells and to reconstruct three-dimensional tissues down to the subcellular level. It's both visually impressive and medically fascinating.

But the real workhorse is still genomics. We generate tens of terabytes of genomic data every week, so the machines must run 24 hours a day to keep up with analysis of the pipeline. Over the last decade or so, genomic data has represented around 80 percent

At a Glance

- *Scientific computing involves high-performance analysis, advanced visualization and modeling, and day-to-day laboratory data management*
- *Those who work in scientific computing divide their time between providing research services and designing and building new technology infrastructure*
- *Laboratory medicine professionals should never be afraid to ask questions about their data, networking, or infrastructure capabilities – especially before buying expensive equipment*
- *Microscopy has the capacity to generate more data than sequencing – and as science and medicine become more data-heavy, the paths of pathologists and computer scientists will cross more frequently*

of the data produced and processed here at the Institute, and it's about to ramp up; the next generation of equipment can generate data at a terrifying rate – one that will actually push the boundaries of modern networking capabilities.

Conversely, microscopy has traditionally been very human-driven – a pathologist was always needed to manually examine and annotate the images. But it's amazing how much microscopy has advanced. We used to be limited by the diffraction barrier, but now? So many techniques bypass it that it's rarely even mentioned anymore! Even with a light microscope, we are able to see single cells in incredible resolution – and combined with other techniques, we don't need to stop at just one cell; we can do hundreds at once. We're still catching up to our own capabilities in that respect, because our old, familiar techniques – counting, measuring, highlighting – are time-consuming. It's all well and good generating 100 cells' worth of data in a single microscopy session, but without a computer to analyze the data at the other end, there's little point – the limiting step will always be the pathologist. Once you have the algorithms and automated techniques to make it worthwhile, though, microscopy could easily generate more data than sequencing. I think we'll soon see new imaging platforms that are much more heavily automated than previous generations.

Know your needs

The Cambridge Institute has a dedicated scientific computing department in part because we don't expect biomedical scientists to know everything that can be done with technology. Our role is to understand just enough about the biology and the available technology to help researchers identify their needs and design their ideal system. Right now, for instance, one research group is buying a new light sheet microscope, so we're discussing storage, analysis, and workstation options – along with anything else they may need to know. My team's approach is to maintain a close working relationship with scientists and clinicians so that we can let them know what's possible – and what's not.

"It's all well and good generating 100 cells' worth of data in a single microscopy session, but without a computer to analyze the data at the other end, there's little point – the limiting step will always be the pathologist."

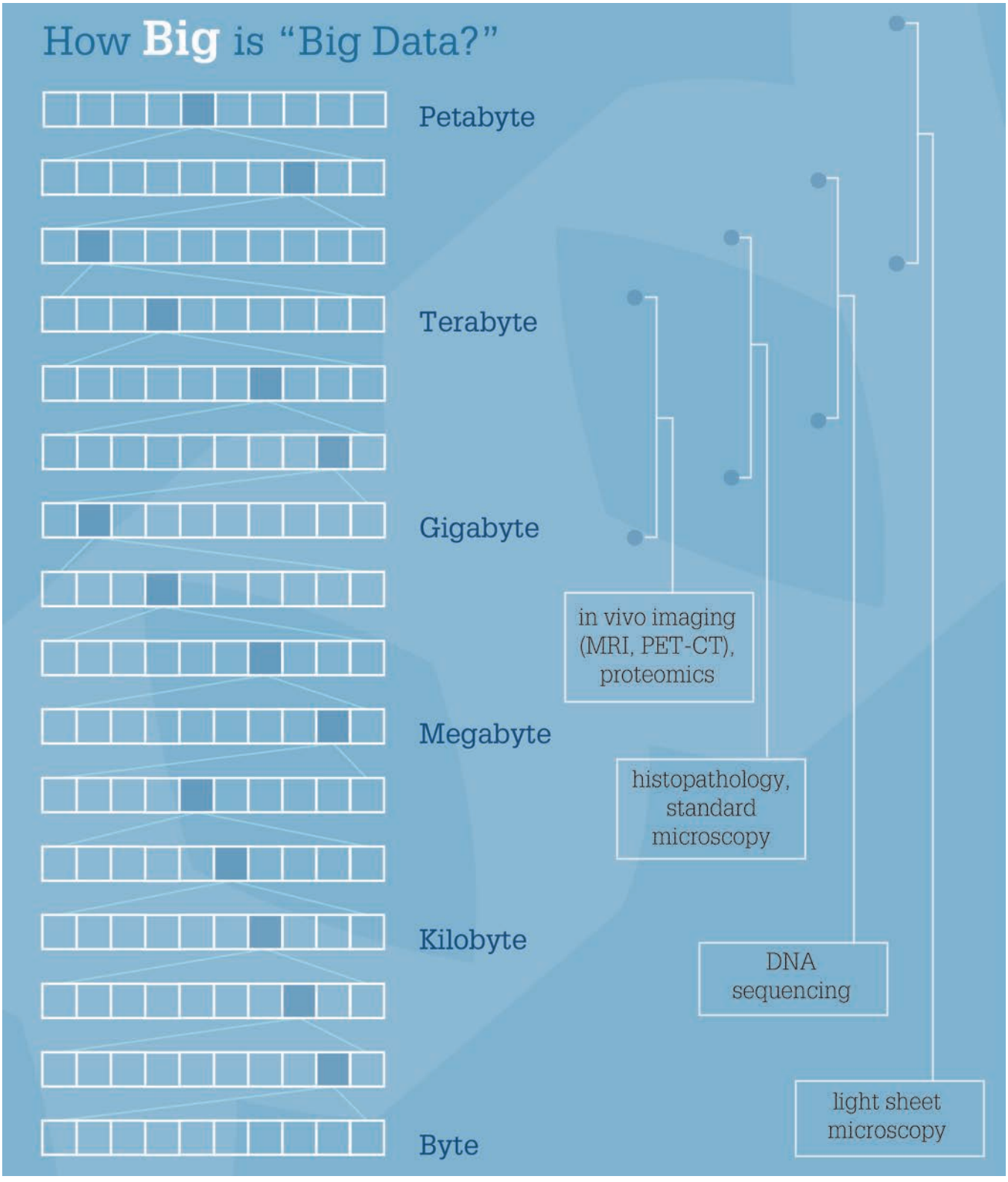
The other thing we're seeing, especially in genomics, is a shift in the way research groups are structured. Gone are the days when a group was entirely composed of biologists, maybe bringing in a statistician for mathematics-heavy work. Nowadays, successful groups always have at least one bioinformatician for analysis and data management, which also avoids the need to partner with an analysis team that can increase miscommunication or dilute the author list on an eventual publication. I don't think we are quite at the stage where every research group needs someone who can build their own computer architecture. Why? Because, no matter what you're researching, there's almost always someone at least one step ahead of you – and most of them are perfectly happy to talk about their technical architecture. All you have to do is ask questions, which is something we do on behalf of our researchers.

Practical computing

That said, there is definitely an argument for having all life sciences researchers trained in at least basic bioinformatics. Not very long ago, you could probably get away with being a biologist or a clinician without knowing statistics (though if you had a good grounding, you would go further and faster). PhD students used to have a couple of spreadsheets of data and a few images to analyze; now, it's a couple of terabytes of data and a few thousand images. You can't do that manually, so data manipulation is now a standard part of any biomedical researcher's toolkit.

If you're looking to move into data-heavy research, don't assume you need to know everything about computer science. Focus on the skills you need. You can often figure out what those are by seeing what others in your field have learned. Then, start with something you're going to use. Don't go off and learn how to program in C++ if what you need to do is manipulate files and analyze data. Tools like PERL, PYTHON and R are designed for biologists – they're a good way to get into scientific computing. Once you're familiar, you can begin to understand how much you can do with the available tools and to what extent your unique needs may call for something more advanced. Even in the latter case, don't jump in at the deep end. Start with a bioinformatics course rather than going straight into computer science studies. Learn skills that follow on from what you already know.

The key benefit to scientific computing is that you can design experiments that generate a lot more data. For example, in


How Big is "Big Data?"
Petabyte
Terabyte
Gigabyte
Megabyte
Kilobyte
Byte
in vivo imaging (MRI, PET-CT), proteomics
histopathology, standard microscopy
DNA sequencing
light sheet microscopy

the days of Sanger sequencing, you had to establish a very simple hypothesis and be careful about what you chose to sequence. Now, you can look at clonal mixtures in cancer, see the signature of each clone, and work out their relative amounts; you can create complex mathematical models for causally driven experiments; you can examine effects down to the cellular level. In other words, your experiments can be more powerful, allowing you to generate great amounts of data in parallel – and that makes your science much more quantitative, gives your hypotheses better support, and may even allow you to discover things you didn't know to look for.

The downside? As you acquire more data, the likelihood of losing discoveries in the noise and complexity is much higher. Therefore, you need access to far better mathematical modelers and statisticians than in the past to help you pick out the interesting things. The good news is that, with the increase in data volume, there are many more of those interesting things than before!

Working with your computing department

I came from a chemistry and physics background where the line between my discipline and computer science was always blurred. When I first started biomedical research, there was a gulf between the biologists and clinicians and the bioinformaticians and computer scientists. But the gulf is narrowing fast; firstly, because the general population is much more computer-literate and secondly, because quality (and therefore publishable) science nowadays demands complicated analyses of large datasets. Successful research groups know they need mathematical, statistical and programming expertise, so they either learn the skills or partner with someone who already has them. People no longer knock on the scientific computing department's door with basic computing questions; they come to us with large-scale physical infrastructure needs.

There are two things I'd like people to consider: one, those in scientific computing are there because they're interested in science – otherwise, they'd be working in a bank. There can be a tendency to bring problems to us only at the point when they've become technology issues, rather than higher-scale computing problems. I'd like our research and clinical colleagues to know that it's never too soon to involve your computing team in the design of your experiments and systems. And two, never, ever buy expensive lab equipment without asking some hard questions about the type of data it's going to produce – and whether you have the infrastructure to support it. Look at the infrastructure others in the field have put in place to get an idea of the scale of computing you'll need. And don't wait until after you've bought the device before you talk to your computing providers about whether your network and systems can cope with it. When our first next generation sequencers arrived, we had to completely change the IT infrastructure of the building; now, as our new microscopes arrive, we're having to do it again. Those kinds of changes have a big impact on us – so don't let a salesperson sell you a new technology. Get the opportunity to see it in someone's working environment first, so that you can anticipate the infrastructure changes it will necessitate. Talk to them, and then talk to us!

What lies ahead

One big challenge for the future is that there are not enough computing people with life sciences skills. The next generation of bioinformaticians and image analysts will increasingly have to take on the role of scientific computing expert. In the physical sciences, researchers have always done their own analytical computing, and I think that will increasingly become true in biology and medicine. Computer scientists understand computing, but we don't necessarily understand the techniques biomedical researchers use or how best to apply them. As technologies on both sides advance, we'll have to work more closely together than ever.

Another challenge is the sheer amount of data. We'll have to store it, move it, back it up, and make decisions about what and when to keep or discard. There are technologies that can cope with it all, but they're not all necessarily in the same place – so we have to use something most people have heard of, but fewer understand: "the Cloud." Users have to learn that the Cloud is not a single place; it's many places, and you have to build up a mental map of where your data is, where you need it to be, and how you can get it from one place to another. And if you're not sure, ask your computing department! People should never be afraid to ask where their data is and how they can access it. Sometimes, just understanding what's going on can save you a fortune or a lot of time – or prevent a data loss disaster.

On the whole, the future of scientific computing looks good. We're seeing a shift from CPU to GPU computing, which means that computations that now take minutes should soon take only seconds – although we'll have to stay on top of the change (GPUs require very different programming; analyses that work on current computers will need to be ported to these new technologies). Changes to memory hierarchies are also underway, which means that people's interactions with computers, from simple email all the way to high-level image analysis, will become much faster. Data storage technology is advancing rapidly – driven by Facebook and YouTube, of course, but we in science benefit from it as well! I'm looking forward to seeing how the paths of researchers, clinicians and computer scientists converge over the next few years – and excited about the knowledge we stand to gain as a result.

Peter Maccallum is head of the IT and Scientific Computing team at the Cancer Research UK Cambridge Institute, Cambridge, UK.

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DNA on the Cutting Room Floor

CRISPR technology has revolutionized genomic editing – but is there still a place for first-generation tools?

By Charlotte Barker

There's no doubt CRISPR (clustered regularly interspaced short palindromic repeats) technology has been a game changer for genome editing. Cheap, easy, and efficient, it has resulted in an explosion of research in the field, with scientists using the new tool for everything from studying the origins of cancer to developing diagnostic tests to differentiate between strains of the Zika virus. However, it is by no means the first or only technology to allow genome alteration. And though CRISPR may be the "latest and greatest", it isn't necessarily the best option for every application.

There are three main categories of engineered nucleases on the market: zinc finger nucleases (ZFNs), transcription activator-like effector nucleases (TALENs), and CRISPR. All are targeted "genomic scissors" that combine an engineered DNA-binding protein with a DNA-cleaving enzyme to make a double-strand break at a specified location in the organism's DNA. After the relevant sequence has been snipped out, the breaks are sewn neatly back together by the cell's own repair machinery.

"It is a very exciting time for people like me who are interested in genome editing and now have access to this great toolkit," says Jon Chesnut, Senior Director of Synthetic Biology and R&D at Thermo Fisher Scientific.

DNA scissor debut

ZFNs were the first onto the market and opened up a whole new world, recalls Supriya Shivakumar, Head of Strategy and Portfolio Development, Gene Editing and Novel Modalities at MilliporeSigma, which licenses the technology for research use.

"We already had the ability to downregulate genes using RNA, but we were missing a piece of the puzzle – the ability to knock out a gene entirely," says Shivakumar.

Each zinc finger recognizes three or four bases, and by combining these modules in different configurations, almost any sequence can be targeted. ZFNs are heterodimers, with the zinc fingers joined to a FokI endonuclease domain that cleaves the DNA. FokI will only produce the desired double-strand break when dimerized, which increases specificity by ensuring that cleavage only occurs when two DNA-binding events occur together.

ZFNs cannot really be described as "do-it-yourself" technology – they are time-consuming and expensive to make, so most users turn to vendors for custom-made solutions. "ZFNs are hard to get completely right. We have an archive of experimentally-derived information, and without it there is a real chance that longer nucleotide recognition sequences won't work," says Shivakumar.

An alternative to ZFNs became available in the late 2000s – TALENs. They harness plant pathogen proteins (TAL effectors) for DNA binding, again linked to a nuclease that snips the DNA.

> *"It is a very exciting time for people like me who are interested in genome editing and now have access to this great toolkit."*

TALENs are built from arrays of 33–35 amino acids – each array targets a single base pair. Constructing DNA-binding domains with TALENs is less complex than with ZFNs, meaning that labs can save money by creating their own. However, they are large molecules, which can make them difficult to deliver efficiently, and still require a level of skill to engineer.

CRISPR fever

"TALENS and ZFNs are expensive and time-consuming, and so are typically used when you want to create a specific cell line. What was missing was the 'what if?' – the ability to play and explore," says

At a Glance

- *CRISPR has been a game changer for genome editing; it's cheap, efficient and has propelled the field of translational science*
- *It's not the only tool out there for genome alteration, though; zinc finger nucleases (ZFNs) and transcriptor activator-like effector nucleases (TALENs), have their place in the genome editing toolbox, too*
- *Though expensive and time-consuming, ZFNs and TALENs are well-established technologies that have proven effectiveness, with no off-target effects or toxicity. The ongoing patent dispute over CRISPR/Cas has also introduced uncertainty around the technology*

Shivakumar. Enter CRISPR/Cas.

CRISPR/Cas originated as a form of adaptive immunity in bacteria. When a bacterial cell is infected, short sequences of the viral genome (CRISPRs) are incorporated into the bacterial genome. CRISPR-associated (Cas) proteins process these sequences and attack the virus by cutting matching DNA sequences in the viral genome. By engineering plasmids encoding both CRISPRs and Cas, a hugely efficient genomic editing tool is created.

"The biggest benefit to CRISPR/Cas is ease of design," says Chesnut. "You can change the specificity of the nuclease just by changing the sequence of a small piece of RNA, which has really opened up genome editing."

Most labs are very comfortable with the technology; as Shivakumar puts

Precarious Patents

The well-publicized patent dispute over CRISPR/Cas looks set to run and run

Although the sequences were first described by Osaka University researchers in the late 1980s, the term CRISPR wasn't coined until the early 2000s. The potential of CRISPR/Cas in genome editing became clear when University of California, Berkeley (UCB) researcher Jennifer Doudna and collaborators published work in 2012 showing that they had reprogrammed the system to target specific sites in bacterial DNA. In early 2013, several groups, including one led by the Broad Institute's Feng Zhang, reported that the system also worked in eukaryotic cells, including human cells. Both UCB and Broad Institute have filed patents covering the fundamentals of genome editing by CRISPR/Cas, and licensed them to a number of companies. Now they are locked in a fierce dispute through the US Patent and Trademark Office (USPTO) and European Patent Office.

It's thought the proceedings may drag on for years as the authorities try to determine whether the use of CRISPR/Cas in eukaryotic cells was an obvious follow-on from Doudna's original work, or a separate (and patentable) breakthrough. The battle has become less diplomatic in recent months, with harsh words and accusations of impropriety being exchanged by the opposing institutions. Given the huge potential earnings for the institutions and their licensees, it seems likely that the fight will be a long and drawn-out one.

The mudslinging and high profile of the scientists involved has ensured that most of the attention has been focused on the foundational patents described above. However, a number of smaller groups have also filed important patents relating to CRISPR/Cas, including MilliporeSigma. "It's interesting that the whole focus has been on the dispute between these two major scientific institutes. I think there are some dark horses in this race," says MilliporeSigma's Supriya Shivakumar.

"The IP situation surrounding the newer technology could also prove a major headache for those looking to bring a CRISPR/Cas-based gene therapy to market."

it, "You can make CRISPRs in your garage." High speed, low cost, and impressive efficacy make CRISPR suitable for screening studies. For example, researchers can knock out thousands of different genes in cancer cell cultures to find out which are responsible for drug resistance. "That puts it in a different category to ZFNs and TALENs – you can not only study known targets, but find entirely new targets," says Shivakumar.

Many companies now provide off-the-shelf or custom-designed libraries for screening studies, says Chesnut. "We just launched our Lenti-based arrayed CRISPR libraries, and we hope to cover the entire human genome by early 2017."

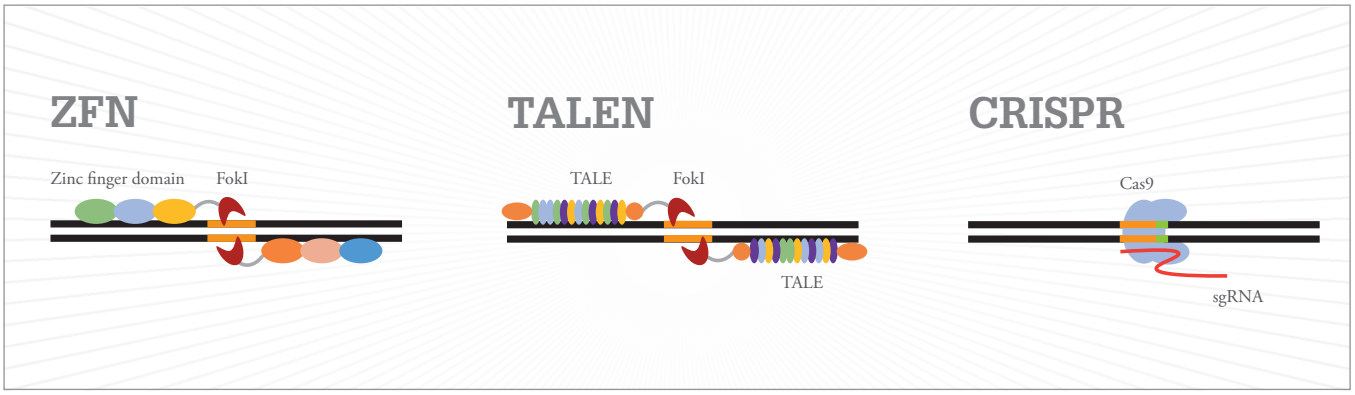
Shivakumar also notes the rise of library platforms: "We don't want to convince someone to buy CRISPRs from us if it is quicker and cheaper to do it themselves, so we haven't focused on making individual CRISPRs, but rather making whole-genome libraries with the Sanger–Wellcome Trust and the Broad Institute."

Ultimately, what makes CRISPR so exciting is the freedom it offers. "The 'sandbox' environment that CRISPR enables is where great leaps in science originate," says Shivakumar. "It has opened the door to a number of new technologies that we never predicted."

Cut to the chase

If CRISPR is the fastest, cheapest, and most efficient technology, why would you consider using ZFNs or TALENs? Well, there are some situations in which the older technologies actually work better, says Chesnut. "We know of applications where TALENs are technically more effective than CRISPR. In transcriptional modification, TAL effectors appear to be at least as efficient as CRISPRs in delivering transcriptional activators and repressors."

Particularly relevant to the translational field is the fact that CRISPR/Cas is still very much the new kid on the block. "With CRISPR, you can play. But once you have a target that



Mechanisms of ZFN, TALEN and CRISPR/Cas9 genome editing.

works, there are a couple of reasons to switch to a more established tool, such as ZFNs or TALENs," says Shivakumar. "ZFNs were one of the first technologies on the market and there has been a lot of work to show that there are no off-target effects or toxicity. It was one of the first to be used clinically, so there is a proven pathway."

The IP situation surrounding the newer technology could also prove a major headache for those looking to bring a CRISPR/Cas-based gene therapy to market. The ongoing patent dispute (outlined in "Precarious Patents") could be a source of unwelcome uncertainty for years to come. "We are watching the patent dispute around CRISPR closely, both in terms of how it may affect our customers, and as a fascinating view into how an emerging technology can stir up so much discussion. Scientists aren't usually so emotionally invested in the subject – at least in public," says Shivakumar.

"There's a significant amount of confusion about who's going to end up owning the IP rights for CRISPR, in contrast to the clear IP landscape for TALENs and ZFNs," says Chesnut. "It comes down to what your end goals are. If you want to create SNP-edited or knockout cell lines, certainly CRISPR seems to be the go-to. But if you are thinking further ahead and want to commercialize, then you have to consider IP."

Gene editing: the sequel

Will CRISPRs be all-conquering, or will they themselves be replaced by the next big breakthrough technology? What great advances in science and medicine will result? The field is moving so fast that it's hard to tell what the future holds. "Whatever happens – it's going to be surprising," says Shivakumar.

"Perhaps one day we'll have the equivalent of a Star Trek tricorder."

Gene therapy – a dirty word just a decade ago – is once again a major research focus, bolstered by the success of CAR-T cell therapy for cancer. "In our lifetime, I think we will see gene and cell therapy in regular use," says Shivakumar.

Genome editing is also finding applications in the pharmaceutical industry, creating in vitro models for drug safety and toxicity testing, and replacing RNAi screens for discovery. "We devote a lot of effort to working with pharma customers to use genome editing to create better cell screening models for drug discovery – both specifically edited cell lines and screening library approaches," says Chesnut.

Shivakumar believes that using CRISPR in detection technologies could have a big impact on day-to-day life. For example, farmers could grow plants that would change color to indicate nitrogen levels in the soil. In medicine, this could take the form of sophisticated sensors for disease detection and monitoring. "Perhaps one day we'll all have the equivalent of a Star Trek tricorder," she suggests.

However, lest we get swept away by the brave new world of CRISPR/Cas, Shivakumar also strikes a note of caution. "With the explosion of papers coming out, there has been a sense that if you tie your work to CRISPR, it will get a wider audience. So my advice to researchers new to the field would be to regard reported advances with a critical eye, and make sure you are using the right assay for your needs. No matter what you are doing – the better your assay, the better the process."

Charlotte Barker is Associate Editorial Director of Texere Publishing, publishers of The Pathologist.

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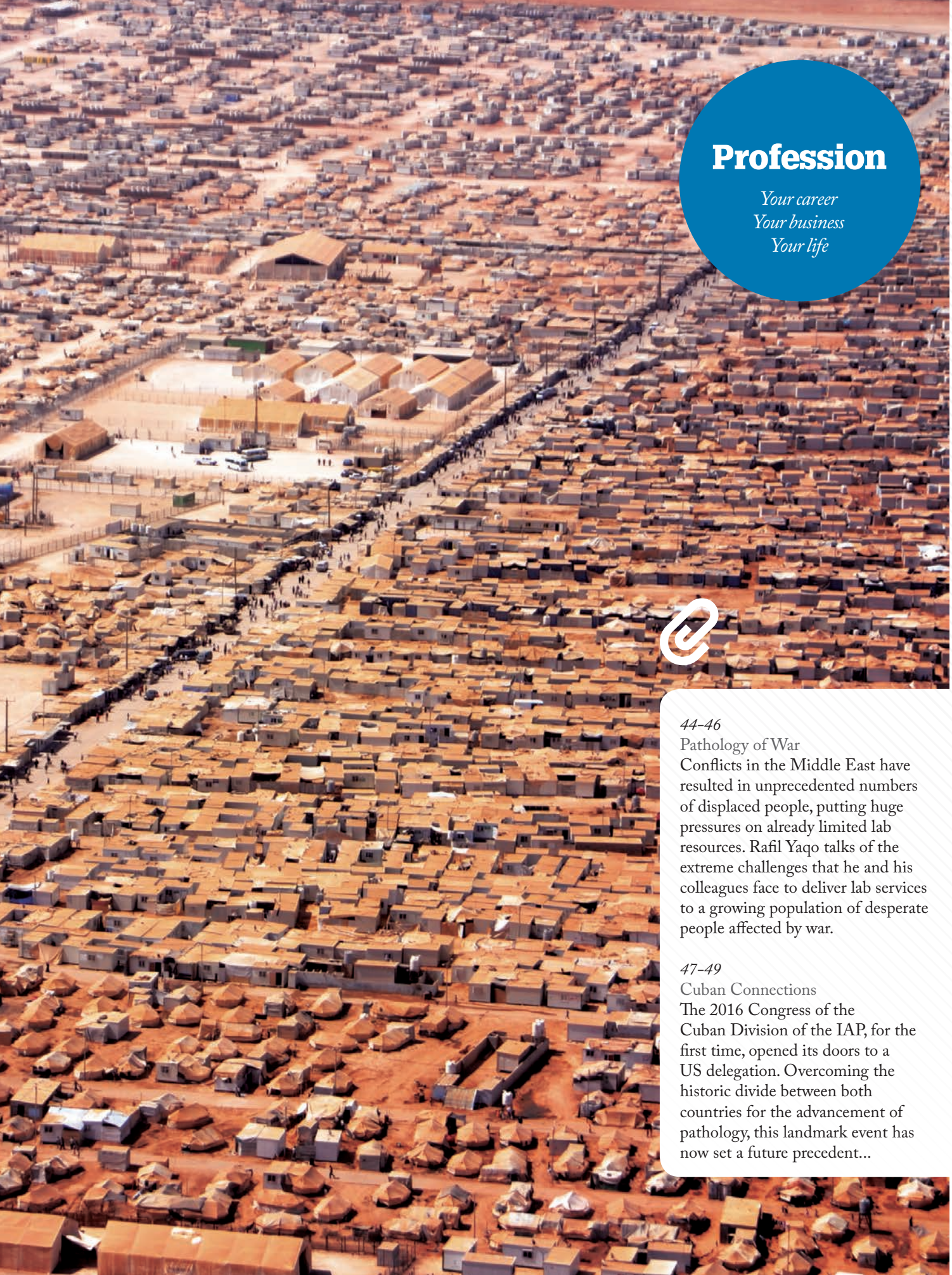

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Pathology of War

A despairing world has impotently watched destructive conflicts in Iraq and neighboring countries for many years. The inevitable outcomes include unprecedented numbers of displaced people and war casualties, and huge pressures on already limited resources, including in the laboratory...

By Rafil Yaqo

I was born in Nineveh (Mosul), and raised in the mountainous Duhok Kurdistan region of Iraq. It's the smallest province in Iraq, but you can find Kurds, Chaldeans, Assyrians, Arabs, Muslims, Christians and Yezidis all living and working there, so it's an interesting place. And it's full of history – there are caves and sculptures dating from the times of the Medes and Assyrians. I have a lot of beautiful memories from my childhood!

At a Glance

- *Duhok Province, which borders Mosul in northern Iraq, has seen its population grow by ~60 percent as people seek to escape the war*
- *This, together with budget constraints, has led to unprecedented demands on the Duhok Department of Health*
- *The Duhok Specialized Laboratory Centre healthcare professionals are highly motivated – but determination alone cannot replace medicines and ambulances*
- *Continued and extended support from UN agencies is vital if the needs of refugees and war casualties are to be met*

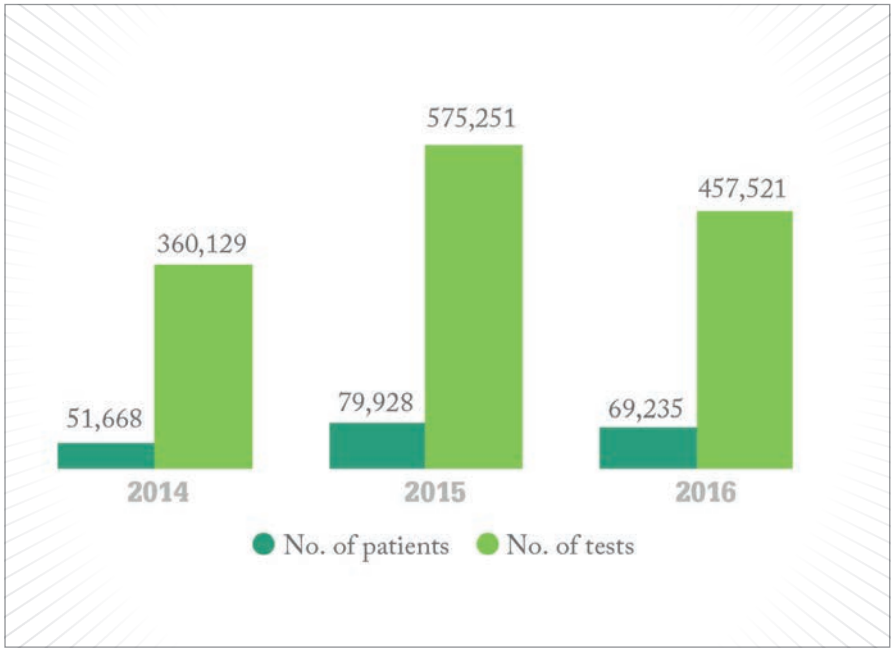


Figure 1. Number of investigations conducted in Duhok Specialized Laboratory Center from 2014–2016.

Unique specialty, unprecedented demands

I also remember that, as a child, I hated doctors, because of injections. As I grew up, however, I began to understand the important service physicians provide for the community. Eventually I came to admire them, and I ended up training as a doctor myself, and graduated from Duhok University Medical College in June 2000. During my studies, which included rotational internships in Azadi Teaching Hospital, I came to realize that pathologists are unique among specialists in that they help not just patients but also clinicians and surgeons, too. This decided the direction of my career, and after passing my pathology exams I joined the Duhok Specialized Laboratory Centre (DSLC).

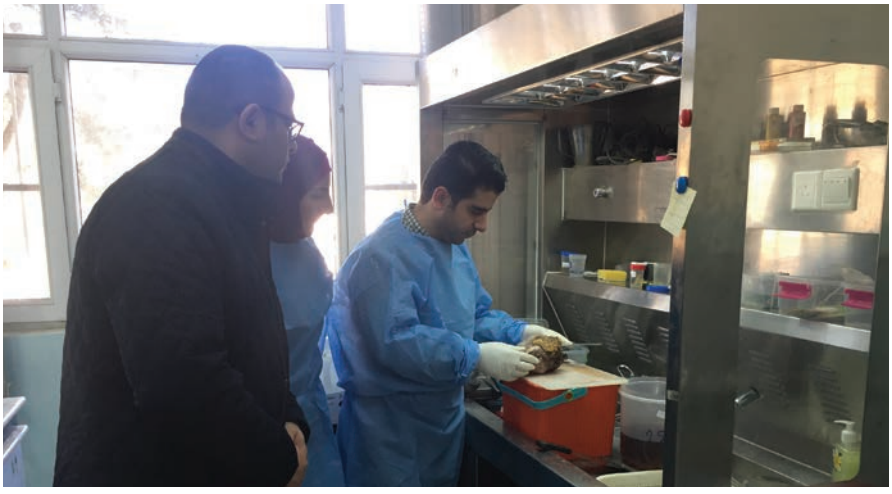
Together with Duhok University, the DSLC is the main site for training of undergraduate and postgraduate molecular biologists, biochemists and laboratory biotechnology specialists in Iraq. Its major role, however, is to process samples from primary health centers and hospitals throughout Duhok. This is a significant task, as Duhok has been a safe haven for internationally displaced persons (IDPs) since 1991. The IDP population has been increased even further in recent times, though, as a consequence of the ISIS / Mosul and Syria situations, such that Duhok's normal population of about 1.4 million now hosts an additional 0.74 million IDPs and 0.1 million Syrian refugees, including refugees from Sinjar Mountain. As a consequence, patient referrals have tripled compared with the original number of samples processed by the center (see Figure 1). This drain on resources has been exacerbated by the financial crisis suffered by the Kurdistan Regional Government since 2014.

It's tough, but it's personal

Unfortunately, it is the medical staff that bears the load in terms of dealing with war casualties, IDPs, and refugees – we keep our primary healthcare centers open 24/7, which is exhausting. However, we are highly motivated; some of my colleagues have family members in the Peshmerga at the front line, or relatives who have been

"Some of my colleagues have family members in the Peshmerga at the front line, or relatives who have been kidnapped or killed by ISIS."

Figure 2. Vaccine administration in Duhok province.



Rafil Yaqo overseeing a gross section assessment.

kidnapped or killed by ISIS. So we do whatever we can to help. In addition, we are not entirely alone; international and non-governmental organizations have had an important role in providing training, consultation and financial support to our staff, and that has been very helpful.

Much of our work involves administration of vaccines and provision of medical consultations and diagnostic tests so as to prevent outbreaks of communicable diseases like TB, measles, cholera and polio (see Figure 2). However, in addition to screening IDPs and refugees, and maintaining surveillance of communicable diseases, we have to diagnose and manage patients with chronic diseases like cancer. These are referred to a specialized centre in Duhok city which also looks after the indigenous residents. So DOH-Duhok, in spite of severe resource constraints, has succeeded in responding to the mass IDP and refugee crisis that has persisted since 2014.

Challenges do not end with war

Nevertheless, we face tremendous difficulties in view of the sustained and growing crisis (see Sidebar "Public Health Challenges in Duhok"). On one level, we endure ongoing challenges in terms of routine pathology. For example, we may see interesting cases which need a diagnostic test that is unavailable in the lab due to resource constraints; sadly, we can't always help these types of patient.

On another level, challenges arise from the increase in demand for health services due to a growing refugee / IDP population, and the increased numbers of war casualties we see as the Mosul operation proceeds. The burden on the host community is becoming increasingly difficult to bear: host public health facilities are overwhelmed with IDP and refugee patients, more than 70 percent of whom live outside camps. This is forcing host people to seek medical care at private health facilities, and has led to catastrophic levels of health expenditure for many families in the host community. Even if the war were to end tomorrow, it's likely

Public Health Challenges in Duhok

Current challenges

- DOH-Duhok operating budget is limited and has no provision for the large number of IDPs and refugees inside and outside camps and liberated areas
- Strategic health infrastructure projects such as hospital construction, have been suspended
- Medicines and medical and laboratory supplies are increasingly depleted; health infrastructure, facilities and medical equipment are over-used and inadequately maintained
- Providing access to health services in liberated areas remote from Duhok center is difficult, and complicated by weak coordination of DoH-Mosul with DoH-Duhok in terms of deployment of staff and medical supplies
- Healthcare personnel are exhausted due to personnel shortages and workload / overtime demands far beyond accepted norms

Anticipated challenges

- New wave of IDPs (500,000-1,000,000) expected during the liberation of Mosul
- This will result in additional resource challenges, increase the congestion in camps and raise the risk for communicable disease outbreaks
- Continued insecurity and potential for conflict in the Kurdistan regions outside the jurisdiction of Kurdistan Regional Government may lead to further challenges in healthcare resources and provision

that up to 40 percent of IDPs would stay in Duhok governorate for decades, unless their homeland infrastructure were rebuilt. Another 20 percent or more will probably never return to their place of origin in any case, regardless of infrastructure investment. Furthermore, there remain many unsolved problems in this region, and we are concerned that these may trigger other conflicts.

International support is good, but not good enough

So the problems we face are not limited to the short-term. Against this background, it is clear that international and UN organizations are very important. They provide supplies of drugs and consumables, funds for construction of new primary health centres and purchase of ambulances, resources for vaccination campaigns, training for medical staff – for example, on how to deal with war injuries – and advice to help the Peshmerga prepare for possible chemical attacks by ISIS. This is all enormously helpful, and I would like to thank all of these organizations for their continued support of our institutes and staff during this critical period.

Even so, it has to be said that the support that we get does not fully meet the urgent needs of IDPs and refugees. Furthermore, INGOs and UN agencies don't focus on host infrastructure, and in consequence we find it increasingly challenging to maintain existing health service provision in the host community. As mentioned, over 70 percent of IDPs live outside camps and seek medical care at host health facilities where infrastructure and equipment are sparse and staff are exhausted. Many anticipated capital-intensive projects have been suspended, including hospitals for emergency, cancer, and obstetrics and gynecology. We urgently need these projects to be funded so that we can sustain the existing health services at host facilities. Additional resources would be very helpful, but we should also consider doing more with what we have; for example, separating public and private health services would avoid duplication of practice and thereby reduce unnecessary expense.

Under these circumstances, we would urge continued international support not only for IDPs and refugees but also for the host community. This will help to maintain equity of access to health services for all residents in Duhok governorate. Support for regional and central government to maintain security and overcome the financial crisis is crucial to prevent future conflicts and disease outbreaks.

So it's true to say that our circumstances are not easy; but even when faced with such large challenges, I take comfort in remembering that the small things remain important: the support of family and friends, and the satisfaction of helping each patient, one by one.

Rafil Yaqo is Director of the Duhok Specialized Laboratory Center (DSLC), Duhok Health Directorate, Duhok Province, Iraq.

Cuban Connections

Bridging a historic divide for the advancement of pathology

By Robin Stombler

"While it is no easy task, it is my responsibility to update you on the development of our specialty in our country,"* explained Professor Israel Borrajero Martinez, President of the Organizing Committee of Patología 2016. A routine, even blasé, reporting for many medical leaders, this unveiling of the state of pathology in Cuba was remarkable and awe-inspiring. I was fortunate enough to be seated on the dais at the Palacio de Convenciones in Havana, Cuba when Borrajero spoke these words in November 2016.

At a Glance

- *The Congress of the Cuban Division of the International Academy of Pathology in November 2016 welcomed, for the first time, an official US delegation*
- *This "first" was spearheaded by the American Registry of Pathology (ARP) in an effort to cultivate medical education exchanges between the two countries*
- *A previous attempt for visa entry into the restricted country had been denied, but perseverance paid off and a portion of the 2016 Congress program was delivered by the American delegation*
- *This landmark occurrence has truly opened up the dialogue between these two countries and provided an important opportunity for mutual learning, sharing of knowledge and improved patient care*

Cultivating Cuban-US relations

The Congress of the Cuban Division of the International Academy of Pathology, or Patología, was not a new endeavor. In fact, this is the fourth time this biennial event was held. It was the first time, however, that the United States attended as a delegation since there has been a move toward normalization in relations between Cuba and the US. This delegation was conceived and led by the American Registry of Pathology (ARP).

Agustin Chong Lopez, President of the Sociedad Cubana de Anatomía Patología, in opening the medical conclave, explained that participation from American colleagues took many years to materialize.

In fact, about seven years ago, William A. Gardner, Jr., ARP Executive Director, casually mentioned that he thought it would be a great idea for the ARP to travel to Havana to communicate with Cuban pathologists. Gardner was a whirlwind of ideas, especially when it came to the global sharing of pathology knowledge. ARP, under his direction, donated its Atlas of Tumor Pathology and Atlas of Non-Tumor Pathology to areas of the world where access to such information was difficult to come by. Now he wanted to assemble a group of prominent American pathologists to enter a restricted country. He tasked me

and my firm, Auburn Health Strategies, as his accomplice.

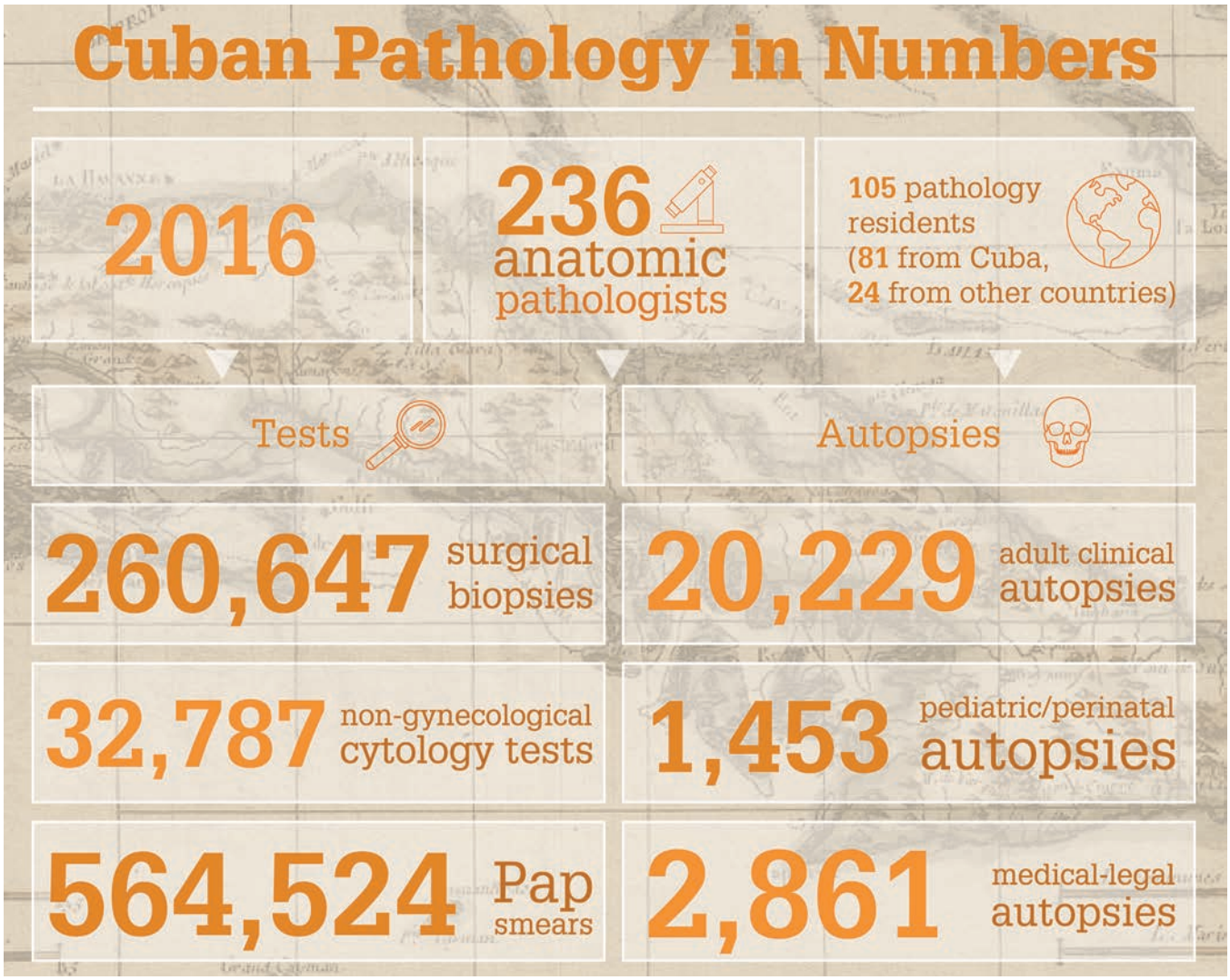
Unchartered territory

While we are accustomed to devising and implementing big ideas, this one involved two countries that were not particularly interested in normalizing relations for the sake of pathology. This did not inhibit Gardner's enthusiasm, though; on the contrary, it incited it. So, we went to work in establishing crucial relationships with Cuban pathologists and diplomats, creating a roster of potential US pathologists to invite, and beginning the process of obtaining visas to travel. Despite these efforts, our request to travel was denied.

So, Gardner vowed to try again, but he passed away before his mission was accomplished. ARP, its Board of Directors and new Executive Director, Cynthia Thomas, agreed to continue the quest.

The ARP is known in the pathology community for its support of preeminent collections of pathology specimens, scientific peer review and educational programs and publications. Its vision is to expand global knowledge of pathology and science. Its role in Patología 2016 was to present and share scientific topics with colleagues from Cuba and other Latin and South American countries.

Members of the ARP delegation making presentations included Peter Burger, Stephen Cina, Brad Goskowicz, Charla Marshall, Dennis O'Malley, Elizabeth Montgomery, Stuart Schnitt, and Robin Stombler. Topics ranged from pathologic diagnosis of central nervous system tumors; medical autopsies; infectious disease standards; best practices and emerging trends in DNA analysis; lymphomas;



myeloproliferative disorders; spindle cell tumors of the gastrointestinal tract; breast lumpectomy margin evaluation; and laboratory quality. G. Frederick Worsham and Thomas rounded out the delegation.

Out of mutual respect for pathology education, ARP presented to Cuban colleagues a significant number of fascicles from its Atlas of Tumor Pathology and Atlas of Non-tumor Pathology. In underwriting this gift, Microbiologics, a Minnesota-based company, noted that "its mission to create a safer, healthier world just expanded through this important collaboration."

"Cuba maintains a national medical autopsy rate of 50–60 percent, which is 20 times higher than our own."

The state of pathology in Cuba

Borrajero, who was declared a national hero in Cuba for his tenured work in the science sector, explained that while some medical specialties flourished in the period prior to 1959, anatomic pathology in Cuba was only represented through 13 laboratories or departments, of which seven were for autopsies. These departments were distributed in the provinces of Santiago de Cuba, Camagüey, Holguín and La Habana. He noted how these departments were directed by autodidact pathologists. Some, through intelligence and dedication, rose to the status of professors.

In the 1960s and 70s, a process of creating and strengthening hospital centers in Cuba began. New hospitals in various provinces emerged with new departments of anatomic pathology. In parallel, an accelerated program for the training of medical and technical staff was developed. Consequently, in 1963, a restructuring of the undergraduate teaching of the discipline was carried out in the Escuela de Medicina de la Universidad de La Habana. Those young interns and student assistants at the time, who remained in the country, formed the foundation for the new age of pathology. Many are the senior leaders of the profession today.

With the development of these new medical faculties, hospitals and health programs, a growth in the qualitative and quantitative approach to anatomic pathology was realized. Twenty-eight departments of anatomic pathology were created by 1965 as well as the first official residency program for anatomic pathology and a training program for laboratorians, which we refer to as medical laboratory scientists. By 1986, there were 78 departments, which we would refer to as laboratories, in the country and 190 pathologists. And today, Cuba boasts 236 anatomic pathology specialists and an increasing number of residents (see Infographic).

Sharing goals and gains

Both ARP and the Cuban pathologists have expressed an interest in continuing this important dialogue. While pathology and laboratory programs in each country are structured differently, there is a common thirst for knowledge.

We can learn from one another. Per capita, it appears that Cuba performs more autopsies than the United States, and uses that knowledge to improve clinical care for the living. Stephen Cina, CEO of Cina & Cina Forensic Consulting in Loveland, Colorado, explained, "Cuba maintains a national medical autopsy rate of 50-60 percent, which is 20 times higher than our own. They recognize the value of the autopsy for patient's families and the advancement of medicine."

Yet, molecular pathology, as utilized by American pathologists, is a relatively new field for Cuba. Dennis O'Malley, Adjunct Associate Professor at MD Anderson Cancer Center/ University of Texas and a Pathologist with Neogenomics Laboratories, noted the "clear interest in innovation" from Cuban pathologists.

G. Frederick Worsham, President of Charleston Pathology in Charleston, South Carolina, remarked on the similarities between US and Cuban pathologists noting both "see their role as central and essential to cancer management."

As Borrajero summed up, "We now have the responsibility to look to the future. The integration of classical and modern technology with the principle that diseased cells and tissues are the responsibility of the pathologist."* He added that the true duty of pathology is the patient. To that end, we can all agree.

**Translated from Spanish*

Robin Stombler is President of Auburn Health Strategies, Arlington, Virginia, USA.

Mother of Ambition

Sitting Down With...
Tania Roskams, Chair of the Department of Imaging & Pathology, Head of Translational Cell & Tissue Research and Professor of the Faculty of Medicine, University of Leuven, Belgium

What attracted you to liver pathology?

I've always had a great interest in research; I was intrigued by what was happening in tissues and cells, and pathology allows you to see it all. I put my interest in liver pathology down to coincidence. During my first year of training, I was working on a liver biopsy when I came across some unusual cells alongside a liver tumor that had never been published before. They turned out to be neuroendocrine features of bile ductules. Although accidental, this was a very important discovery; I had shown special characteristics of potential stem cells in the human liver. My research was published in the American Journal of Pathology and I decided to start a PhD thereafter.

You then focused on the role of stem cells in liver cancer formation...

Right. I also studied their role in liver regeneration. It was during a period when there was a lot of hype around stem cells, but convincing people that they existed in the human liver was not easy – no one believed it at first. Some years later, I led a consensus panel on a standardized classification of liver stem cells, and later another to develop a standardized classification of pre-malignant lesions with rationalized nomenclature. This was challenging, in particular because tumor classification criteria were quite different between the Far East and the West, and the threshold for tumor resection in the Far East was much lower. Reaching a consensus was a major achievement.

How do you approach management of imaging and pathology under one umbrella?

Close interaction is the key to its success. For example, directly comparing pathology analyses with radiology images of tumors allows us to provide a more accurate diagnosis – and it supports research, too. Furthermore, pathology and radiology are service-driven professions; it's so important that we speak up and defend our disciplines because we can easily be outvoiced by clinicians who feel their opinions are more important than those who "just look down a microscope."

I plan to encourage more collaboration in my new role, hopefully by incorporating other imaging departments, including animal imaging. It's really important for pathologists to recognize that they are at the interface of basic research and clinical application – translational research is a key role for us.

"We have to work much harder than our male colleagues to prove ourselves."

How can pathologists keep up with the many advances?

It's impossible to follow it all. I see a big role for academic centers that are capable of super-specializing in one organ. In our institute, we have clusters of organ specialist groups and we have an obligation to pathologists and clinicians to attend conferences and educate them in the diagnostic developments in those particular organs. An advantage that we have as pathology educators is that, compared with clinicians, we are less dependent on industry, which I think is important, especially when it comes to the integrity of our research and the interpretation of results.

You are mayor of your hometown, you have a working farm, and you've raised three children – how do you do it?

Many women do it – it's basically down to good time management. Admittedly, pathology is a good career for those women who want to combine it with motherhood, as you can work effectively from home. I'm the type of person who always likes to take on numerous responsibilities. In my tenures on the committees of the European Association for the Study of the Liver, and the European Gastroenterology Federation, I often had to travel in Europe and overseas for meetings. I served on those boards for the maximum term, and when that was over I thought, "I've got some spare time now," so I put myself forward as a candidate for mayor and I was elected. It's very rewarding to be able to accomplish projects – like building new schools or integrating heritage into housing projects – in your own local environment.

Is gender inequality still an issue for women in science?

Absolutely! It's a big problem; we have to work much harder than our male colleagues to prove ourselves. You really have to be committed to your job and I don't think that women who have families want to travel quite as much as I did. But if you like your job, you can do it!

I managed my work/life priorities by taking my children to every overseas meeting that I attended. When I was working in the country, I had home-based childcare initially, and I would coordinate any late night working with my husband. It wasn't always easy, but having a supportive partner helps.

How can the inequality gap be narrowed?

The more women we have in senior positions, the more likely it is that certain common working practices will change to support a good work/life balance. Women are still in the minority though, especially in academia. I would like to encourage our younger female colleagues to aim high. My top piece of advice is: don't labor over the consequences of having a good profession and a family. If you think about it too much, you will never push yourself to have both. Just go for it and you'll find solutions as you go.

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