OCTOBER 2015 # 12

the Pathologist

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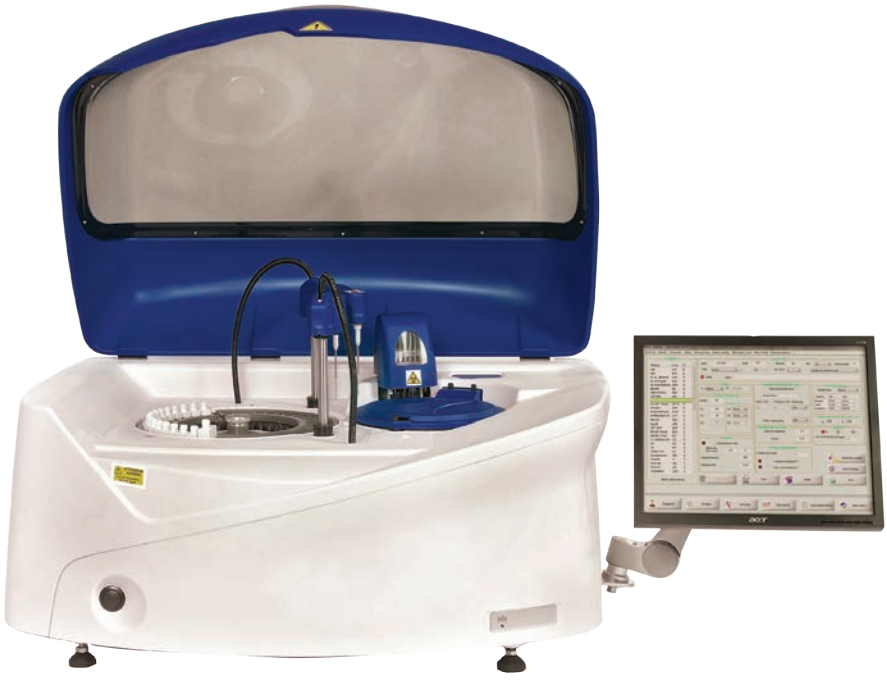

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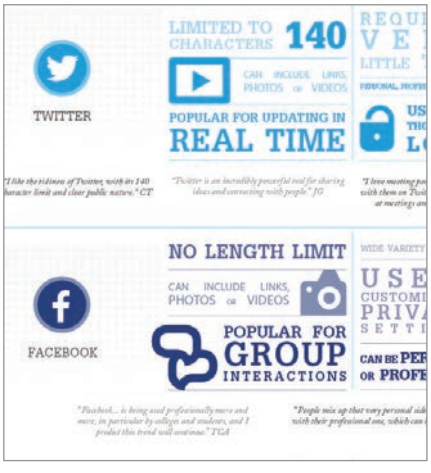

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Sitting Down With…Sharon Weiss, Professor of Pathology and Laboratory Medicine @emoryhealthsci
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Sara Jiang, MD @Sara_Jiang
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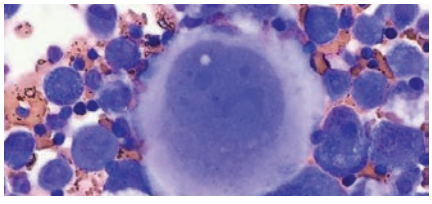

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#ESP President Han van Krieken on the changing face of #pathology:
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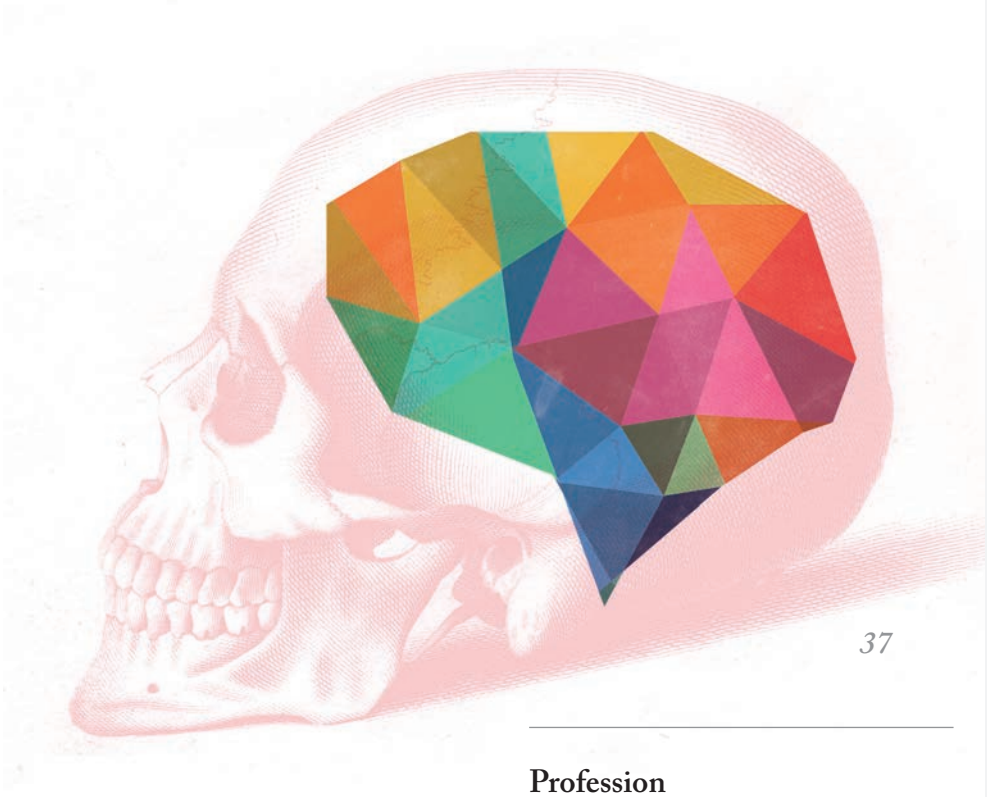

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Profession

Sitting Down With

the Pathologist

ISSUE 12 - OCTOBER 2015

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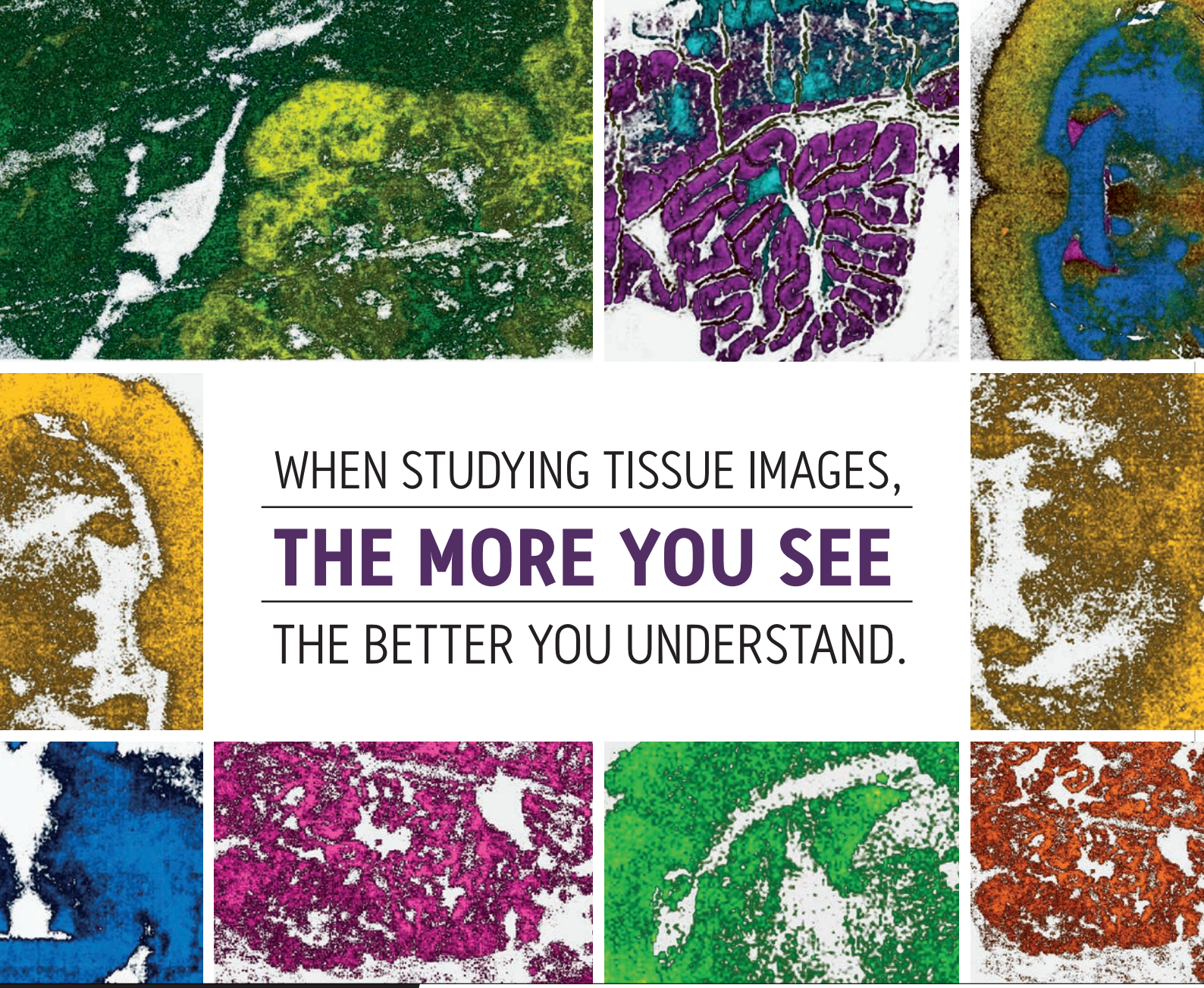

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Coming to a Cinema Near You…

…the story of the pathologist who rattled the US sporting world

We've made it one of our missions to highlight and tackle (pun intended) the low public perception of pathology, the damaging consequences of poor awareness (or complete lack thereof), and the urgent need for positive promotion of the field. So when I learned of a new movie that features Hollywood A-lister Will Smith as a pathologist, I thought: Bingo!

The story of Bennet Omalu, a man who battled against the odds in a quest for a diagnostic breakthrough, clearly caught the eye of the film star. What were those "odds"? Well, just the might of the most powerful and lucrative sports league in the world. The untimely death of 50-year-old, former National Football League (NFL) player Mike Webster – and the autopsy performed by Omalu – led to the discovery of a new condition: chronic traumatic encephalopathy (CTE), which he linked directly to the trauma induced by the sport. Not a typical day in the office; the autopsy changed the course of Omalu's life.

Unsurprisingly, his research came under intense criticism from the NFL, which accused him of fraud – the first of many attempts by the sporting body to discredit and quieten the doctor. And it didn't stop there. In a 2013 interview with FRONTLINE, Omalu stated he had been accused of attacking the "American way of life" (1). His Nigerian heritage featured quite heavily in the abuse that he received from angry sports fans. Undeterred, Omalu continued his research and uncovered many similar cases. Unable to fight the evidence any longer, the NFL finally relented, stating in federal court documents that it expects nearly one in three retired NFL players to develop long-term cognitive problems at "notably younger ages" than the general population (2).

Even President Obama has openly admitted that, if he had a son, he would not let the boy play football (3). Now that's a result! The determination of one pathologist has shaken neuroscience and sports medicine – and demonstrated the true value of pathology.

Titled "Concussion", the film will hit cinema screens towards the end of 2015. If you're anything like me, you'll be eager to see how Smith portrays the inspirational and tenacious pathologist. But I'm even more interested to find out how the whole field can benefit from Concussion...

Fedra Pavlou
Editor

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2. *New York Times, "Brain trauma to affect one in three players, NFL agrees". Accessed October 6, 2015 at http://nyti.ms/1m19KbI.*
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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: fedra.pavlou@texerepublishing.com

One-Stop-Shop for Virus Detection

Could a technique that detects all known human viruses take the guesswork out of ordering lab tests?

Diagnosing viral infection can be a challenge. Although there are sophisticated tests available, you need to know what you're looking for; many tests can only detect one, or at best a few, infectious agents. Physician expertise, patient history and clinical symptoms can all provide crucial information, but reaching a diagnosis often still requires some guesswork. What if there was a simple way to check for every known human virus, in one sample? A test developed by researchers at the Center for Infection and Immunity (CII), Colombia University, New York, USA, might be able to do just that, by screening for all viruses that infect vertebrates, including genetic variants and mutations.

The technique involves high throughput sequencing coupled with a probe capture-based system. It required the creation of a library of 1,993,176 oligonucleotide probes in order to capture all viral taxa containing viruses known to infect vertebrates, which can then be targeted for enrichment and sequencing. The developers tested their approach on human lung tissue and whole blood, spiked with varying amounts of viral nucleic acid. When compared with standard high-throughput sequencing processes, they found a 100- to 1,000-fold increase in viral matches, and a reduction of host background matches of 31.5 percent in lung tissue, and over 60 percent in blood. Sequencing coverage also increased, with near full-length sequences being obtained for detected viruses (1).

With comparable sensitivity to targeted real-time PCR, and the added advantage of picking up sequence variants PCR might miss – and in some cases, a variant differing by even a single point mutation can display variations in transmissibility and pathogenicity – the system certainly seems promising. The ability to provide near-complete genome sequences also means the test can provide information on viral diversity and evolution, with obvious applications in epidemiology and public health. And with a cost of US$40 per sample using a multiplex (20 sample) format, the technique is not prohibitively expensive.

But the most important use of the sequencing method, say it's creators, will be its potential applications in a clinical setting – when viral disease is suspected, or when standard tests are drawing a blank, a test with the potential to identify any virus would be a powerful diagnostic tool. *RM*

Reference

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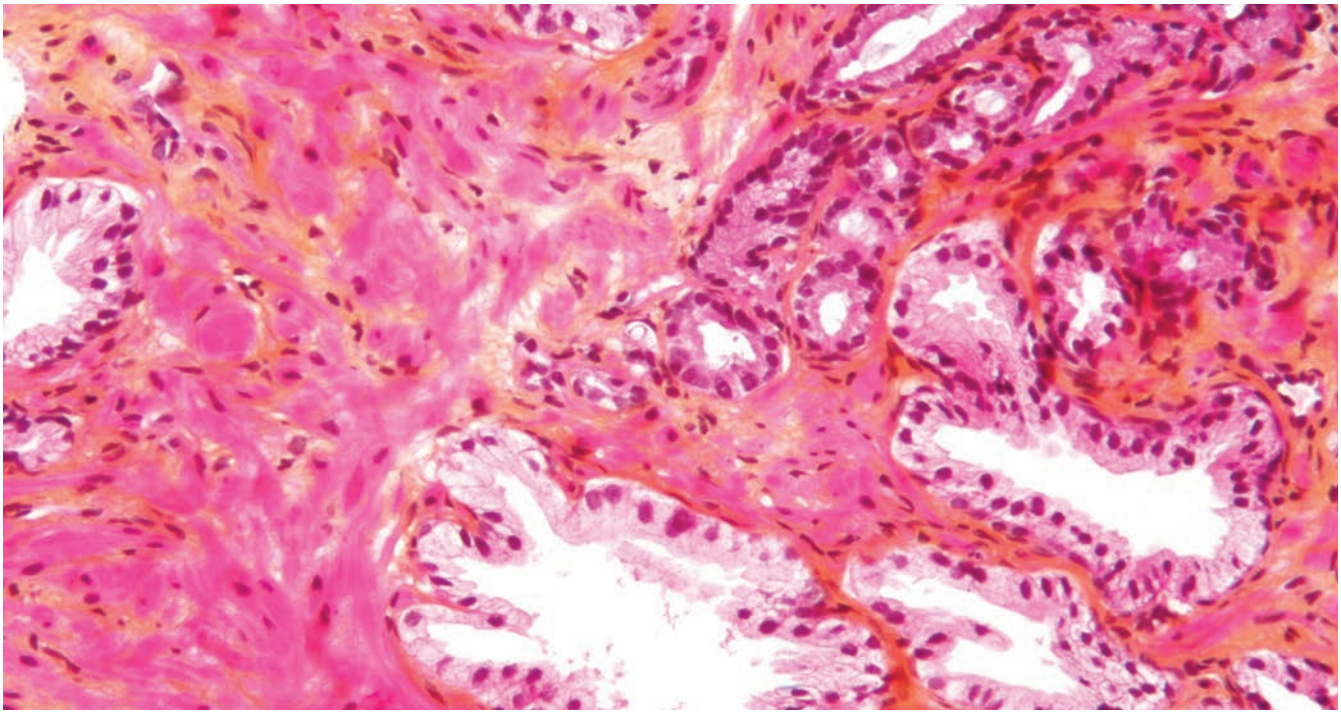
PSA Accuracy Boost

A genetic test for prostate cancer risk could be used in screening, and improve the diagnostic value of PSA

Prostate-specific antigen (PSA) screening is a source of controversy – amid concerns surrounding possible overdiagnosis and unnecessary treatment, some organizations



no longer recommend the assay, even as others argue that there is no alternative for early diagnosis of prostate cancer (PrCa) (1). Now, a genome-wide association study (GWAS) suggests that genetic testing could identify men at high risk of PrCa using blood or urine – and could increase the accuracy of PSA testing, too.

In a multicenter, international effort including the University of California, San Francisco (UCSF), US, PrCa risk factor status of 7,783 men with the disease were compared with that of 38,595 controls. Using 105 single nucleotide polymorphisms (SNPs) known to be associated with PrCa to produce an overall risk score, the selected SNPs were shown to explain 7.8 percent of disease heritability. However, the predictability was substantially higher using the entire GWAS array, which was able to account for around one-third (33.4 percent) of disease heritability (2). This strongly suggests that, as well as the known risks for the disease, there are many genetic factors still to be discovered.

The researchers also determined that men with risk scores in the top 10 percent of the group were six times more likely to be diagnosed with PrCa compared with those in the lowest 10 percent. This is comparable to the breast cancer risk of women who carry a BRCA1/2 mutation, points out study co-author, and UCSF professor of epidemiology and biostatistics, John Witte. But in contrast to BRCA, a validated test to determine PrCa mutation status has yet to be developed.

A genetic test could not only aid screening, says Witte, but also augment the value of the PSA test: "We are presently assessing the biological and functional relevance of the novel genetic variants we detected here. We are also now searching for variants that affect a man's constitutive levels of PSA. With such information we could 'normalize' a man vs PSA levels to assess if they are inherently high or low PSA producers (i.e., regardless of PrCa status), and improve the ability of this test to more accurately screen for PrCa," he says.

The significant differences in risk observed in the study are promising, especially in such a large dataset. If genetic analysis could be used to both increase PSA accuracy and to identify men at high risk of cancer, it could provide a valuable improvement to current screening techniques. The team now plan to correlate genetic variations to men who relapse despite treatment, with an aim of identifying men most likely to develop aggressive cancers. *RM*

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A Crystal Clear View

Liquid crystal displays are ubiquitous, but could the technology be used to detect early-stage amyloid fibril formation?

Most of us are familiar with liquid crystals as a technology involved in creating television and computer screens, but now, researchers at the University of Chicago's Institute for Molecular Engineering have found a very different use for them – detecting amyloid fibrils, which are widely implicated in neurodegenerative diseases such as Alzheimer's, Huntington's and Parkinson's (1), and are also suspected of playing a role in type 2 diabetes (2).

Current methods for detecting amyloid fibrils are less than ideal – the fibers are thought to be at their most toxic early on in their formation, when they are still too small to study using optical microscopy. This means costly and complex techniques using fluorescence or neutron scattering are required.

Liquid crystals could provide a simple and relatively inexpensive way to study the tiny fibers, according to the University researchers. The method exploits the way the crystals respond to surface disturbances – a light-blocking layer is added to a film of liquid crystals, and on top of this a membrane, covered in water, is added. The molecules that form the toxic amyloid aggregates are injected into the water layer, and as the aggregates form and grow on the membrane, they imprint their shape into the liquid crystal underneath. This distorts the molecules present in the light-blocking layer, allowing light to shine through, explains co-author of the associated paper (3), Juan de Pablo.

Though the fibers themselves are still too small to view, their effect is magnified by the imprint they leave, and is large enough to view using a simple optical microscope. "The liquid crystal is actually reporting what's happening to the aggregates at the interface, and these bright spots become bigger and adopt the shape of the actual fibers that the protein is forming. Except you're not seeing the fibers, you're seeing the liquid crystal's response to the fibers," says de Pablo.

The team is now working on a way to use their method in emulsion as opposed to a flat surface, and they hope that eventually the technology could be used to create a method for testing small samples of blood or other body fluids, or to study the effects of different drugs on aggregate growth.

"For research in type 2 diabetes, or Alzheimer's or Parkinson's, having this simple platform to perform these tests at a fraction of the cost of what's required for fluorescence or neutron scattering would be very useful," says de Pablo. *RM*

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21 Questions

Gene expression panel could help breast cancer patients with a low risk of recurrence avoid unnecessary chemotherapy

Breast cancer has the highest incidence and mortality rate of any female cancer (1), and in 2001, a National Institutes of Health-sponsored panel recommended that adjuvant chemotherapy should be offered to the majority of women with localized disease, regardless of variables such as hormone receptor status (2). However, it's generally accepted that many with estrogen-receptor-positive breast cancer respond well to adjuvant endocrine therapy alone, which means that a substantial number of women could be getting needlessly overtreated under current guidelines.

This might not be the case for long though. According to a recent study published in the New England Journal of Medicine (3), a gene expression assay could help oncologists identify those women who can safely forgo chemotherapy, without a high risk of cancer recurrence. The test analyzes the expression of 21 genes, including locations associated with cancer proliferation (such as Ki67) and invasion (MMP11) on a tumor sample, and assigns the tumor a score between 0 and 100 – the lower the score, the lower the chance of cancer recurrence following treatment with endocrine therapy.

In a multicenter validation study of over 10,000 women with hormone-receptor-positive, HER2-negative, axillary node-negative breast cancer, those with scores of 10 or lower did not receive chemo, and five years on, there was less than a 2 percent risk of metastasis, and overall patient survival of 98 percent. Women with a score of 11 to 25 – which accounted for nearly 68 percent of trial participants – were randomly assigned to either chemo and endocrine therapy or endocrine therapy alone; follow-up assessments are currently underway. It will be very interesting to see the impact on survival in these two groups. If endocrine therapy proves sufficiently effective in this study, it could substantially impact breast cancer treatment and potentially kickstart an update to the 2001 recommendations. *RM*

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The IoM Takes on Diagnostic Error

New recommendations on improving the diagnostic process focus on errors, communication, and putting the patient at the center of healthcare

A long-awaited follow up to the US Institute of Medicine's (IoM) medical error and healthcare quality reports, "To Err is Human" (2000) and "Crossing the Quality Chasm" (2001) has set its sights on yet another troubling area in healthcare – diagnostic error.

The new report focuses on three major challenges lab specialists face during the diagnostic process: diagnostic error and the lack of reliable data available on error rates, the importance of ensuring the diagnostic process is patient-centered, and the need for collaboration between the laboratory and the clinic (see Table).

The report authors emphasize that, in order to bring about improvement in this crucial aspect of healthcare, commitment is needed from healthcare professionals, researchers, policy makers and patients themselves. They conclude that, unless more is done to tackle the current issues, "diagnostic errors will likely worsen as the delivery of healthcare and the diagnostic process continue to increase in complexity". *RM*

Reference

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A Summary of Key IoM Recommendations on Improving the Diagnostic Process (1)

Improving Interdisciplinary Collaboration	Healthcare organizations should: • Facilitate and support collaboration among pathologists, radiologists, other diagnosticians and treating healthcare professionals to improve diagnostic testing processes • Develop and implement processes to ensure effective and timely communication between diagnostic testing healthcare professionals and treating healthcare professionals across all healthcare delivery settings Educators should: • Address performance in the diagnostic process, including in areas like teamwork, communication, the appropriate use of diagnostic tests, and the application of results on subsequent decision making
Reducing Diagnostic Error	Accreditation organizations should: • Require healthcare organizations to have programs in place to monitor the diagnostic process and identify, learn from and reduce diagnostic error Healthcare organizations should: • Implement procedures and practices to provide feedback on diagnostic performance to individual healthcare professionals, care teams, and clinical and organizational leaders
Ensuring Patient-Centered Diagnostics	Healthcare professionals and organizations should: • Partner with patients and their families as diagnostic team members, encourage engagement, and provide opportunities to learn about the diagnostic process • Ensure patient access to health records and test results to facilitate engagement, and allow patients to review records for accuracy

"Lab in a Needle" a Not Too Distant Reality?

Researchers hope to create a device that can draw, process and test blood in just 30 minutes

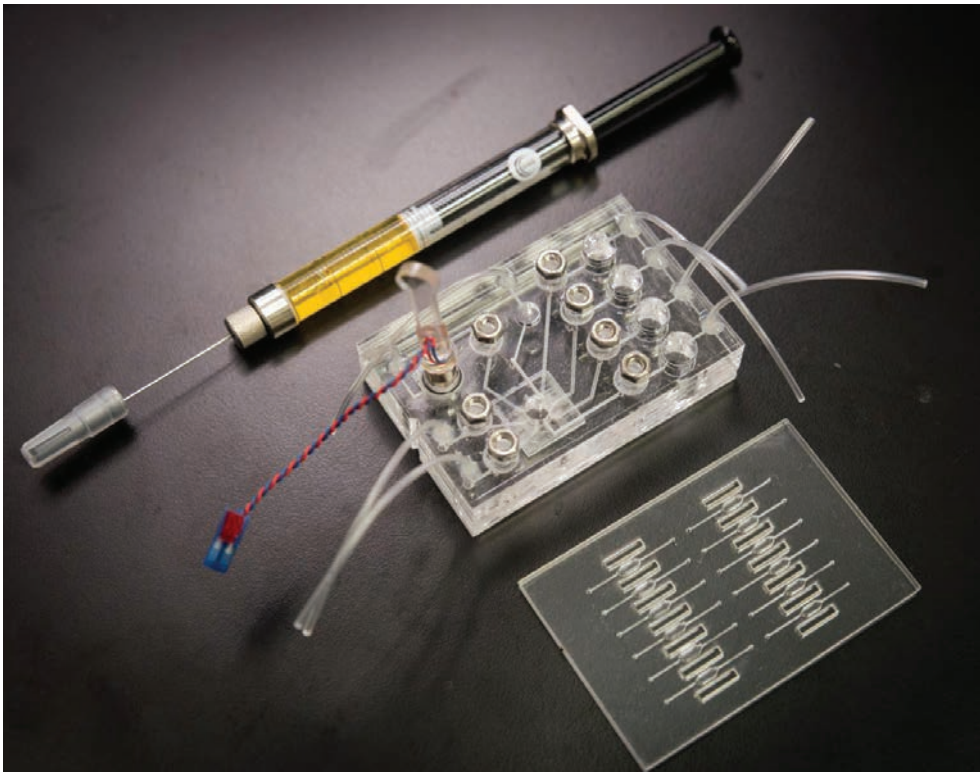

Figure 1. The two key lab-in-a-chip components with a syringe for scale, which will allow for rapid liver toxicity tests. Credit: NTU Singapore.

What if the needle and syringe used to take a blood draw could also process and analyze the sample, and (with the help of a fluorescence detection system) display the test result? An international group of researchers believe they can make the self-contained "lab in a needle" a reality with the help of microfluidics technology.

"We used the concept of lab on a chip, which compresses the entire function of a laboratory diagnostic test onto a tiny microfluidics chip, to create lab in a needle," says Stephen Wong, chair of Systems Medicine and Bioengineering at Houston Methodist Research Institute, Texas, US, and co-author of the associated paper (1). "Our goal is to integrate sample acquisition and preparation into one device, a significant challenge that has slowed the development of point-of-care testing," he added.

The prototype device is the first of its kind to integrate all the steps needed to process a sample for hepatotoxicity testing. Made up of two modules (see Figure 1), the system contains a chip which prepares the sample by performing tissue lysis and purifying mRNA. The second chip performs quantitative reverse transcriptase PCR in order to carry out gene expression analysis for two biomarkers associated with liver toxicity; alanine transaminase (ALT) and aspartate transaminase (AST).

In an initial study of the device, liver samples of mice which had been dosed with the alkylating agent cyclophosphamide were analyzed. The researchers found that increased dosage with the drug could be correlated with increased expression of ALT and AST, which could be detected by their prototype. The device is not yet fully self-contained, and currently requires external instrumentation, but the team plans to create a smaller, more integrated version that could be used to test liver function in outpatients, in patients' homes, or even in the field.

It goes without saying that an accurate point-of-care hepatotoxicity test could be incredibly beneficial, in particular given that current tests for liver function can take days to return a result, while the prototype "lab in a needle" could theoretically do it in just 30 minutes. The technology could also be applied to a range of lab tests, shortening the time it takes to get results and potentially bringing traditional lab tests to underserved areas, says Wong. He acknowledges that this is a disruptive technology, admitting that, "We actually move all the people-processing steps into the box, and automate them." Further research with the prototype is ongoing, and if successful – as with most point-of-care devices – the assumption is that it would be complementary, rather than a replacement, to standard lab testing. *RM*

Reference

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The Promise of Pembrolizumab

But what does the recent approval of this immunotherapy mean for pathology labs?

October 2nd saw the approval by the US Food and Drug Administration (FDA) of an eagerly-anticipated immune therapy for advanced non-small cell lung cancer (NSCLC), pembrolizumab, in conjunction with its companion diagnostic, the PD-L1 IHC 22C3 pharmDx test – the first test designed to detect PD-L1 expression in non-small cell lung tumors – making this a pretty big development for pathologists. Already approved for the treatment of melanoma, the therapy is a PD-1/PD-L1 pathway blocker, a mechanism that has been shown to be effective in destroying cancer cells. How? Recent research has shown that blocking the PD-L1 protein on the surfaces of cancer cells, or its corresponding receptor PD-1 on immune cells, may allow patients' immune systems to detect and destroy cancer cells and it's on this basis that pembrolizumab exerts its effects.

Another item now added to the precision medicine toolkit against cancer, the approval is welcome news for oncologists and patients, and it further highlights the new role of the pathologist – as a true partner to the oncologist. This changing role is a positive development for the profession, which is struggling to gain recognition amongst the public and its healthcare peers, but with this change comes something that most labs will struggle to absorb – an increased workload. We spoke with Kenneth Bloom, Clarient's chief medical officer, about what this recent development means for pathologists and about being selected as one of three reference laboratories in the US to conduct pembrolizumab's companion diagnostic test.

What does the approval of pembrolizumab and its companion diagnostic mean for pathologists?

Pembrolizumab is a member of a new class of emerging therapies known as immunotherapies, but it's also a "precision drug." Only patients who express the PD-L1 biomarker on the majority of their lung cancer tumor cells demonstrate improved outcomes with pembrolizumab. That means oncologists will rely heavily on pathologists to help them select patients to receive the drug. The companion diagnostic provides a better understanding of the tumor and its environment and helps us determine whether or not a patient expresses sufficient PD-L1 to be a good choice for pembrolizumab treatment. This approval broadens the treatment options for patients, and helps ensure they're receiving the best available therapy.

How did Clarient's pathology laboratory become one of three in the US certified to perform the companion diagnostic test?

We acquired the kit – which was investigational at the time – and went through a rigorous training and certification process. Our pathologists were tested on 45 cases over two days to ensure that they could accurately interpret slides and get reproducible results on patient samples, based on the 50 percent detection cut-off for PD-L1. Any lab could undergo the same process, but we believe that our history in companion diagnostic testing and our pathologists' deep domain expertise in cancer pathology contributed to our selection as a national reference laboratory for pembrolizumab.

Do oncologists fully understand when to use, and how to interpret, the PD-L1 test?

Not always. Because our understanding of cancer changes every day, it's often a battle for oncologists to keep up with the latest test and treatment options. There are different PD-1 therapies and PD-L1 tests on the market, and it's hugely important for oncologists to order the right tests for their drugs of choice, as each companion diagnostic is different. Pathologists need to partner with oncologists to ensure that the right assay is being used and the result interpreted appropriately. As a reference lab, if a pathologist or oncologist sends us a tumor biopsy without knowing which drug might be best suited for the patient, we can explore the possible options.

Might increased testing volume and companion diagnostic assay pricing exclude smaller labs from conducting these tests?

As precision medicine advances and more of these drugs become available, it will be harder for smaller labs to keep up. Taking on a companion diagnostic means acquiring the kit, training lab personnel, deep pathology expertise to assess slides appropriately, and the infrastructure to efficiently process a variety of tests – a heavy resource burden. Luckily, most of a pathologist's job doesn't require a rapidly growing arsenal of equipment and personnel, so there'll always be a place for smaller labs to perform routine pathology services. For companion diagnostics and emerging diagnostic technologies, this is where larger labs comes into play; we have the capacity, technicians, pathologists, equipment, resources and expertise to provide access to the critical tests necessary in the era of precision medicine. We make sure that every patient can access tests that ensure the

most appropriate therapy, even if their local hospital lacks the resources.

As precision medicine continues to grow, how can pathology services keep up?

I think centralizing experts is the answer to providing expert pathology services. Centralization can be physical or virtual, providing access to labs that can run the gamut of companion diagnostic kits. Precision medicine rests on the need to obtain much more than a positive/negative test result; it relies on a detailed analysis of the tumor – what it looks like, what's driving it and how it interacts with its environment. As targeted healthcare leads us down the road to a broader range of potential treatments, physicians will need scalable labs to meet the growing demand for companion diagnostics and other complex laboratory tests.

Tissue Cartography

A new imaging modality could make it possible to navigate tissue specimens with the speed and detail of Google Maps

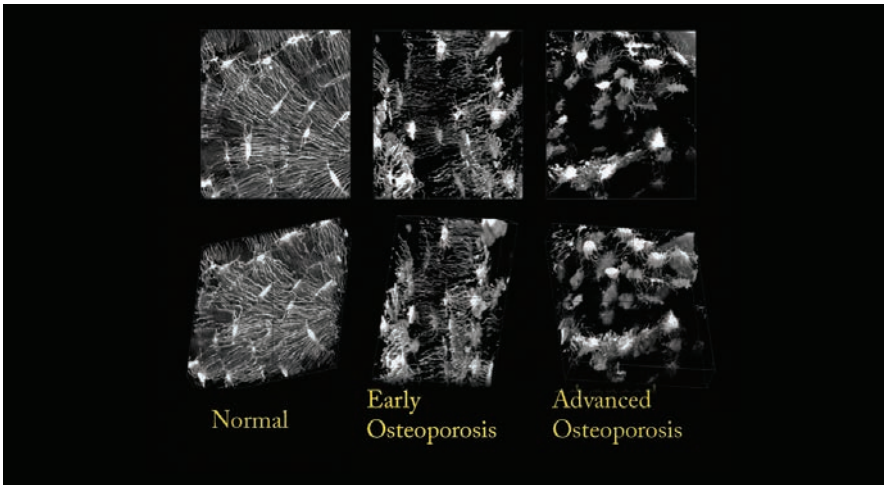

Figure 1. Normal osteocytes compared with early and advanced osteoporosis using the tissue mapping technique.

If you've ever been lost in a new location with your trusty smartphone to hand, then you know how useful a tool Google Maps is – the web mapping service provides an abundance of information on the world around us, and can quickly switch from an overview of the entire earth, to a detailed, panoramic view of a single street. But what if you could perform a comparably detailed navigation of a tissue or organ, zooming from gross to microscopic study with a simple click of your mouse? A team from the University of New South Wales (UNSW), Australia, are doing just that, and are currently working to apply the technology to osteoporosis and osteoarthritis.

"I've often compared the complex physiology of the human body to, for example, the Amazon rainforest. Previous imaging modalities could show us the whole hip, or the individual cells, but in order to understand the interactions between the health of a complex system, its cellular communities, and individual cells, we needed to be able to move seamlessly between them," explains Melissa Knothe Tate, the Paul Trainor Chair of Biomedical Engineering, UNSW, who led the research.

The imaging method relies on rapid-throughput, multibeam scanning electron microscopy, which allows fast processing of tissue blocks at a high resolution, and can be used with specimens up to 10 cm in diameter (1). Originally developed for quality control in the semiconductor industry, the technology is now being teamed with Google algorithms in order to make the best use of the high volume of data it provides. Each processed tissue sample produces roughly a terabyte of data, and when Knothe and her team began creating their first "Google Map", putting the information together became a two-million piece puzzle. "When I brought the relatively huge human samples to our histology technicians, they thought I had lost my mind," she adds.

The work has shown that it is feasible to create a "Google Map"-style image of an organ or tissue, with a prototype map of an osteoarthritic human hip (Figure 1), which can visualize details on a nanometer scale (2). With its high speed and ability to allow the user to explore a tissue sample in precise detail, the technology could hold a great deal of potential for digital pathology. *RM*

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2. *University of South Wales, Prototype map, example available at http://bit.ly/1heqBpn.*

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 editor at fedra.pavlou@texerepublishing.com

Testing Times for POC

The accuracy of point-of-care glucose testing and its impact on the management of critically ill patients is raising concerns. What are the alternatives?

By Kathie Hermayer, professor of Medicine and director of Diabetes Management at the Department of Medicine, Medical University of South Carolina and the Ralph H. Johnson Veterans Affairs Medical Center, Charleston, South Carolina, USA, and Yusheng Zhu, associate professor of Pathology and director of Clinical Chemistry & Toxicology at the Department of Pathology & Laboratory Medicine, Medical University of South Carolina, USA.

The quickest and least expensive form of testing blood glucose (BG) is by point-of-care (POC) testing. However, critically ill patients have many coexisting conditions that raise the risk of an incorrect BG test result, and they may be taking therapeutics for those conditions that contribute to test inaccuracy too. This raises pretty big concerns, in particular because standard parameters of BG testing of critically ill patients have yet to be fully defined, and because current alternatives don't fully address the concerns we have.

Currently, hospital POC BG devices must meet the same standards as a device that's used in the outpatient setting. According to the 2003 ISO 15197 standard, the parameters are BG <75 mg/dL, 95 percent of values within +15 mg/dL, and BG >75 mg/dL, 95 percent of values within +20 percent of the "reference" value (laboratory analyzed BG). However, the US Food and Drug Administration (FDA) is currently reviewing tighter BG parameters for allowable POC BG devices in the hospital, and in fact, an updated 2014 FDA draft recommendation is for a BG <70 mg/dL, 99 percent of values within +7 mg/dL of the reference range and the other 1 percent must not exceed +15 mg/dL. Also, for a BG >70 mg/dL, 99 percent of values within +10 percent of the "reference" value and the other 1 percent must not exceed +20 percent. The newer FDA parameters would permit a smaller glycemic range for different BG values, which would serve to enhance patient safety for BG readings. This is good news!

"More studies are necessary to analyze which critically ill patients are at greatest risk."

Other modalities for testing BG in the critical care setting do exist, and include arterial blood gas analyzers, Hemocue (for bedside hemoglobin testing), an i-STAT handheld blood analyzer, and laboratory tests of serum glucose. There are still concerns with these modalities though: cost of testing, sample volumes, accuracy, and turnaround time. And, generally, arterial blood demonstrates

5–10 mg/dL higher glucose levels compared with capillary and venous whole blood concentrations because of high glucose use in the extrahepatic tissues, mainly in the muscles.

Thankfully, the FDA is responding to these concerns and on January 7, 2014, it changed the labeling for all BG monitoring systems to include the following statement: "Performance of this system has not been evaluated on critically ill patients." Similarly, in November, 2014, the Centers for Medicare and Medicaid Services (CMS) issued a warning in a Survey and Certification letter stating that use of a test outside of its intended FDA-approved/cleared use, limitations, or precautions, as indicated in the manufacturer's instructions, would be considered off-label use and default the test to CLIA high-complexity.

Then on March 13, 2015, the CMS stated in a draft memorandum, "In short, off-label use is not prohibited but does trigger the need for additional safeguards." CMS also requested comments on the draft guidance.

In response to the FDA and CMS labeling change, the Medical University of South Carolina changed its policy. In order to comply with the FDA and CMS ruling, patients at MUSC who have anasarca, hypothermia (91.4 degrees Fahrenheit or 33 degrees Celsius), or hypotension requiring vasopressor support, need to have alternative means for BG testing other than capillary blood glucose (CBG) POC. Other routes for testing BG would be to obtain blood from the arterial line or venous site for POC BG (not CBG), use an i-STAT analyzer for BG, measure the arterial/venous glucose using a blood gas analyzer, or send the venous blood to the central lab for serum/plasma glucose.

In our view, moving forward, it is important to approve the FDA 2014 draft recommendations. Indeed, it would be helpful for BG meter manufacturers to develop apparatus with improved accuracy. And, it would be beneficial to delay enforcement of the new standard for POC BG testing. Importantly, more studies are necessary to analyze which critically ill patients are at greatest risk of POC BG inaccuracy, and to determine which mode of testing is appropriate in select populations of patients.

In light of these developments, we have two key questions that we would like to present to readers:

1. Should POC BG testing be allowed for use in critical illness?
2. What alternative methodologies are available to measure glucose in patients who are critically ill?

We welcome your input!

Barcode Tracking Simplified

What you need to think about before choosing the best system for your lab

By Tim Morken, pathology site manager, Parnassus Campus, Supervisor, Electron Microscopy/Neuromuscular Special Studies, Department of Pathology, UC San Francisco Medical Center, California, USA.

In the last five years or so, anatomic pathology (AP) laboratories have finally received the tools and software they need to implement barcode tracking of specimens and materials from accessioning through to grossing, histology/cytology, immunohistochemistry (IHC), specials stains and reporting.

Developing the technology needed by pathology labs has not been without its challenges though. For example, 2D codes need to withstand all the rough handling and solvents used in processing tissue and still be printed directly onto the plastic tissue cassette and read by a scanner. Slide labels also need to be applied as soon as the slide is produced and the slide label must withstand processing chemicals as well as high heat from the slide drying, antigen retrieval used for IHC and the wide variety of other chemicals used for special stains,

"Developing the technology needed by pathology labs has not been without its challenges."

from strong acids to strong bases. The labeling system vendors finally worked out how to meet our demanding requirements and now we can reliably pass these materials through the entire gamut of histology processing and staining and the labeling information is still intact at the end.

The puzzling piece of the barcoding evolution, however, was the late

entry into the field by the laboratory information system (LIS) vendors. Ten years ago, I worked for a company that manufactured an IHC stainer that had cornered half of the market. We developed a barcoding system for the stainer and then approached several major LIS vendors about linking the stainer to the LIS using the barcode with an interface for stain orders. It was like talking to people who had never heard of a barcode. A VP of one of the companies we spoke with actually said, "Why would anyone want to do that?" We were astonished that these supposed computer-centric companies were so far behind the curve that they could not even comprehend what was coming.

"Some labs went to the extreme of producing their own barcoding systems after their frustrating experiences with their LIS vendors."

Indeed, these companies were so lacking in vision, and so late to the game, that IHC instrument vendors grew tired of waiting for them to catch up and developed their own barcode specimen tracking systems that would link to their instruments. Some labs, independently of the vendors, went to the extreme of producing their own barcoding systems after their frustrating experiences with their LIS vendors. Now five years after the first commercial products from instrument vendors came on the market, the LIS vendors have finally caught up.

A pathology department can now implement a barcoding system using commercially available products, but it's not an easy process. Anyone contemplating this should approach it with the understanding that whatever system your lab selects, there will be tradeoffs. So, it is important to study the compromises very closely, and demand what you need and not settle solely on what's on offer. You probably won't get everything you would like and you will need to decide between the necessary and the nice-to-have features.

One of the first things to do is to find out precisely what your current LIS vendor offers and if it will match your requirements. You will probably find that most can now supply barcoding and tracking from accessioning through to general histology slide labeling. Some can offer cytology; however, custom programming for some instruments may be needed. Outside consult case accessing is another matter altogether and may require extensive custom programming.

If your vendor does not offer any barcoding solution, or if the product is lacking in some way, there are third-party vendors that offer very good alternatives. However, they will (most likely) hold tracking system data in their own databases and not in the primary LIS. And, you may not be able to write data entered into the third-party system to the primary LIS database tables. If that is the case, it just becomes a tracking system and you will use the primary LIS for data entry (including, new blocks, stain orders, etc.).

Additionally, if you want to use a third-party tracking system, you need to understand how it interacts with the primary LIS. There will be a communication protocol, but how does it work, and will it need additional software? In the extreme case, I have seen a primary LIS that requires its own barcoding system installing as the middleware for any third-party system. Of course, that may defeat any purpose of the third-party system.

It is important to examine the software interface for the instruments you have in your lab. Most LIS's can link an IHC or special stains instrument to the LIS, but can the stainer read your LIS barcode/2D code? Or, will you need to double-label the slides just for the stainer? What happens after that in terms of tracking? If you have a mix of instruments from different vendors, how does that affect the labeling workflow – do some slides flow easily using the LIS barcode and others need double labeling for specific instruments? And, should you even have a mix of instruments?

The vast amount of data produced by a barcoded system includes location and time stamps to turnaround time, to individual workload, and so on. But, does the system offer real-time tracking with dashboards that make it easy to access the information you want (i.e., blocks/stains currently in various stages of processing), or do you need to run occasional static reports to get the information? Can you produce custom dashboards and reports? Third-party vendors offer solutions to this as well by tapping directly into the LIS tables and allowing the user to build custom real-time reports/charts for production management.

So, although AP barcoding systems are available commercially, doing your homework will pinpoint the problem areas you need to be aware of before contacting vendors. Plan onsite visits to institutions that use your LIS and a barcoding system to see what they did and what problems they encountered and had to solve. Trust me, this is time well-spent and your pre-planning work will pay off when you come to implementing the system.

Let's Fast in Harmony

Why we need to harmonize fasting definitions for blood sampling

By Mads Nybo, associate professor and clinical biochemistry specialist, Odense University Hospital, Denmark.

Fasting. This is a term that we hear often, but it's seldom well-defined – and, in the context of blood sampling, it requires harmonization. Indeed, doctors generally base their fasting definitions on their personal experiences as interns or students. But, on investigation, they don't have a clear definition for it. This is also the case when authors use it in research literature and textbooks (1).

There are sufficient evidence-based accounts, however, that show proper fasting does matter when it comes to reference intervals for a wide variety of blood analytes. And, because qualitative studies have shown how difficult it is to predict the impact of improper fasting on laboratory results, I believe that it is important to implement a harmonized definition as soon as possible. Such a clear definition would also benefit patients, making it easier for them to follow the required fasting regimen.

So, let's develop and implement a harmonized fasting definition that we can use internationally. As with most definitions, it will be tested, challenged and found flawed. But, experience shows that it is much easier to end up with the best solution possible if the process is initiated and then optimized. Of course, a harmonized fasting definition should be as evidence-based as possible, but we also need consensus in order to move forward.

There is some movement already. A working group that is investigating preanalytical issues under the European Federation of Laboratory Medicine (EFLM) has proposed a harmonized fasting definition, which they hope can be disseminated and used as widely as possible within clinical biochemistry. The proposed definition is simple and it is supported by literature (2). Briefly, it comprises the following:

- Blood for all tests is drawn preferably in the morning between 07.00 am and 09.00 am
- The fast should be for 12 hours (plus/minus half an hour)
- Water consumption should mirror the usual intake
- Caffeine-containing beverages (coffee, tea) should be avoided on the morning of the blood sampling
- Alcohol intake should be avoided 24 hours prior to blood sampling
- The patient should refrain from smoking the morning of the blood sampling.

If it is discovered that the patient has not fasted properly, then blood sampling should be cancelled (as recommend by the EFLM working group) – or alternatively, the analyses in the blood sample requisition should be converted to non-fasting entities. But, most importantly, such situations should be avoided by informing the patients carefully about the outcome if they do not fast properly. The worst-case scenario resulting from their improper fasting (which I find worth describing to patients), is that reference ranges can be misleading, the diagnosis will be erroneous and their safety will be compromised. Therefore, the most important task in this context is to ensure implementation of correct fasting by the patient; and, also the key users of blood sampling need to understand the definition and the outcome if it is not adequately followed.

> *"Fasting. This is a term that we hear often, but it's seldom well-defined."*

So, in summary, I'd like to make a call for the harmonization of a fasting definition. If you do not have a national guideline, address this with your national society – and use the EFLM working group recommendation as an example. When you have defined it, ensure that the information is disseminated, especially to the doctors and GPs who deal with the patients prior to blood sampling. And remember that sharing information is one of the most difficult tasks in medical care, so the message must be repeated as often as possible, nationally as well as internationally.

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Education for the Gamer Generation

Learning games are underused, but offer an effective way to engage students and could help them understand and retain knowledge. With educational needs of pathology students increasing all the time, maybe it's time to think of a new way of teaching…

Michael Schubert interviews Judy Gnarpe

Educational games are everywhere. Though most of the software bearing that label is aimed at children in the early years of school, there's also great, though mostly unexplored, potential in creating learning games as serious teaching tools for students in higher education. Though many would raise a cynical eyebrow, I can attest to the fact that educational gaming works.

Recognizing the potential value of game-based teaching some years ago, I developed a game generator for my students in the medical sciences. BrainSpan games are asynchronous multiplayer learning games, meaning that all of my students can play them if and when it's convenient for them. They can test their knowledge, challenge one another, interact with their instructors, and gain more information, all from the comfort of their own computers – or even their mobile phones while on the go. This kind of on-demand studying lets students take advantage of downtime for review, and the "fun" aspect actually encourages them to study! As new generations of students become more and more immersed in the digital world, I think interactive online teaching tools like these may be the way of the future – and I encourage other medical teachers to get involved, too.

How BrainSpan was born

I have been using games in my courses since about 2003 – so for most of my teaching career – but it was 10 years ago that I came across an interesting asynchronous multiplayer game developed in Tasmania and got in touch with the fellow who was running it, a computer programmer called Mike Capstick (http://cybertrain.info/). He and I decided to work together to make a new game for the courses I was teaching at the time – a medical microbiology and immunology course for nursing students, and an infection, inflammation and immunity course for medical students. When we first created that prototype game, I wasn't able to add or change my own questions, which was quite a pain, as my Tasmanian colleague had to do everything for me. It was another year before the dean of medicine hosted a Halloween party for the medicine dentistry students – and that's when he first heard them rave about this "really cool game" they were playing in my class. They were all competing for points and really enjoying it. At the same time, they recognized that, while they were having fun, they were also learning new material and testing their knowledge of the old.

So one morning soon after Halloween, the dean called me into his office to tell me that we had to start running a game

like that in all of the undergraduate medical courses – that is, 11 different classes spaced over two years. And at that point, I realized we needed to make and host our own version of the game, so that we could add and remove questions, update information and do all of the necessary maintenance ourselves. That moment was the birth of BrainSpan. Fortunately, the University of Alberta, Canada, has a special grant, known as the Teaching and Learning Enhancement Fund, aimed at new educational projects within the university. Applying to that earned us C$128,000, but we got even luckier – the Faculty of Medicine and Dentistry kindly topped it up with another C$100,000, and we got some additional funding from my department as well.

But getting the money together was only the first hurdle we had to cross. Next, I had to work with the central IT department to create our own purpose-built game from scratch. Initially, it didn't turn out exactly the way I'd hoped it would, but given the costs of building something as complex and involved as an asynchronous multiplayer game, we simply had to do the best we could. The content, of course, was even more important than the structure. We needed to assemble a different set of custom game questions for each of the courses, so I hired three medical students for a summer. Their job was to write a list of questions for every course and then liaise with the course coordinators to make sure the questions were appropriate. I should say, they made questions for every course except my own two – because I wanted to write those lists myself!

Testing the newly created games took the best part of a year, but the games were finally ready to launch in the fall of 2008. "Games" is perhaps not strictly accurate; BrainSpan is not a single game, but a game generator. You can use it to develop as many individual games as you need, and each game can be aimed at a specific set of players – you can add a class list, a subsection, a list of testers; anything you need. You can even include media in the questions and answers – images, weblinks, or even documents – to enrich their value.

But long story short, I've now been using the BrainSpan games for over seven years – and they've spread. Not only do I use them to teach nursing, medical and dental students microbiology; other professors use them for subjects from biochemistry to physiology to medical laboratory science. BrainSpan hasn't spread beyond medicine and science yet, but I see its potential in almost any discipline. Right now, I would guess that there are about 2,000 students using BrainSpan each semester, but I hope that number continues to grow for a long time!

The evolution of educational gaming

When we first began using it, access to BrainSpan was restricted to students at the University of Alberta. Two years ago, the Faculty of Medicine and Dentistry decided it would be a good idea to make the games available to people outside the university. We hoped that a small fee for the use of the games would help us obtain the resources we needed to keep the game running on our servers – and eventually, we wanted to grant other schools institutional access, now that we knew we had a valuable teaching tool. Unfortunately, the economic situation was not on our side. While outside users are still able to make BrainSpan accounts without needing a university-based email address, our plan of trying to host the games for other schools has yet to come to fruition.

But that doesn't mean we've stopped expanding BrainSpan's capabilities. Without extensive funding, we had to make creative use of resources – by which I mean that I partnered with a computer science professor who had four senior students in need of a project for one of their classes. Thanks to their hard work, we're now able to offer both a mobile-friendly game and a BrainSpan app. Portable computing is becoming more and more important, especially as apps for remote diagnostics become increasingly effective – so why not get students engaged early with apps for their classes, too?

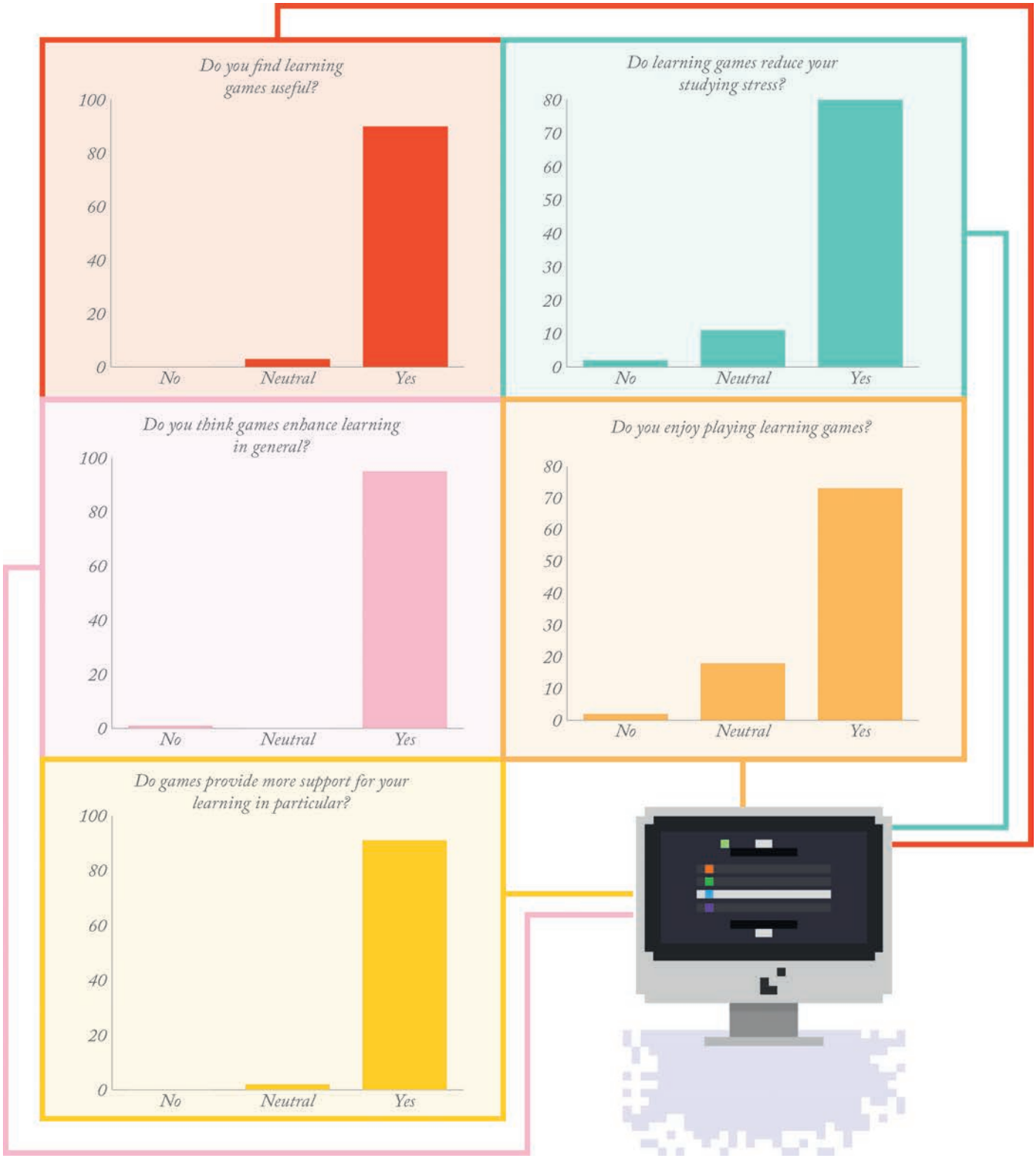
The key features of a teaching tool

In my opinion, the most important feature of BrainSpan is the feedback it provides. Students using the games have access to more than one kind of feedback. The first and most obvious kind is the explanations given along with the answers to every question; they help students understand why their answers were right or wrong, rather than just marking it "correct" or "incorrect." The other type of feedback, which I think is equally important, is retrospective. Users can check their own performance in a game, or over a number of games – at any point, they can call up a list of the questions they've answered incorrectly in the past, along with the correct answers. And it isn't just the software itself that provides feedback. One unique aspect of our games that I really enjoy is that they facilitate student-teacher interaction. Students can send messages directly to their instructors from any question in the game – meaning that they can clear up confusion in the moment, rather than trying to remember it for later, and instructors can see exactly which subjects cause the most difficulties and why.

The direct messaging system is one way for teachers to see how good the questions themselves are, but it isn't the only one, especially if the goal is to improve the games for future players. Instructors can also "vet" new questions to see how they work by putting them into a specific type of game that can't be replayed. Students are then given access to the game and asked to complete it within a certain timeframe. We send the resulting game data file to our university's department in charge of test scoring and questionnaires; they run item analysis statistics on the questions to help us understand how challenging the questions are, identify "trouble" questions, weed out distractors (the wrong answers in a multiple-choice question) and more. Being able to evaluate the quality of our questions and their suitability for our target populations lets us refine the games, making them even more useful for teaching.

Screenshots from the BrainSpan quiz game. a) The starting screen for a game. b) Players answer a series of multiple-choice quiz questions. c) Both correct and incorrect answers provide an opportunity to learn more. d) "Learn more" information often includes explanations, images, or links to external online resources. e) The questions themselves can also include images. f) Leaderboards showing scores and rankings appeal to students' competitive drive.

The best teaching tools are the ones that can be used at students' convenience – because those are the ones students are most likely to use! With BrainSpan, we've recently implemented an app, as well as a mobile web format of the game for users who aren't able to download the app. Portability makes it more likely that students will engage with the games on the train, between classes, in waiting rooms, and anytime they might otherwise have difficulty studying with bulky textbooks and extensive notes. It also helps that students can start a game, do a few questions whenever they have time, and have their answers saved when they log off, so that they can



Student responses to survey questions about the value of learning games in education.

pick up where they left off the next time they have an opportunity. BrainSpan's convenience is one of the things that encourages students to get involved with it, so we're pleased with how well it can be adapted to its users' lives.

Success with struggling students

In the empirical sense, no one has ever been able to show consistently that any e-learning tools actually impact student success. Essentially, the bright kids will do well regardless of the resources available to them – and the less motivated students don't use those resources enough to gain anything from them. I think that tools like BrainSpan actually offer the most benefit to students who struggle a bit. We all know that the plural of anecdote is not data, but my experiences have been pretty consistent – for instance, in a required class for an after-degree nursing course, I worked with a mother of four small children. Because of her lack of time and all of the other pressures of her life, she was only pulling off a grade of about 60 percent in the course. She got into BrainSpan and started doing that whenever she could find a few minutes – and in the end, she increased her overall score in the course by 20 percent! Ultimately, she ended up with a pretty decent mark, and that's the sort of thing I've seen again and again from students who, after having difficulty, start using these less typical resources.

A number of years ago, I surveyed my students to find out what they thought of BrainSpan. In general, they were very positive. They valued that the instructors actually cared about their learning and provided them with extra resources. One student said, "I find it much more interesting to learn [through digital games] than by just going through the notes on my own. It inspires me to learn more when I get points for it and need to know the answers to move on. As well, it helps me know what to focus my studying on." Another commented, "Some of the quizzes from other courses are very dry and not that relevant to what's expected of you. But the MMI website is awesome for its relevance and motivational aspects. I love the drawings, the cases were very amusing and informative, and the Microbe Slayer game is a real hoot." Students also found that the games were good for reviewing course materials. "For some subjects, like anatomy and microbiology, there is a lot of memorization, so the games are a fun way to reinforce the learning."

Of course, the feedback is not all flawless. There are always a few students who don't like computers and, by extension, e-learning. Students have made comments like, "I have never played digital games and therefore am reluctant to learn how to use them," or, "I don't really enjoy sitting in front of a computer; I would much rather be in a library going over lecture material." But no one teaching tool will suit every type of learner, and I hope that, as newer generations of students are increasingly familiar with the digital world, BrainSpan's popularity will continue to grow. In fact, much of the

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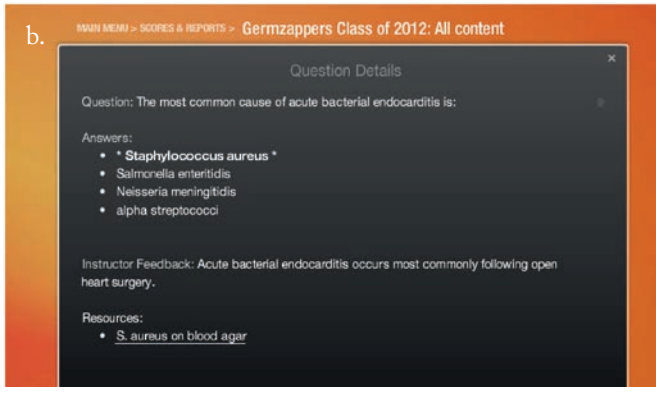
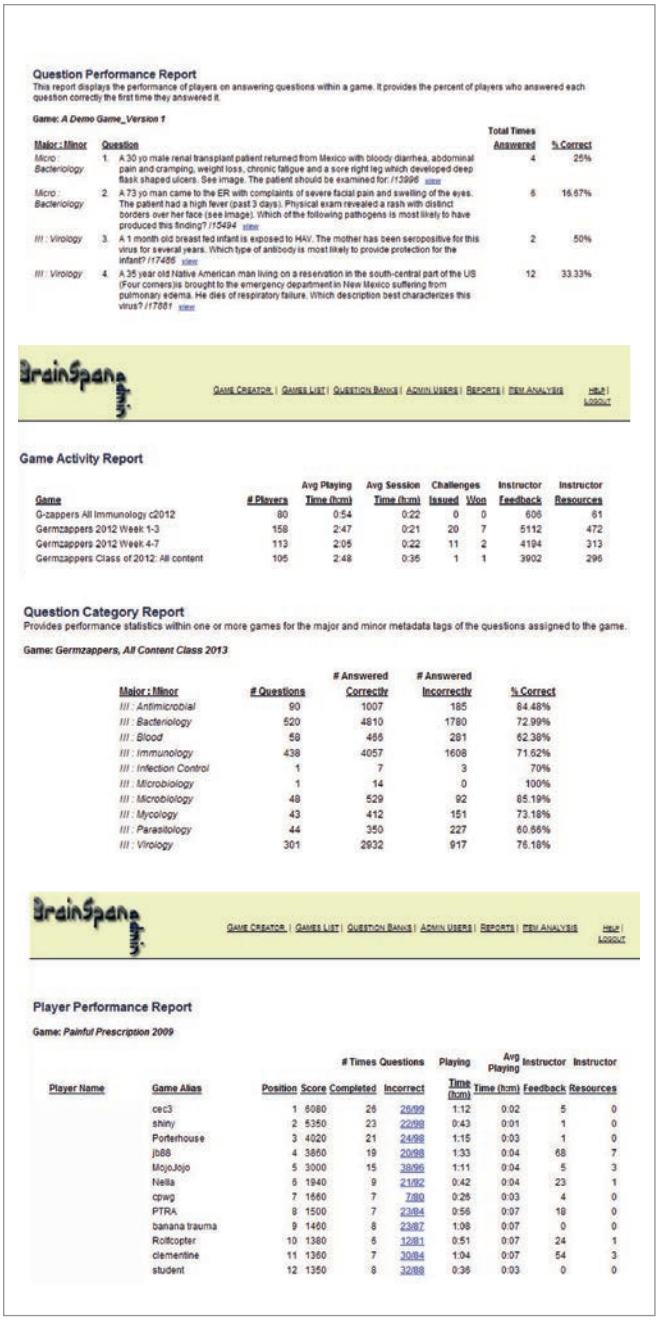


c.

Screenshots from the BrainSpan student interface. a) Each student has a list of playable games based on the classes he or she is taking. b) At any point, students can take a closer look at questions they've answered to learn more. c) Students can also get a breakdown of how well they are performing in each study subject.

a.



Question Performance Report

This report displays the performance of players on answering questions within a game. It provides the percent of players who answered each question correctly the first time they answered it.

Game: *A Demo Game_Version 1*

Major : Minor	Question	Total Times Answered	% Correct
Micro : Bacteriology	1. A 30 yo male renal transplant patient returned from Mexico with bloody diarrhea, abdominal pain and cramping, weight loss, chronic fatigue and a sore right leg which developed deep flask shaped ulcers. See image. The patient should be examined for: *i13996* view	4	25%
Micro : Bacteriology	2. A 73 yo man came to the ER with complaints of severe facial pain and swelling of the eyes. The patient had a high fever (past 3 days). Physical exam revealed a rash with distinct borders over her face (see image). Which of the following pathogens is most likely to have produced this finding? *i15494* view	6	16.67%
III : Virology	3. A 1 month old breast fed infant is exposed to HAV. The mother has been seropositive for this virus for several years. Which type of antibody is most likely to provide protection for the infant? *i17456* view	2	50%
III : Virology	4. A 35 year old Native American man living on a reservation in the south-central part of the US (Four corners)is brought to the emergency department in New Mexico suffering from pulmonary edema. He dies of respiratory failure. Which description best characterizes this virus? *i17881* view	12	33.33%

b.

BrainSpan

GAME CREATOR | GAMES LIST | QUESTION BANKS | ADMIN USERS | REPORTS | ITEM ANALYSIS HELP | LOGOUT

Game Activity Report

Game	# Players	Avg Playing Time (hrs)	Avg Session Time (hrs)	Challenges Issued	Challenges Won	Instructor Feedback	Instructor Resources
G-zappers All Immunology c2012	80	0:54	0:22	0	0	606	61
Germzappers 2012 Week 1-3	158	2:47	0:21	20	7	5112	472
Germzappers 2012 Week 4-7	113	2:05	0:22	11	2	4194	313
Germzappers Class of 2012: All content	105	2:48	0:35	1	1	3902	296

c.

Question Category Report

Provides performance statistics within one or more games for the major and minor metadata tags of the questions assigned to the game.

Game: *Germzappers, All Content Class 2013*

Major : Minor	# Questions	# Answered Correctly	# Answered Incorrectly	% Correct
III : Antimicrobial	90	1007	185	84.48%
III : Bacteriology	520	4810	1780	72.99%
III : Blood	59	466	281	62.38%
III : Immunology	438	4057	1608	71.62%
III : Infection Control	1	7	3	70%
III : Microbiology	1	14	0	100%
III : Microbiology	48	529	92	85.19%
III : Mycology	43	412	151	73.18%
III : Parasitology	44	350	227	60.66%
III : Virology	301	2932	917	76.18%

d.

BrainSpan

GAME CREATOR | GAMES LIST | QUESTION BANKS | ADMIN USERS | REPORTS | ITEM ANALYSIS HELP | LOGOUT

Player Performance Report

Game: *Painful Prescription 2009*

Player Name	Game Alias	Position	Score	# Times Questions Completed	# Times Questions Incorrect	Playing Time (hrs)	Avg Playing Time (hrs)	Instructor Feedback	Instructor Resources
	cec3	1	6080	26	26/99	1:12	0:02	5	0
	shiny	2	5350	23	22/98	0:43	0:01	1	0
	Porterhouse	3	4020	21	24/98	1:15	0:03	1	0
	jb88	4	3860	19	20/98	1:33	0:04	68	7
	MojoJojo	5	3000	15	38/96	1:11	0:04	5	3
	Nella	6	1940	9	21/92	0:42	0:04	23	1
	cpwg	7	1660	7	7/80	0:26	0:03	4	0
	PTRA	8	1500	7	23/84	0:56	0:07	18	0
	banana trauma	9	1460	8	23/87	1:08	0:07	0	0
	Rollcopter	10	1380	6	12/81	0:51	0:07	24	1
	clementine	11	1360	7	30/84	1:04	0:07	54	3
	student	12	1350	8	32/88	0:36	0:03	0	0

Screenshots from the BrainSpan instructor interface. a) Instructors can get performance reports for each question, showing the number of responses and the percentage correct, in order to determine where students are having difficulty. b) They can also look at the activity reports for each game, showing total and average playing times, performance, and use of resources. c) Categories can also be compared to one another. d) Player performance reports show how much individual students are playing and how well they perform.

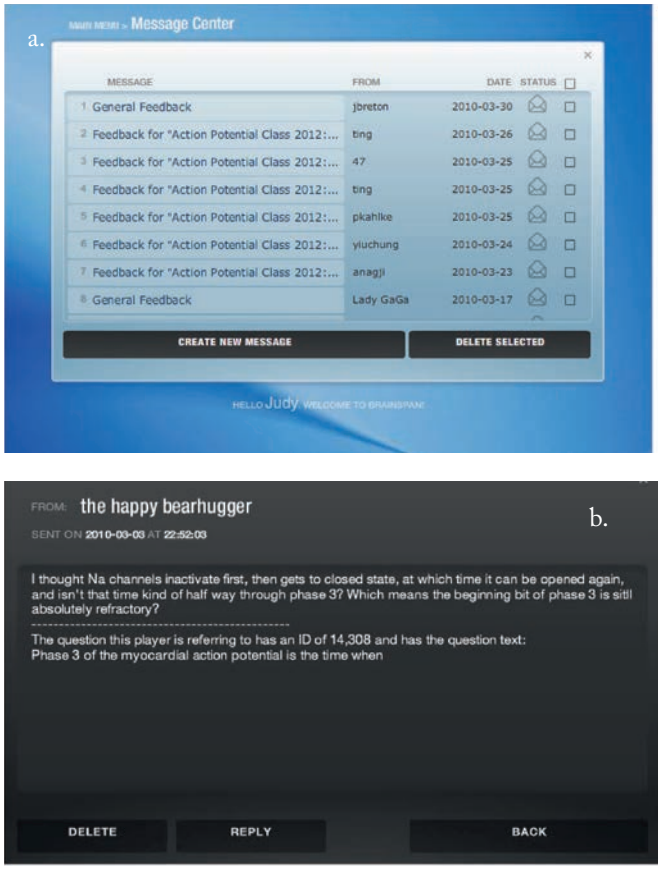
feedback I received dealt with the opposite problem – students wanted even more from the game, or wished they had more time to play it. These are the kinds of problems I like to hear, because they mean students are engaged and want to use BrainSpan!

Looking forward to future versions

I have a lot of ideas for the future of BrainSpan. One that stands out in particular is the ability to provide real, in-game motivation on an individual basis as well as between students. When we first built the BrainSpan game generator, we had to sacrifice one of my favorite aspects of the Tasmanian game that inspired it. In that game, the points you earned by answering questions correctly weren't just for bragging rights – you received rewards when you reached a certain number of points. You could use those rewards to buy things like strength or immunity – things that added another dimension to the gameplay. I wish a similar reward system were present in the current version of BrainSpan. At the moment, you play, you accumulate points, and you can use those points to challenge other students – you wager points on a particular question, and if the person you challenge gets it right, you lose those points. If they answer the question incorrectly, you win extra points. But that's actually another thing I'd like to change about the current version – the challenge system isn't set up very well, as you need to exit the game in progress to visit the message center where the challenges are sent. Unfortunately, that means the challenges – which I think are a great way for students to motivate one another and enjoy a spirit of camaraderie – aren't used as much as I'd like at the moment.

Another thing I'd like is to be able to link questions together. Right now, they're all self-contained, but one day it would be good to be able to run case studies. We could have a set of attached questions that harken back to the case, allowing students to work through it in a manner similar to the continuing medical education healthcare professionals must complete after qualifying. This was part of the plan for BrainSpan from the start, but unfortunately we lacked the funds to bring it to fruition. I still hope we'll have the opportunity to implement case studies one day, as I feel that they would be very beneficial for students on track to becoming medical professionals.

I think the game would probably have to be rebuilt to incorporate the changes I'd like to see, especially the ability to receive a challenge in real-time while you are playing a game. I'd like a pop-up notification that said something like "You have been challenged – will you accept this challenge?" The ability to earn rewards, whether in the form of merit badges, ranks, titles like "grand master," or anything else, might involve a bit of work as well – but certainly not as much as adding the ability to use your points to purchase attributes that help you compete with other students. I have a lot of ideas for those attributes: things like getting twice the points wagered in a challenge if you have



a) The message center allows instructors to receive student feedback.
b) Students can ask about individual questions, and each item of feedback is tagged with its originating question.

earned a particular merit badge, or immunity to challenges so that you don't lose points even if you miss a question.

Some changes to the internal workings of the game generator would be good, too; for instance, I'd like game creators to have more administrative power. At the moment, we can't do simple things like print out lists of questions from our games, or have the messages students write within the game sent directly to the instructor's email address. We could also use some more complicated functions, like the ability to copy a whole game over and start fresh when you want to add a new student cohort without losing the questions you wrote for the earlier game. Right now, you have to create the new game from scratch and import all of the questions you want to use, which is much more time-consuming. It's not just for instructors, either; students would benefit from a few tweaks to the interface, too. For example, we can include images with questions or answer explanations. Right now, users can click on the images to enlarge them, but can't move them on the screen or enlarge them on touchscreens by pinch-zooming. Little things like that would add a lot of convenience for everyone.

The only thing I may never be able to change about BrainSpan is its availability. In my soul, I believe that these types of learning resources should always be free to access. Of course, I understand that there is always a cost associated with building and hosting software, and I understand that the faculty sponsoring BrainSpan's existence does need funds to keep it online. Still, it would be nice if one day, we found a way to make learning games available to everyone, without having to charge a fee to do it.

Tips for teachers

It would be wonderful if more educators – not just in medicine and the sciences, but in all disciplines – took advantage of new media resources like BrainSpan. If you decide that asynchronous multiplayer games are the right tools for your classroom, remember that they need reinforcement, just like any other teaching tool. If you want your students to use the resources you provide, you have to remind them and advertise the resources in class. For quiz games in particular, it's important to make sure they stay current by keeping up with the course curriculum, making sure the questions are relevant and the answers correct, and including feedback that helps students learn not just what the right answer is, but why.

Judy Gnarpe is a teaching professor and faculty services officer in the Department of Medical Microbiology and Immunology, Faculty of Medicine and Dentistry, at the University of Alberta, Edmonton, Canada. As a clinical microbiologist, she teaches medical microbiology and immunology to medical and dentistry students, laboratory residents, pharmacy, nursing and dental hygiene students.

Living the Molecular Revolution

New technologies and molecular discoveries are changing the way diagnoses are made. But how will already burdened molecular pathology labs cope with more cases and restricted budgets? And will all pathologists enthusiastically grasp this new role they have, at the center of patient care? Patrick Pauwels remains optimistic.

What have been the biggest molecular pathology game-changers?

The fact that we now have molecular alterations that we can target is game-changing in itself. The tyrosine kinase (TK) story is a good example of how molecular pathology changed our life and our way of thinking. After its approval in 2001, the tyrosine kinase inhibitor (TKI) therapy imatinib caused an almost doubling of survival rate in people with chronic myeloid leukemia and gastrointestinal stromal tumors.

Diagnostic technologies have also undergone a substantial evolution; we now have reliable, sensitive tools that can identify mutations. We realize that low levels of targetable mutant cells in tumors matter, and these technologies allow us to find them.

As the importance of molecular diagnostics increases, what difficulties might pathologists face?

Education is a big challenge. Pathologists are under constant pressure to keep track of developments and we are only just starting to address this knowledge gap. I'm president of the newly formed Belgian molecular pathology working group and we're aiming to remedy the situation in my home country by uniting academic and clinical pathologists to share knowledge, which we'll do through regular meetings, newsletters and journal publications. Unfortunately, pathology residents are not well-trained in molecular pathology. How can we expect full-time pathologists to keep on top of the latest developments in this area if they have no foundation from their initial training? So as part of the working group, we will look to introduce molecular education into residents' training programs.

And in spite of many pathologists' and oncologists' concerns about the changes that will inevitably be accompanied by the rising importance of molecular pathology, the thirst for the knowledge is there. For instance, we are running an educational workshop in Brussels this month on immuno-oncology. We expected 50 people to attend, but we have 170 registered! Pathologists and oncologists understand that if they don't learn about these new advances, they'll be left behind.

Another key challenge for pathologists is the need to understand new technology platforms. Even if they are sending material to another lab to be tested, it's so important that pathologists understand the technology that's used in testing their material; in particular how reliable it is, how sensitive it is, and what the detection limits are.

Though many pathologists have been reluctant to adopt these new techniques and technologies, they need to be assured that molecular pathology is becoming part of their job.

How have the technologies and techniques that you use changed in the last few years?

We started out using Sanger sequencing and polymerase chain reaction (PCR). But now we work with next-generation sequencing (NGS), liquid biopsy, and

digital automated PCR technologies, such as Idylla (Biocartis). Our needs have changed a lot over the years; we need speed, reliability, sensitivity, high-quality. Newer technologies are giving us that, allowing us to make better diagnoses than ever before.

In our lab we currently receive around 2,500 cases per year, 80 percent of which are from other hospitals. We run a lot of HER2 FISH tests for breast, RAS tests for colon, and EGFR and ALK tests for lung cancers. We also conduct a lot of BRAF testing for melanoma and identify rarer forms of cancer, such as Ewing's sarcoma. I'm very excited about the advances in molecular pathology – they are allowing us to play a central role in improving patient survival! Having said that, our increasing knowledge and capabilities have their downsides too.

Downsides, such as…?

The volume of data generated by NGS. Our problem is having too much of it; we are overwhelmed. Also, our understanding of disease has advanced so much that we are now expected to run regular molecular tests for cancer patients not only for

diagnostic purposes but also for follow-up. For example, in NSCLC, I receive plasma samples from lung cancer patients receiving TKI's every three months to look for T790M resistance mutations. It's great, in that we can identify the 50 percent of patients affected by resistance but it is important that new drugs can be used to treat these resistant mutation. In the future, this kind of monitoring testing will become increasingly important and will account for much more work. These patients can have survival rates of three to four years, so it goes without saying that the huge burden on molecular pathology services will only worsen.

How will pathology services cope?

This is a difficult question to answer – I don't know. I'm hoping that more hospitals will conduct molecular testing with a short turnaround time. Turnaround times for these tests are so important, and waiting for one month or more for a result is unacceptable.

Molecular tumor boards are also very important. We already run these in our hospital; we meet weekly to discuss cases, in particular when non-classical mutations are found, and work to find solutions and treatment pathways. More hospitals need to run similar tumor boards, but for them to be truly effective, the pathologists and oncologists need to be kept updated of developments, otherwise they won't work.

Where will the money come from to expand molecular services?

Governments. I can't deny it won't be easy though. When I speak with government officials about the advances in molecular diagnostic technologies and what installing them will mean for patient outcomes, they're enthusiastic. But when we come to the issue of cost, the conversation ends. We are in hard financial times and every idea that costs more to healthcare services is not an easy sell. I do think that governments will back these technologies once they become cheaper. Remember when PCR was first introduced? Only academic institutes had a PCR because they were viewed as expensive and complex; I believe there were only around five or six systems in Belgium. Nowadays you can get a PCR for next to nothing. If these new platforms start to reduce in price, prove themselves reliable, easy to handle, and sensitive, why wouldn't almost every hospital have one? I believe this is the only way that we will be able to cope with the continuously expanding demands on molecular services.

I am very happy that I am not the Minister of Health – that must be such a tough job!

What technological improvements are still needed?

Fluids that can stabilize DNA so that it is easier to transport sample materials would be very helpful to us. If we consider the current process with plasma samples. First you have to take a 10 ml blood sample, then you have to centrifuge it within 1.5 hours, then you have to transport it immediately (or in dry ice), and it needs to make it to the testing lab as soon as possible. Improvements in stability to make all of these factors less critical would be ideal. Also, you need a lot of DNA to have a reliable test result and it would be helpful if analytical equipment could test DNA with lower blood volumes.

Manufacturers are making good progress, though. This is a commercially-competitive field and we can only benefit from that.

What are your predictions for the future of molecular pathology?

Follow-up testing of patients will become more important than ever. Also, our approach to diagnosis will need to change. For example, in the past, we would use traditional methods to diagnose lung cancer and this would be followed by molecular techniques to identify EGFR mutations. In the future, I believe we will look immediately for targetable mutations in a tumor.

One thing we can't predict though is the future influence of immuno-modulatory therapy on oncology. Advances in this field will change things for us. Currently I know of five firms that are trialing PD-1/PDL-1 antibodies, but they are being developed with their own partnered diagnostic assay. The fact that we may only be able to recommend new treatments with a specific companion diagnostic test result is a catastrophe for those of us who run the tests.

We are in need of new biomarkers too. I was speaking with someone at the recent ESMO congress in Vienna who said that, PDL-1 immunohistochemical tests "were the best of a bad bunch." We know they're not optimal predictive tests for PD-1 immunomodulatory therapy, but we currently have no alternatives.

Are you optimistic?

Always! When I was a resident, the impact of the pathologist on treatment decisions was sometimes limited. Nowadays, oncologists can do absolutely nothing without the pathologist. They don't know how to treat their patients unless they have all of the molecular information from us. So we are moving from the periphery of the clinical field to the central part of it. But we are not used to that. Pathologists are starting to understand though that, in order to progress in this field, they have to embrace this central role. Pathologists know it's time to change and I'm very optimistic about the future of our profession.

Patrick Pauwels is professor of Pathology at Antwerp University Hospital and director of the Molecular Pathology Unit. He is also president of the Belgian Molecular Tumor Working Group Antwerp (TOGA). He is an advisor to the Belgian Ministry of Health (lung cancer diagnosis and treatment working group) and of the Luxemburg Ministry of Health.

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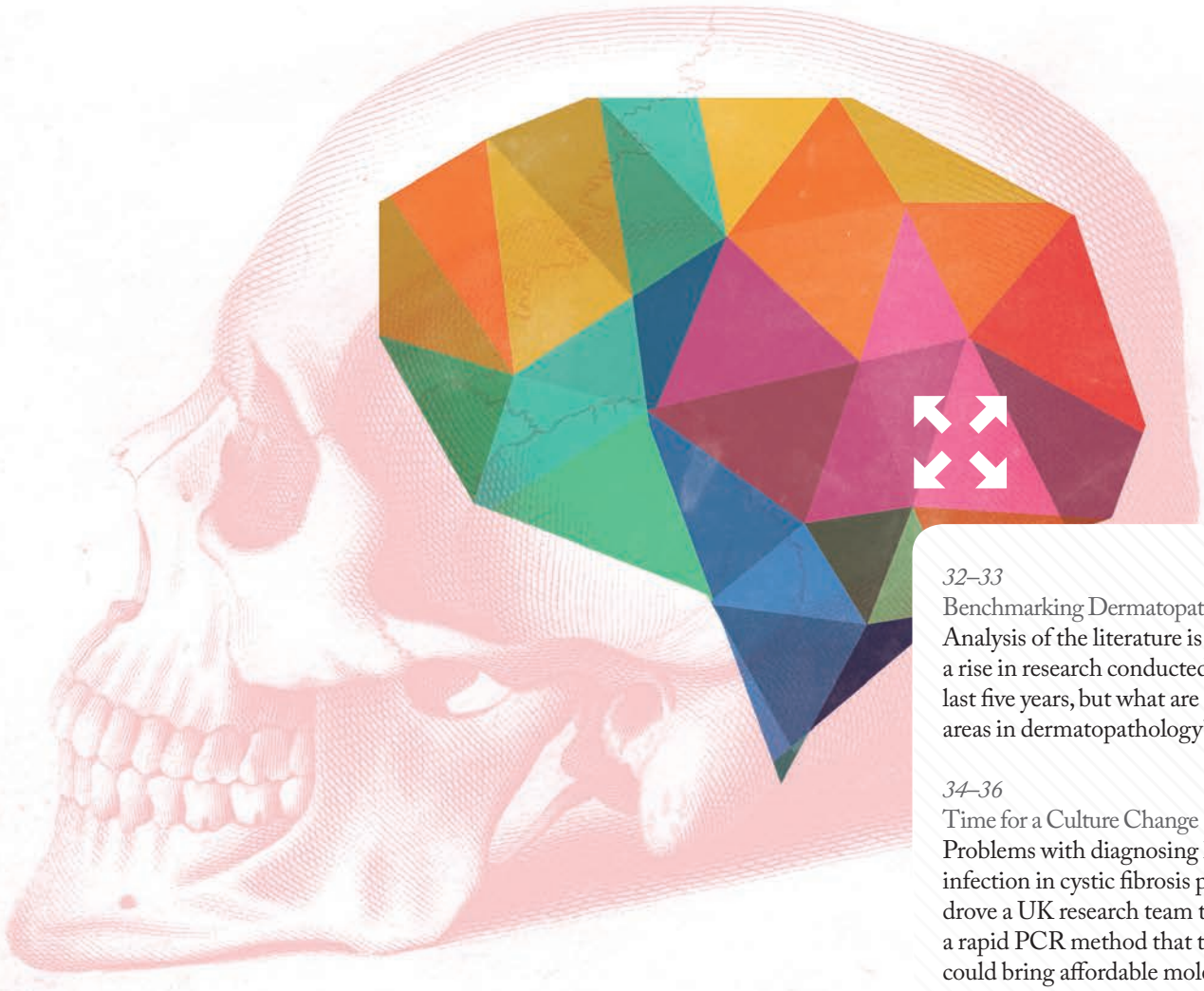


Benchmarking Dermatopathology

What does analysis of the last five years of the literature on dermatopathology tell us about the priorities of this field and the major contributors to it?

By Roisin McGuigan

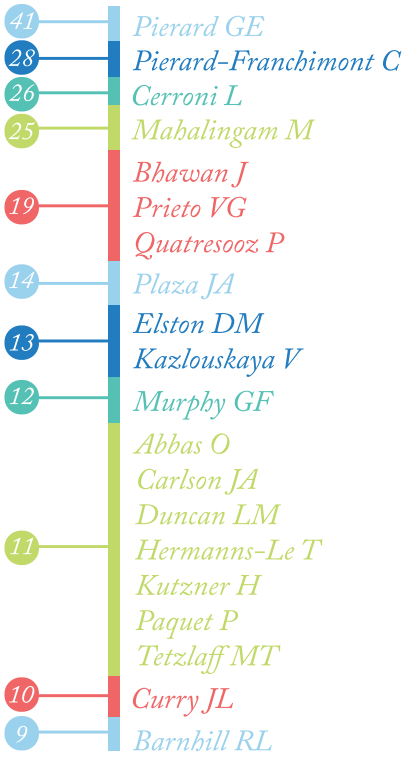
The term *dermato-pathologia* was coined in 1972 by the doctor Henry Seguin Jackson, to describe "the pathology and proximate cause of diseases of the true skin". Today, dermatopathology is a large and varied field, encompassing gross, microscopic and molecular study of the largest human organ. The number of disorders affecting the skin reach into the thousands, requiring a broad knowledge base, and overlap with other disciplines, such as oncology and immunology. In this month's benchmarking exercise, we take a closer look at this diverse specialty…

To provide insight into the past research priorities and predictions for the future of the field, a series of metrics were applied to the last five years of the published literature. We asked:

- What are the major topics for the field?
- Which publications have the greatest impact?
- How is the knowledge available online?
- Who are the most prolific authors?

PubMed was searched for "Dermatopathology" with results limited to the last five years, in humans (for a clinical focus). The data were analyzed in Microsoft Excel 2013.

Top 20 Authors by Number of Publications

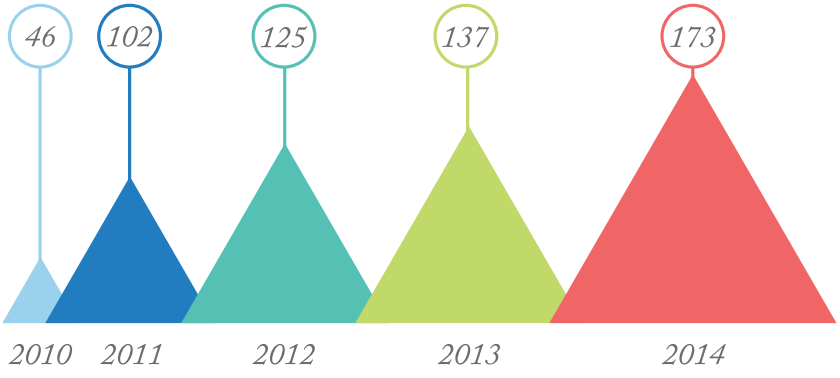


Top Five Journals by Number of Publications

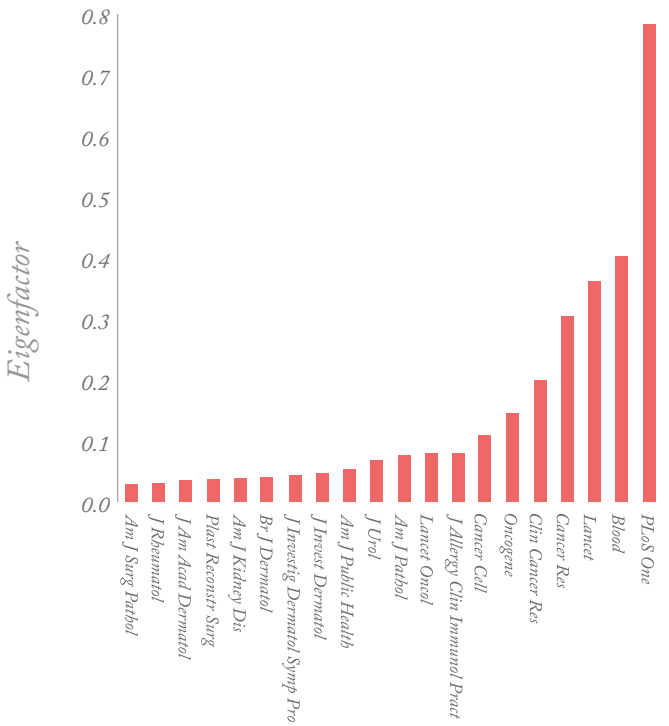
Top Five Topics

Articles in MEDLINE are indexed by Medical Subject headings (MeSH) topics, that describe the articles' main topics. Here are the top five MeSH terms over the last five years of human dermatopathology literature.

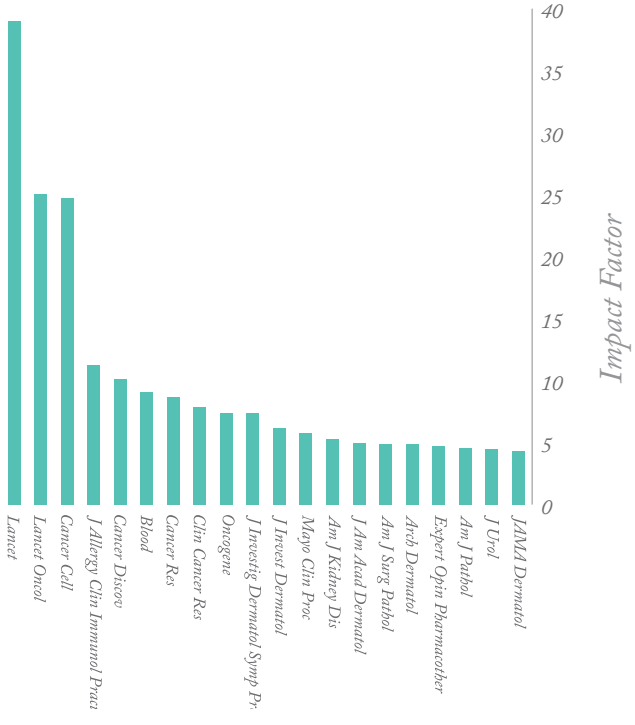
Publications per Year



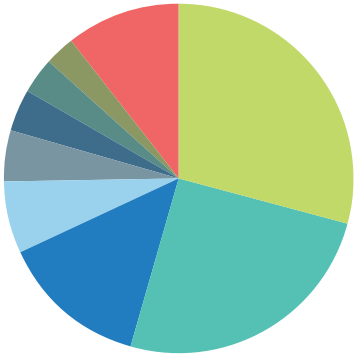
Top 20 Journals by Eigenfactor



Top 20 Journals by Impact Factor



Categorization of Articles



- Other 10%
- Profession 3%
- Comment 3%
- Clinical Trial 4%
- Comparative Study 5%
- Evaluation Study 7%
- Basic Research 14%
- Case Report/Series 25%
- Review 29%

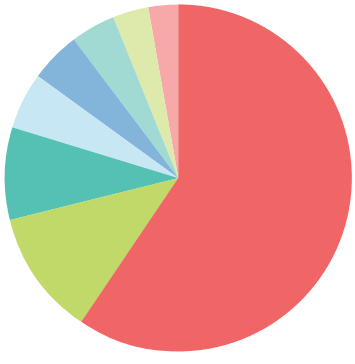
Articles are categorized according to PubMed criteria.

Fee or Free?

- Free Full Text 34%
- Full text available upon payment/subscription 83%
- Unavailable Online 3%

Proportion of articles by availability online.

Publications by Country



- Spain 3%
- Austria 3%
- Italy 4%
- UK 5%
- Germany 5%
- Belgium 8%
- Other 12%
- USA 60%

Time for a Culture Change

Molecular techniques can offer rapid, accurate diagnosis of lung infections in cystic fibrosis, but most labs feel the technologies are out of reach. What if there was an affordable alternative?

By Eshwar Mahenthiralingam

Frequent lung infections are a hallmark of cystic fibrosis (CF), can lead to severe clinical decline, and contribute to the cause of death in the vast majority of cases. Traditionally, lung infection is diagnosed by plating sputum from patients onto different microbial media, and looking for the growth of major CF pathogens such as the bacterium *Pseudomonas*. But this culture-based approach has not substantially changed in half a century, even though it's well known that CF sputum contains many different bacterial species, not all of which are easy to grow in medium (see Figure 1). Getting results can take days, and a culture of the dominant or disease-causing pathogen is not guaranteed. The problems we observed motivated my research team, and our clinical collaborators at the Manchester Adult Cystic Fibrosis Centre, UK, to tackle the challenge of developing a straightforward molecular test that could be used by clinical microbiology labs to better diagnose CF infections in public health settings.

At a Glance

- *Lung infections in patients with cystic fibrosis are commonly diagnosed using microbial culture*
- *The traditional method is far from perfect though; it's subject to bias, can miss disease-causing bacteria, and may take several days to return a diagnosis*
- *Molecular methods are frequently used in research settings and demonstrate the diversity of bacteria found in lung infections, but many hospital labs currently lack the resources*
- *A rapid and accurate PCR method described here, carried out in tandem with viral analysis, could bring affordable molecular testing to hospital labs*

"The approach has been fine-tuned to allow the capture and identification of key pathogens, but it frequently ignores other bacteria."

Culturing concerns

Culture is a tried and tested method for identifying and quantifying the bacterial species present in a sample, but its known to be open to multiple flaws and biases. The approach has been fine-tuned to allow the capture and identification of key pathogens, but it frequently ignores other bacteria (1). It is known that numerous infections are polymicrobial, including lung and other respiratory infections, urinary tract infections, wounds, ulcers, abscesses and many others. Molecular analyses have also demonstrated that

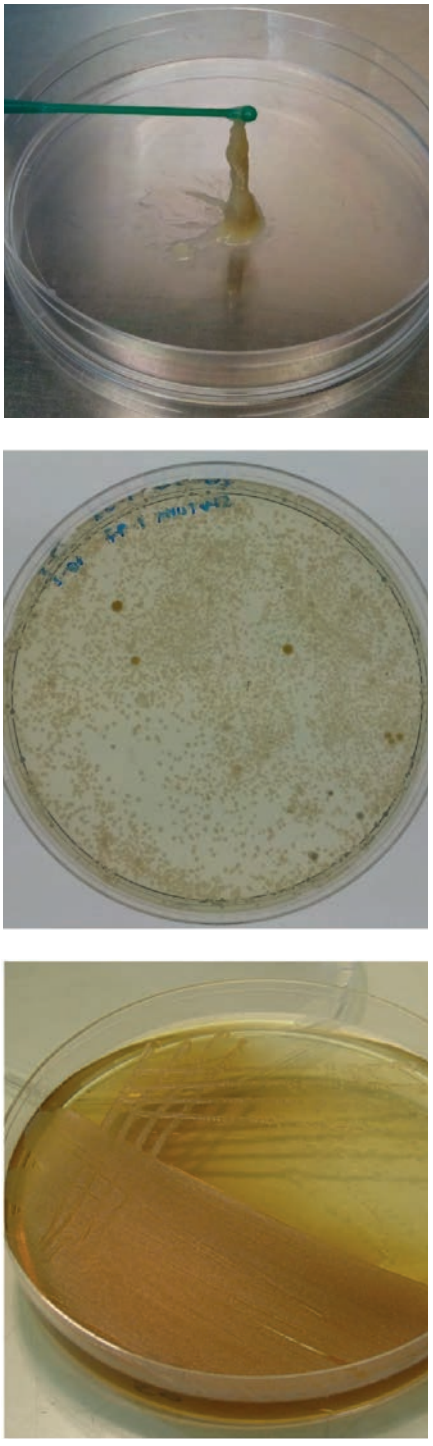


Figure 1. Sputum from patients with CF. It is a polymicrobial and difficult to process specimen type, containing a mixture of bacteria, some of which may fail to grow in culture.

anaerobic bacteria are present in large numbers in many infections, but most standard aerobic diagnostic methods cannot account for them. In contrast, molecular tests can detect all bacteria (and other microorganisms) present in these infections from their characteristic DNA signatures, and can return results much faster. I believe their applicability, accuracy and speed makes them an obvious candidate for more widespread use, and could bring many advantages to clinical bacteriology, but with the complexity and expense of most molecular technologies, smaller labs often feel these genetic tools are out of their reach.

Moving to molecular, inexpensively

In the last 10 years, multiple research studies have already adopted molecular methods. But DNA sequencing-based techniques, although the "gold standard", are currently beyond the capability of many diagnostic microbiology labs.

We evaluated a simple diagnostic PCR method, known as ribosomal intergenic spacer analysis (RISA) PCR, to see if it could be used as an alternative to expensive sequencing methods to rapidly (and inexpensively) profile the mixture of bacteria, and detect problematic pathogens, in CF sputum. RISA PCR amplifies the space between two ribosomal genes that are present in all bacteria, allowing universal detection, but crucially the size of this spacer region varies between different species – for example, *Pseudomonas* has a 753 base spacer, in contrast *Achromobacter* has an 887 base spacer. So, if we analyze DNA from a sample containing these two bacteria, two PCR bands will be seen, giving a simple profile that captures the bacterial diversity in the sample (see Figure 2).

We collected 200 sputum samples from 93 adult CF patients, and each sample was split for use in culture, and molecular analysis. In 11 cases, a CF pathogen was not found in culture, but was identified using the RISA profile. Some of these samples were characterized as containing "normal flora", despite known CF pathogens being detected using the molecular profiling tests (2).

We simplified the process further by using readily-available DNA from the sputum samples, which had been robotically extracted in order to test for viruses, such as influenza – molecular testing for viral infections is much more routine, as they are extremely difficult to grow in culture. Making use of this readily-available DNA would allow for a two-pronged diagnostic approach to simultaneously and rapidly diagnose bacterial and viral lung infection, using resources already available to many hospital labs.

Spotting missing microbes

When we put the RISA technique to the test, we were successful in quickly identifying CF patients with lung infections dominated by bacteria such as *Pseudomonas* and other multidrug resistant microbes known as emerging, non-fermenting, Gram-negative bacteria. Worryingly, we also found that in 11 percent of cases, these pathogens, which are associated with severe infection, were missed by routine growth-based bacteriology. The clinical condition of people with lung infections dominated with these bacteria will deteriorate unless the infection is treated appropriately, and we believe our research provides a means of identifying and addressing these infections, something that isn't always possible with non-molecular methods.

Profiling bacterial diversity in CF has other uses, too – when carrying out ribosomal ribonucleic acid (rRNA) gene pyrosequencing in a subset of 59 patients, we found that poor lung function significantly correlated to less microbial diversity, including a low abundance of *Streptococcus* in patients with poor lung function. rRNA pyrosequencing is currently considered to be a state-of-the-art method for analysis of lung microbiota (3), but is currently beyond the resources of many labs. We believe that RISA PCR is a useful alternative that can detect both dominant pathogens and a loss of microbial diversity.

"Making use of this readily-available DNA would allow for a two-pronged diagnostic approach to simultaneously and rapidly diagnose bacterial and viral lung infection."

Trials and translations

Molecular diagnosis offers multiple advantages – for the microbiologist, the most important are speed and accuracy. The former has already been demonstrated in molecular tests used routinely for notifiable pathogens such as *Neisseria meningitis* (where speed is crucial to diagnosing meningitis) and *Mycobacterium tuberculosis* (where its slow growth prevents timely diagnosis). Greater application of molecular testing to polymicrobial infections could also offer greater insight to

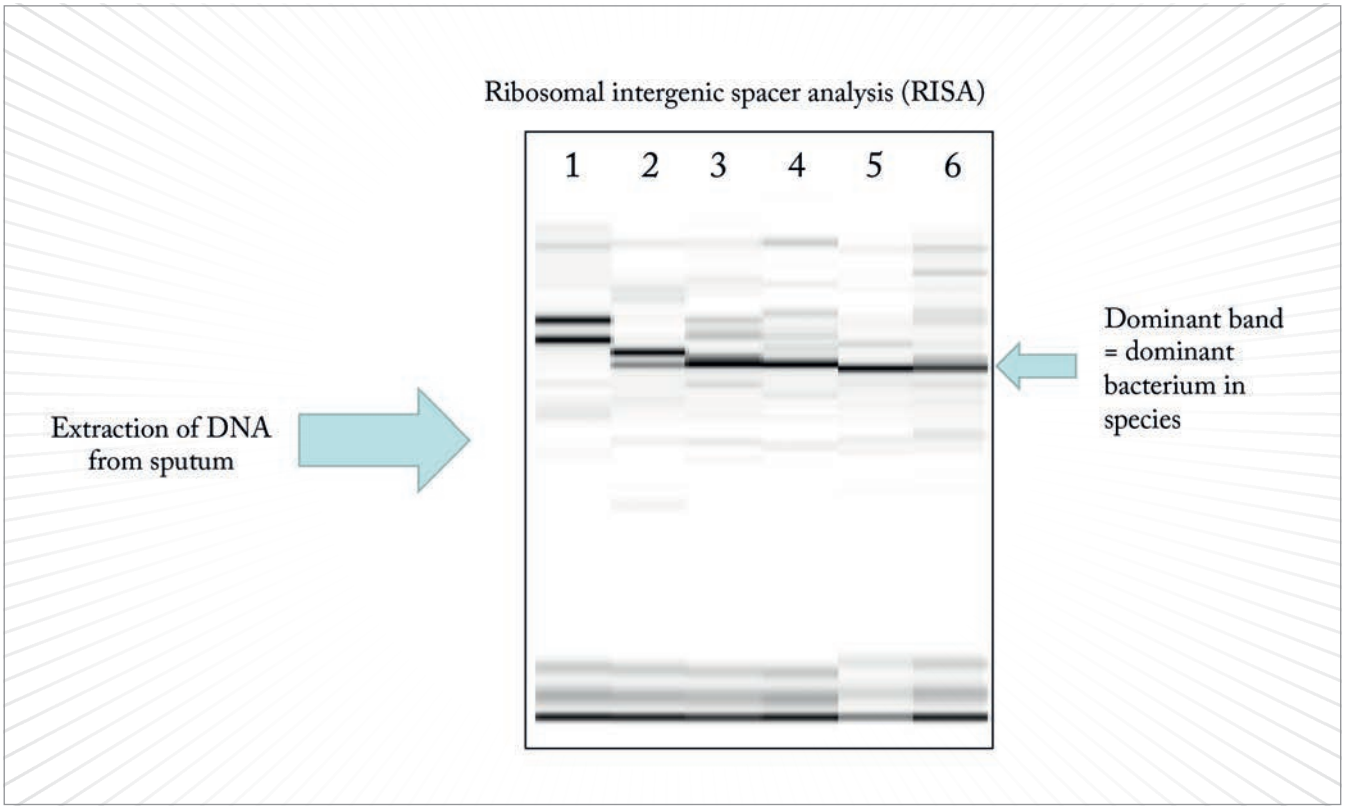


Figure 2. RISA PCR allows for identification of bacteria within the patient sputum sample based on the size of the microbe's ribosomal intergenic spacer.

the pathogens driving disease: it will proportionately identify the bacteria with the greatest abundance, rather than those that are easiest to grow. This may improve the therapies patients receive, by allowing more targeted antibiotics to be prescribed, and avoiding the use of broad spectrum agents which may be driving antibiotic resistance.

Following our promising initial results, we are now seeking translational funding in order to test the approach we have developed in real-time, and to compare it to routine practices for CF infection diagnosis. If our research can demonstrate the clear benefits we have seen so far, then we hope that they could soon be delivered as a new standard of care in CF microbiology. We're also working with the pharmaceutical industry to examine the bacterial diversity in CF sputum samples before and after the application of novel therapeutics; this will be one of the first clinical trials to compare molecular methods with standard bacterial culture as an outcome measure.

The strategy of using the same sample for bacterial and viral testing could also be explored in the future as a means to further investigate the respiratory microbiome in a clinical setting, which could have uses not just in CF, but other respiratory diseases such as chronic obstructive pulmonary lung disease. We believe that molecular testing could potentially bring both improved care and decreased costs to clinical microbiology laboratories, and ultimately improve our understanding of lung infections, both in CF and beyond.

Eshwar Mahenthiralingam is a professor and co-director of research at Cardiff School of Biosciences, Cardiff University, Wales. His research focuses on the biology and virulence of opportunistic bacterial pathogens, using molecular and genomic research strategies, and he has studied cystic fibrosis lung infections for over 20 years.

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Removing Margins of Error

New approaches to tissue analysis using Raman spectroscopy and mass spectrometry could deliver fast diagnoses in brain cancer – but no matter how sophisticated the technology, you can't replace histopathology

By Babar Vaqas

As a neurosurgeon, deciding on tumor resection margins can be a daunting task. Removing and analyzing a frozen section is time-consuming, and taking repeated sections during brain surgery isn't an option. Unlike with other locations in the body where there is a little more room for error, removing healthy tissue in the brain can have serious repercussions – the healthy tissue removed might impact the patient's balance, speech, ability to concentrate, or worse. But of course, failing to remove all the tumor tissue impacts the patient, too.

Although less than 3 percent of malignancies are located in the brain (1), it affects many children and young adults, and as a result it causes more years of life lost than any other cancer. And because it's so rare, funding new technologies and studies can be difficult.

Both Kevin O'Neill, consultant Neurosurgeon at Imperial College Healthcare NHS Trust, and I found the lack of options for treating our patients frustrating, and the particular challenges brain cancer poses during surgery set us out on a quest to tackle them head on. During our investigations, my colleagues and I opted to study two separate but very complementary technologies: Raman spectroscopy, and rapid evaporative ionization mass spectrometry (REIMS). Together, we believed they could bring the diagnostic abilities of the lab right into the operating theatre.

At a Glance

- *Choosing tumor resection margins during neurosurgery can be challenging – but now, a combination of two technologies, Raman spectroscopy and rapid evaporative ionization mass spectrometry, could provide a wealth of tissue data during surgery*
- *If the technology takes off, it could provide substantial therapeutic benefits, and allow treatment to begin much faster, by removing the long wait for a tissue diagnosis from the lab*
- *Pathologists are the obvious candidates for getting involved in this new real-time diagnostic approach, because no matter how sophisticated the spectra, tissue experts will be required to interpret and validate the results*
- *This type of big data is poised to be the future of medicine, and pathologists should embrace the increasing digitization of their specialty in order to remain at the forefront of the diagnostic evolution*

Better together

Raman spectroscopy is optical, involves no destruction of tissue, and gives the surgeon advanced warning that tissue may be abnormal, allowing them to make a decision on whether or not to remove it. A recent study has shown the technology to have 93 percent sensitivity and 91 percent specificity in distinguishing normal tissue from tumor in the brain (2). As tissue is being cut, REIMS provides constant positive feedback that the tissue being removed is indeed cancerous. When the surgeon hits normal tissue, the system will alert them. In a previous intraoperative study involving patients with various cancers (including brain cancers), REIMS analysis of brain tissue matched the histological findings 100 percent of the time (3).

Although both of these technologies are valuable in themselves, the way they interact amplifies their value (see Sidebar "In Harmony"). This combined approach teams a quick and accurate way to predict what's ahead, with a reliable, detailed analysis of the tissue currently being operated on – a fantastic combination!

"It's important that pathologists embrace the increasing digitization of their discipline."

The story so far

We have now tested the two technologies in over 20 patients during surgery, and the method has demonstrated the ability to spot and grade tumor tissue. It's not yet been validated, so it can't be used for a definitive diagnosis, but it appears to characterize tumors very well based on initial results.

The technique we're using has also garnered a good deal of media attention – in fact, the surgery of one of our patients was filmed by the BBC (4), and covered by numerous media channels. During surgery, the patient was asked to speak and sing in order to ensure these abilities weren't affected by the section of brain we were removing. We demonstrated the precision of this combined technological approach, and it was pretty impactful to watch, hence the media attention that came with its filming.

In Harmony

Raman spectroscopy:

- Raman spectroscopy, which is commonly used in chemistry, relies on scattering of light from a laser, which interacts with the molecules of the tissue it's aimed at, providing vibrational information
- This information offers spectral tissue characteristics based on the molecules present
- This system can be used in real-time to distinguish between the molecular signature of normal and cancerous tissue

Rapid evaporative ionization mass spectrometry (REIMS):

- REIMS uses bipolar forceps, which are routinely used during surgery, to cut tissue and control bleeding, to analyze the smoke produced as tissue is cut
- The gas-phase ionic species produced during cutting are sucked up for analysis by mass spectrometry
- The mass spec profiles are specific to the tissue and statistical analysis can provide information on the tumor, including grade in some cases

Diagnostics and big data

I see these two technologies as having three areas of clinical potential. First, they could provide an immediate diagnosis, avoiding the often nerve-wracking waits of a week or more for histological results. For a patient who may have felt perfectly healthy, and has been told they could have brain cancer, this wait is extremely difficult. Further, attaining an accurate diagnosis on the day of surgery means that treatment can be streamlined, allowing for a personalized treatment plan to be devised in a fast and efficient manner, much earlier than is otherwise possible.

Second, it can provide a continuous data flow to the surgeon and therefore a whole new layer of information to aid decision-making in the theatre. Current methods, such as preoperative MRI and ultrasound, leave a lot to be desired, and I know that many neurosurgeons would really value these extra sources of information to work with.

Finally, there are clear implications for personalized medicine. Each time REIMS is used, it generates around 2 million spectral points – that's a lot of data. The extreme level of analysis we achieve with REIMS could help to create the ultimate patient profile, and identify diagnostic biomarkers – it should be possible to mine the data and find out if particular spectrums perhaps predict response to treatment, or disease aggressiveness.

Pushing out pathology?

On hearing of a technology that could potentially diagnose tumor tissue in real-time during surgery, some surgical pathologists may think: "But you'll put us out of a job!" Actually, nothing could be further from the truth.

Pathologists are poised to play a crucial role in these new developments – as long as they embrace the way diagnostics are evolving. These spectra provide additional tissue information which could aid their own diagnostic work; sampling errors during biopsy can result in inaccurate diagnoses. This technology also offers a faster route to diagnosis – with many tools at pathologist's disposal, such as immune-staining and genomic analysis, getting an answer takes time. With REIMS, the answer is instantaneous.

I believe that pathologists are perfectly placed to become the specialists in this technology, advising surgeons on the spectral information being collected in the theatre. After all, as the surgeon acquires this new tissue information, they will need a tissue specialist to guide them. In future studies, it would be great to get more pathologists involved so they can define their own role.

Society is becoming more and more data-rich, and the more available data, the easier it is to classify and characterize disease. Although I believe technologies like this are the future, a human will always be needed to assess if the system is reliable or not. We cannot replace histologists!

But we don't just need the input of pathologists – I find these new technologies so exciting because they are truly cross-disciplinary. It will need pathology, chemistry, physics, electrical engineers, surgeons, and nurses – motivated scientists from many disciplines – to get involved.

Adoption obstacles

So is it likely that the Raman probe and REIMS will gain widespread adoption in the real-time diagnostic setting? As with any new innovation, it is too soon to predict its eventual success or failure. But so far, with the feedback I've had from conferences and colleagues, I am very hopeful.

As is always the case though, obstacles exist. Using these devices in surgery is simple, as it's essentially a "point

and shoot" approach. Interpreting the spectra is a more complex matter, but we are currently developing algorithms to better understand the data the analysis generates, and hope to implement a simple system to distinguish between normal and tumor tissue.

Expense is another problem. At the moment, these are expensive pieces of kit used for research; especially REIMS. But they're equipped with more dimensions than are needed – we won't need everything to be analyzed. Once it's clear what information is important to us, it should be possible to slim down the system. Much like modern smartphones, I expect these tools will become smaller, lighter, and better; and older versions will become progressively cheaper.

One key factor that would support a cost-efficiency argument is that these technologies can be used in other cancer types – the Raman probe has already been trialed in upper gastrointestinal tract malignancy, and colon cancer. REIMS is also being investigated in breast, colon and gynecological cancers. I think in the next five years, we are going to see expansions of these technologies and the different situations they can be used in, as they represent a potential game-changer for many types of surgery. Now that proof-of-concept has been established, larger, interventional studies need to come next.

Facing a digital reality

Cost and training aren't the only issues: for this technology (and others like it) to succeed, I think it's important that pathologists embrace the increasing digitization of their discipline. Essentially, this technique is transforming tissue into digital information, which we can then use to profile the patient. Looking further into the future, I definitely see techniques like this becoming widespread. It gives the surgeon a quick answer, and learning how to further use this kind of complex data is simply a part of modern medicine. With any large change there is resistance; many people tend to be happy with the status quo, but I suspect that, as the applications of this type of technology are more widely understood, it will eventually win over the skeptics.

Babar Vaqas is a neurosurgeon at the Imperial College Healthcare NHS trust, London, UK, and chief investigator of the Raman spectroscopy and REIMS trial. *The project is supported by the BTRC (Brain Tumor Research Campaign) and BTR (Brain Tumor Research).*

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Profession

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Modern Day Telemachus

As the pathology profession evolves and transitioning to work becomes more challenging, the importance of mentoring becomes greater than ever.

By Chelsea Maedler

The transition from residency to practice can be a challenging one – job demographics are changing, and the role of the pathologist within hospitals and labs is evolving. It is therefore no surprise that many residents have concerns over how to make the leap, with many citing fears such as negotiating interviews, adjusting to work, and what to do if their dream job isn't everything they hoped for (See "Top Ten Pathology Resident Concerns").

At a Glance

- *Graduating from residency to practice can be tough, and changing roles and job markets means many residents are unsure how to successfully tackle the role of junior pathologist*
- *Among the top concerns are work-life balance, navigating interviews and how to cope if things go wrong*
- *One potential solution is a mentorship program, which allows a senior pathologist to share their skills and experience with the next generation*
- *Understanding resident worries, and establishing effective mentoring programs with clear ground rules, are key to supporting residents' transition to the workplace*

Ancient, but not out-of-date

Although embarking on a new stage in any career will always be a daunting prospect, it is crucial to give residents the support they need during this transition. One important but underused way to provide this is through the use of mentorship programs.

The fields of management and business have long appreciated and harnessed the power of the mentor. In Greek mythology, Mentor was charged with caring for Odysseus's son, Telemachus. Gifted with wisdom and experience, he was able to guide his younger charge. Contemporary mentorships include any relationship which allows an experienced individual to pass on his or her insight to those who can gain from it, and can be found in many facets of life, both personal and professional.

Despite the long history of mentorship, modern medicine has been slow to embrace and promote the idea. But, things are changing and Institutes are starting to place a greater emphasis on it. For example, the department of Pathology at McGill University, Quebec, Canada, is spearheading efforts to promote mentorship, and is creating a database which will link staff and residents who want to take part. The hope is that mentorship will soon become ingrained into the culture of the pathology department (see "Mentoring: What You Need to Know").

Making mentoring work

Why is this approach important? It's clear that transitioning to practice is difficult for residents; a mentor can provide invaluable support, knowledge and a wealth of experience, helping to prepare residents for the next stage of their career.

In acknowledgement of the challenges faced by residents, the Canadian Association of Pathologists (CAP) hosted an inaugural workshop dinner for residents at its annual congress, where three pathologists shared their personal experiences of transitioning from residency to practice, and stressed the importance of creating strong bonds between staff and trainees. The workshop was created by Bojana Djordjevic and her colleagues from the Universities of Ottawa and Toronto, Canada. I spoke with Bojana about her role in creating the workshop, and how programs like this can help to prepare residents for the end of their training.

"You need to reflect on the career you want, what you want to accomplish, and what you're willing to sacrifice."

You say it's important to provide support at a residents' transition to work. Why?

Through my own work as a mentor, residents have opened up to me about a multitude of issues: fellowships, job interviews, childcare, essentially everything. I realized there was an underlying theme: the transition to practice. It's important to provide all residents with the opportunity to seek guidance from junior staff who have both experience, and fresh memories of what it was like to finish their own training. It's also very valuable for residents to learn from the experiences of pathologists from other career paths, so they could see how many ways there are to get from A to B in pathology. The workshop that I ran at this year's CAP congress was developed precisely with these objectives in mind.

Why are workshops needed?

Teaching residents about these skills in a formal residency curriculum is hard, yet these decisions are pivotal. We aim to cover concerns in an integrated manner, as they are all interconnected – the fellowship you pursue will influence the job you get, which affects your professional role, and this in turn impacts your personal life. It's a domino effect.

What do you think is the biggest obstacle facing newly graduating pathology residents?

I would say finding your first job is the most universal and significant issue. Everyone wants to find a job that suits their career and personal interests. In Canada specifically, changes to the economy and government funding mean pathologists work long into their sixties, and even seventies, and this is changing the job market. I feel tackling these issues is more important now than ever.

What was the biggest hurdle you faced when entering practice?

Finding my path. In training, your path is laid out in front of you. Your years are very structured, but when you get to practice there are really no objectives anymore. You've just spent eight to 10 years in training and now you wonder, "what am I supposed to do?"

The biggest epiphany I had was when I realized that I am now the navigator of my own career path. This is a bit scary initially, but eventually it becomes very liberating. Now, I

Top Ten Pathology Resident Concerns

A recent survey of Canadian pathology residents (1) aimed to identify what they viewed as the most important issues concerning their transition into the role of pathologist – of 32 possible topics, the 10 most prioritized included:

1. Choosing a practice pattern that is suitable
2. Interviewing and negotiating when getting a first job
3. Choosing to practice in the right location
4. The first day of work, and adjusting to a staff workload
5. Getting involved in medical student, resident and fellow education
6. Work-life balance
7. Obtaining fellowship training
8. Having a back-up plan
9. What to do if things don't seem to be working out at a new job
10. Dealing with administrative roles both within and beyond the pathology department

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Mentoring: What You Need To Know

In a departmental workshop in November 2014, the residents and staff at McGill University shared the nine things about mentorship every pathologist should know, based on their own personal experiences.

1. It's Symbiotic

Many pathologists view mentoring as a one-way street, with little reward for the senior pathologist. But when done properly, this perception falls by the wayside. A new way to help others, recognition (including accelerated promotion), and career satisfaction are just a few of the benefits. Being a mentor can give you a sense of pride, and a hand in developing the next generation, allowing you to pass on the expertise and skills you've developed during your career.

2. There Is No Magic Formula, But Ground Rules Help

There is no one way to promote, organize or develop a mentorship program that guarantees a great experience for every trainee. But good ground rules, and understanding the core concepts of mentorship, will help everyone involved. Educating staff and trainees on good practices ensures common mistakes are avoided. Workshops, teaching sessions and retreats are all good ways to establish the "right" mentorship culture. Universities and faculties often have support staff or educators who will be able to help you create effective and engaging discussions.

3. Mentorship Is Not Friendship

This doesn't mean a mentoring relationship should be cold and overly formal. On the contrary, it should be cordial, personal and enjoyable. But remember that the nature of this relationship means the power balance can never be equal – this imbalance is what distinguishes a mentor from a friend, and maintaining an appropriate professional distance is advisable.

4. Follow The 3 "C"S

Competence, confidence and commitment: every successful mentoring relationship is founded on these three attributes, and it has to come from both sides. Competence means sharing your knowledge and experience, maintaining mutual respect and using good judgment. Confidence comes from a mentor's willingness to share their contacts and resources, and also from their willingness to allow their protégé to develop on their own terms. On the flip side, mentees need to show initiative and interest, and share credit for their successes. Commitment is an obvious but commonly overlooked quality. Mentor and mentee need to invest time, energy and effort, and be open to sharing personal experiences, especially negative ones.

5. Faculties Love Mentorship, And So Should You!

Although much of the evidence is still anecdotal, promoting mentorship is thought to contribute to healthier work environments, and possibly improved patient care. It has also been reported as improving professional relations between senior and junior faculty members, as well boosting productivity by encouraging collaboration. It provides an opportunity to air potential problems and find solutions, helping to keep residents satisfied and supported.

6. Hitting The Wall

There are many perceived barriers that need to be overcome before an institution can create a successful program. Many people think they simply don't have time, on top of clinical, research and administrative responsibilities, and a lack of resources and training can also be huge barriers. Failure to recognize the importance and value of mentoring, along with inconsistent implementation, participation, and evaluation, are all issues that can stifle progress if they aren't addressed.

7. Know When You Need To Break Up

Just like your personal and romantic relationships, sometimes you'll find you simply aren't a good fit. Compatibility plays a huge role in the success of a mentorship, and the individuals involved should not be afraid to openly discuss this. If either party feels things simply aren't working, they should be able to comfortably end the relationship in a safe and professional manner. When developing a mentoring program, educating faculty about this concept is crucial, as it makes sure individuals are empowered to address the issue if they need to, and could help to prevent burn out.

8. Mentorship At Every Level

Mentoring relationships are not restricted to resident trainees and staff. Junior staff members have found mentorship with senior staff invaluable to their progress and careers. Pathology assistants, technicians and medical students can all benefit from liaising with more senior staff. Encouraging, promoting and rewarding pathology residents for undertaking mentorship roles with more junior members of the department can help ensure that they continue this tradition throughout their careers.

9. The Myth Of The Perfect Mentor

Don't let being a "perfect mentor" get in the way of being a good one – there is no such thing. Attempting to solve a mentees' every problem or offering advice on situations outside of your expertise can potentially erode trust and cause problems. Stay within your comfort zone, and understand you own limitations. If you're unsure of how to help or support your mentee, be honest.

feel good about breaking my own ground. Career building is a constantly evolving process. You need to reflect on the career you want, what you want to accomplish, and what you're willing to sacrifice.

How can pathology departments improve their residents' transition?

Speaking of my experience in Canada, residency programs need to expose residents to the "real world" caseload of a staff member. But it is a tremendous challenge for programs to strike a balance between exposure to case volume and providing residents with sufficient time to assimilate, study and prepare for their exams. Internationally, I think one solution is graduated responsibility, which can ease residents into the roles and core competencies of a member of staff.

What advice would you offer pathologists in training?

Be ravenous. Take every opportunity to prepare yourself for the next step. If you're a junior resident, aspire to be like a senior resident. If you're a senior resident, try to think like a junior staff member. Treat every case like it's your own and set yourself high standards – your residency sets the tone for the rest of your career.

On the other hand, get into as much trouble as you can! This is a safe time for you to learn in a supervised environment, without worrying about the cost of mistakes. Don't be afraid to look at cases, ask the questions you want to, and above all, to be wrong.

What advice would you offer staff who are interested in helping their trainees?

Get involved, and connect. Everyone has their own story; residents tell me about where they're from, their training background, their family life. By showing others that you don't only care about their medical knowledge, but also their personal journey, you offer them an opportunity to open up to you, and show you how to support them. Whether it's providing childcare resources, or linking them up with the right researcher, you can then help them in the best way, based on their personal needs.

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Bojana Djordjevic is an assistant professor at the University of Ottawa and a gynecologic pathologist at The Ottawa Hospital, Ontario, Canada.

The Invisible Doctor

Pathologists have regressed from eminence to anonymity – how did it happen and what should we do about it?

By José I. López

Going back hundreds of years, pathologists, along with psychiatrists, dominated the field of medicine. They were viewed as eminent members of society, even appearing as lead characters in novels of some of the greatest European writers like Thomas Mann or Hermann Hesse.

Modern anatomic pathology was then born in the 19th century in Germany when Rudolf Virchow stated the third principle of cellular theory and contributed to the greatest ever change in the knowledge of human disease processes. His third principle – summarized in the aphorism *omnis cellula e cellula*, meaning that every cell has been originated from the division of another cell – completed the two other basic principles of cellular theory proposed earlier in the century (1839) by Theodor Schwann and Jakob Schleiden.

To consider disease was the result of cell disturbances, and not of humorism, was a giant leap forward at the time, comparable with the discovery of the double helix in 1953 or to the human genome in 2005. Everything changed: biology was reformulated and nothing was the same thereafter. By the dawn of the 20th century, pathologists were at the summit of scientific knowledge. Virchow was the first pathologist nominated for the Nobel Prize of Medicine – in fact he received three nominations – and although he did not take the prize, two histopathologists shared it in 1906: Camillo Golgi and Santiago Ramón y Cajal.

Clinicopathological correlation – a concept defined by Italian Giovanni Battista Morgagni in the 18th century – supported the great advances made in internal medicine in Europe, in particular in France and Great Britain in the early 20th century, when the best clinicians sought the support of pathologists to further their understanding of disease and its clinical relevance to the living patient. The vanguard of pathology then moved from Europe to the USA where it continued its forward trajectory to modernity.

Tarnished by history

Pathology as a medical discipline has evolved tremendously in the last 50 years. Three major milestones have had a dramatic influence: 1) the development of anesthesia – better surgical interventions became possible and surgical pathology was created; 2) the development of the endoscope – a technology that allowed doctors to reach the most recondite sites through natural body openings for study and take small biopsies if needed; 3) the molecular approach – a trend that is very much at the forefront of our evolution right now.

Biopsies and cytologies replaced the autopsy as our main activity, making pathologists integral to the medical decision-making process. And yet, during this dramatic evolution, pathologists have moved to invisibility. Everyone knows what psychiatrists, gynecologists, dermatologists, and so on, do, but very few know anything about pathologists, other than what they see on television.

> *"Europe has a big history in pathology, but this history may somehow be working against us."*

History and tradition are frequently thought necessary for a sustainable evolution but in pathology's case, both have been a heavy backpack that we have had to carry on our climb up the mountain of modernity. Europe has a big history in pathology, but this history may somehow be working against us; it links us unconsciously with forensics and autopsy in the social collective mind. The US don't have this long history of centuries of autopsies behind them and that can be an advantage for American pathologists. But all around the world we have the bad influence of TV – Dr House, Quincy, CSI – in which pathology appears as a simple and easy-reading task under the microscope that almost any doctor can do. Some

At a Glance

- *Historically, pathologists were viewed as eminent members of society*
- *Since the birth of modern anatomic pathology in the 19th century, pathology has evolved at a dramatic pace; placing it at the center of research and the medical decision-making process*
- *In spite of this, pathologists have become invisible to the public and medical peers*
- *Pathologists are at the forefront of today's most exciting medical advances, and so must take responsibility to reverse this trend, which has caused the future of our field to appear uncertain*

students actually tell me the reason that they were attracted to pathology was because of a TV series! What's worse is that we haven't fought against this attitude.

Sadly, this ignorance does not only affect the general public, it applies to those who are an active part of the healthcare system too.

Dispelling myths

Contrary to a belief among our colleagues of other specialties, pathologists do not read the slide under the microscope because nothing is written in cells and tissues. Under the microscope, the pathologist interprets morphological and immunohistochemical data, integrates them with clinical, analytical, molecular and radiological data, and delivers a pathological diagnosis. The pathological diagnosis is much more than a mere result, it's a complex interpretation of multiple and diverse data. Sometimes it is easy, sometimes is not; our job involves seeking out plenty of wolves in sheep's clothing. We need to take responsibility to communicate this message to our medical colleagues.

For the general public, it's important that they know, at the very least, that a pathologist's diagnosis assigns a name to almost every disease, gives crucial information about the extent of the disease, predicts its prognosis, selects the patients that may receive expensive treatments, and evaluates *a posteriori* the effect of these treatments on the patient. How do we do improve

public perception? We step out of our comfort zone.

Breaking the mould

Given our importance to the healthcare system, why do we find ourselves battling for recognition? Pathologists sell themselves cheap, and I believe we are somehow guilty of our own invisibility. It's particularly shocking to me that pathologists do not meet with patients, a fact that surely would improve the perception of our profession. Patients, and their relatives, should have the opportunity to meet the doctor who has made his/her diagnosis at least once and to have the opportunity to ask about things relating to their condition that they usually do not understand. This way everybody will know what a pathologist does and we will retake the recognition that we deserve. I sincerely feel that patients should see two doctors during their initial oncologic consultation: the one doctor who explains how the diagnosis was arrived at, including details of the condition (pathologist), and the second who defines the therapeutic pathway (oncologist). But this is not a new idea. By 2000, being a visiting pathologist at Princess Margaret Hospital in Toronto, I attended one such meeting. There were endocrinologists, surgeons, and the pathologist in the room, and the patient and her son had the opportunity to find out more about what was going on with her pituitary adenoma and its treatment options. Pathologists need this change in approach to happen and it needs to be driven through the collaboration of multidisciplinary societies. It is going to take a long while to change the paradigm though – easily 10, 15 years – but only if this starts happening today.

A major consequence of this lack of recognition is the menacing shortage of pathologists in Europe today – medical students consider our specialty boring and wordy and don't think to select pathology as a first option. We struggle for healthcare spend, so we're constantly under pressure to deliver more with less, and neither patients nor the general public know about us.

As well as working with societies to encourage patient communication, I also believe that our invisibility can be cured with information strategically disseminated in the media. Some of the key messages that we need to get across include:

1. Pathologists are clinicians, not forensic scientists
2. Pathologists work for living people, even when they perform autopsies
3. Pathologists' reports are not cool results of sophisticated and expensive devices; instead, they are a synthesis of complex interpretations of multiple data
4. Pathologists save money to health organizations helping to select the appropriate treatment for the appropriate patient (personalized medicine)
5. Pathologists are the clinicians closest to basic science
6. Pathologists' opinions are needed to inform difficult multidisciplinary clinical decisions with patients
7. Pathologists keep tissue specimens obtained from patients safe for future research.

Although predictions for the future appear fairly dismal, I will say that the seed grows many times in hostile terrains. In 1914, Ernest Shackleton, needing to recruit a crew for his Transantarctic imperial expedition, published an unusual announcement in The Times newspaper: "Men wanted for hazardous journey, small wages, bitter cold, long months in complete darkness, constant danger, safe return doubtful, honor and recognition in case of success." The announcement inexplicably received 5,000 applications for the 56 positions available.

"It is going to take a long while to change the paradigm though — easily 10, 15 years — but only if this starts happening today."

Trainees need to be advised before boarding that the journey is long and the wages short, that long periods of complete invisibility are expected, that honor and recognition, in case of success, are often taken by others. However, the paradox is that the future has never been so attractive and challenging for us – we are at the center of some of the game-changing future trends in medicine, which is wonderful, and we should also relish in the opportunity that we have to change the perception of our field, forever. These are exciting times for pathology!

What we need to do now is to work together to improve the visibility of our profession. If we don't, its future could be in trouble. It's impossible to change the mindset of society overnight; we need to start changing things today!

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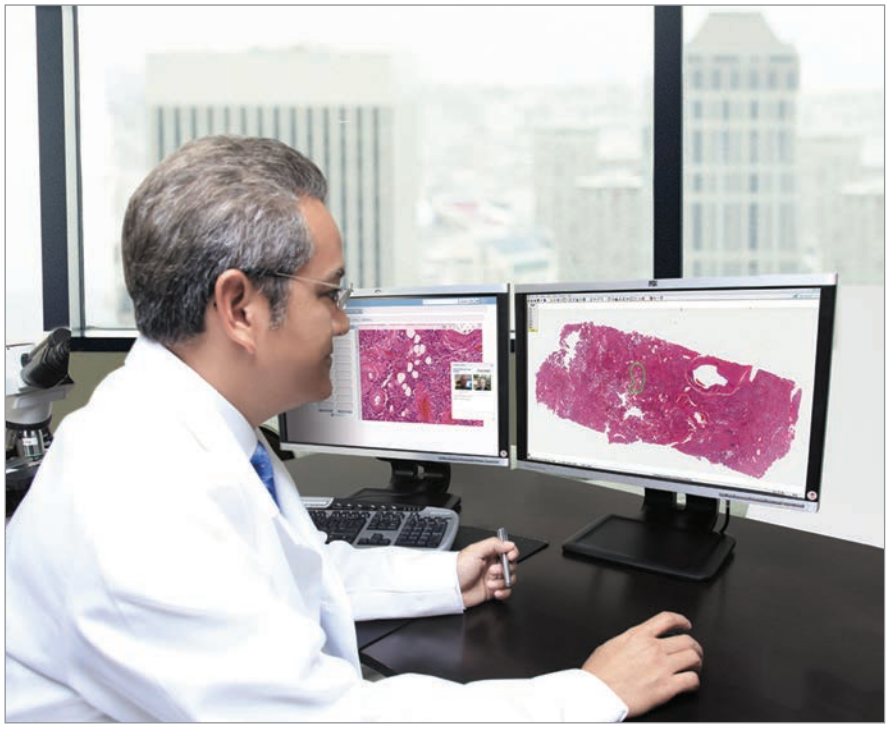
Remote intra-operative diagnosis in neurosurgery

Excerpt from an article by Graham McHardy, Department of Pathology, Aberdeen Royal Infirmary, Foresterhill, Aberdeen, UK

Full article originally published in Hospital Healthcare Europe 2015



Telepathology is the process of digitizing histological images for transmission electronically to remote centres, often for the purposes of diagnosis. The Aperio system from Leica Biosystems described in this report uses Whole Slide Imaging (WSI) to produce a complete digital representation of the tissue.

The loss of the neuropathology post from the pathology department at Aberdeen Royal Infirmary resulted in the suspension of the intra-operative reporting of neurosurgical biopsies. The Aperio CS2 system was installed in early 2014, with the primary aim of re-establishing this important service. In conjunction with this, the neuropathology department at the Western General Hospital in Edinburgh agreed to include the remote reporting of urgent neurosurgical biopsies as part of their overall referral service. This article describes our experience of the Aperio system in its first year of use, during which time approximately 70 urgent neurosurgical cases have been reported.

During the intra-operative procedure, telephone contact between the department and the remote neuropathologist is not continuous, but is made at appropriate stages, for example, when the specimen has newly arrived or when the first slide has been scanned and is available to access remotely.

Specimen sampling and laboratory procedures are carried out following the guidelines and advice of the neuropathology team in Edinburgh.

During its first year of use, the Aperio system has been found to be easy to use, providing excellent image quality, and requiring minimal calibration. For urgent intra-operative cases, we have found that it is possible to have at least one scanned slide ready to view within 15 minutes of receipt of the specimen. There was only one failure of the intra-operative procedure in the first year of use, but this was due to a network problem at the remote site rather than a hardware or software problem.

In the majority of cases, the automatic scanning mode is ideal, especially when scanning frozen sections, which provide a relatively flat surface and a clear outline on the glass. It is possible to load up to five slides at a time for automatic scanning, allowing the operator to attend to other duties.

Allowing for the extra time required for the scanning process, the reporting turnaround time should be only marginally greater than that of a conventional in-house, intra-operative case using a microscope.

Remote reporting obviates the inconvenience, expense and time required for a neuropathologist to travel to other centres. With good communications and a little pre-planning, the referring laboratory can ensure that the whole procedure has minimal impact on the reporting neuropathologist's normal daily working commitments. From our laboratory's perspective, the introduction of scanning for remote reporting has been a necessary new technology, which has restored an important service for the benefit of patient healthcare.

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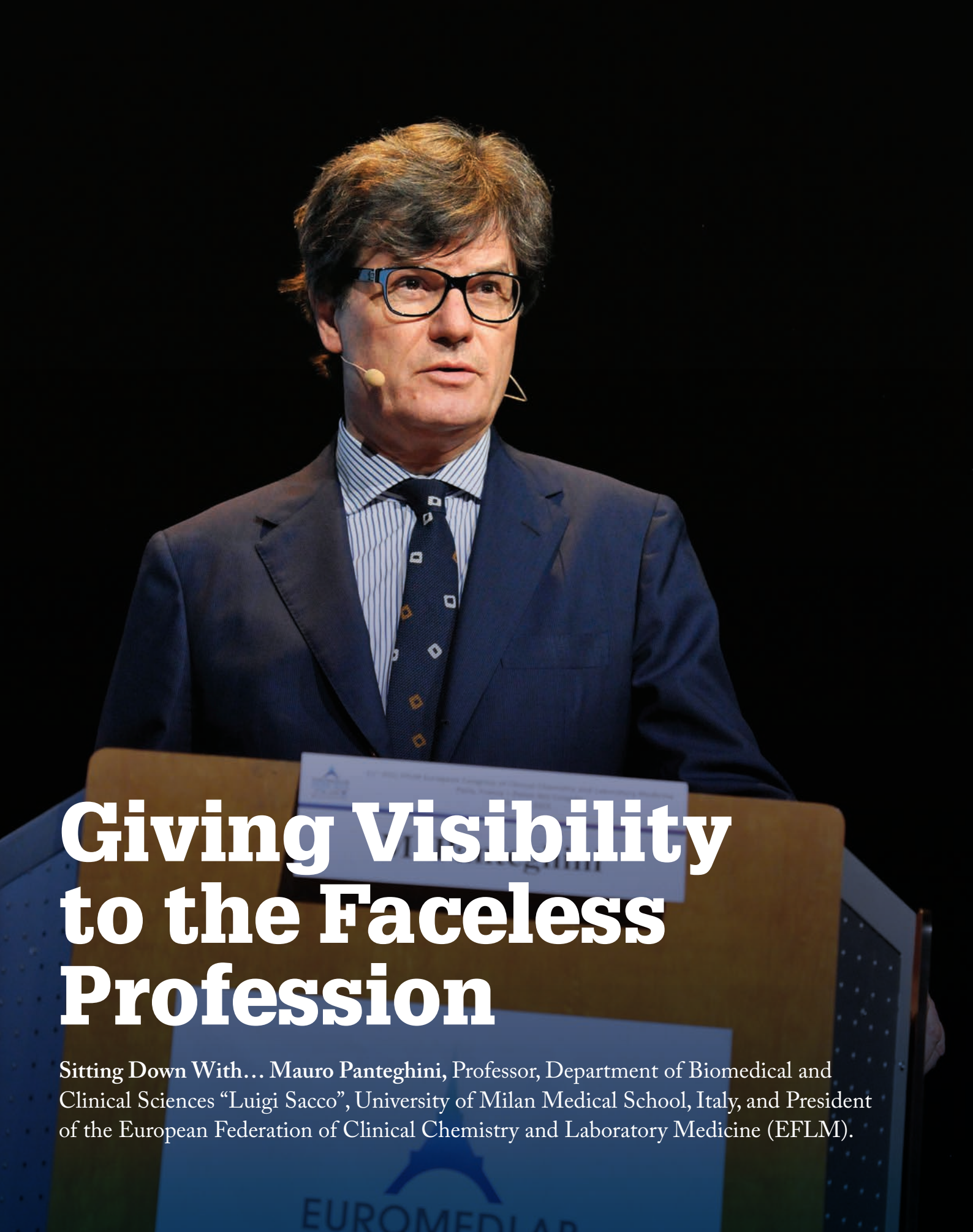

Giving Visibility to the Faceless Profession

Sitting Down With… Mauro Panteghini, Professor, Department of Biomedical and Clinical Sciences "Luigi Sacco", University of Milan Medical School, Italy, and President of the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM).

What challenges are clinical labs currently facing?

Laboratory medicine has been defined as a "profession without a face", as it often lacks visibility to patients and to the public, both as a medical discipline and as a vocation. Within healthcare, laboratory specialists are often perceived simply as lab equipment managers, and not as peers who hold a position of shared clinical leadership.

This challenge is coupled with the significant economic pressures that we're under to cut costs and operate on an increasingly limited budget. The result is often consolidation and regionalization, in some cases with one lab working with multiple healthcare facilities. This disconnect could undermine the influence of lab professionals, and further distance them from clinical decision-making.

The winds of change are coming though, and as our test repertoire and workload increases, we need to work harder to ensure we increase the appropriateness of test requests, for example, by decreasing the number of unnecessary and redundant tests – but that can only happen if we improve our profile, and communicate more effectively with our clinical colleagues in healthcare. Right now, I don't think laboratory scientists advocate well for themselves.

So lab specialists need to take an active role in reducing unnecessary testing?

Absolutely. With their knowledge of diagnostic tests and the rationale behind them, lab specialists are in a unique position to advise clinicians on selecting the appropriate test, interpreting the results, and therefore influencing treatment decisions. However, given the profession's low profile, and the lack of collaboration with clinical colleagues, means this doesn't always happen.

Cardiac troponin is a useful example – when it replaced previous tests for myocardial infarction diagnosis, a significant number of false positive tests was eliminated, saving a huge amount of money in costs of unnecessary therapy – this demonstrates that when lab medicine assumes a central role in introducing new tests, and ensuring obsolete ones are removed, patients and healthcare providers benefit.

More recently, so called "highly sensitive" troponin assays have gained popularity, and have demonstrated an increased ability to reduce morbidity and mortality, by better identifying high-risk patients. However, emergency departments and cardiologists have not welcomed the introduction of highly sensitive assays, as the increased sensitivity affects the interpretation of the results, which leads to confusion if clinicians are not correctly educated. It is therefore of critical importance that lab professionals are involved in conversations around new test introductions and their interpretation from the beginning.

"The communication between the lab and the ward is sometimes very poor, and integration isn't easy."

Studies have also shown that requests for certain tests can vary hugely from practice to practice, in a way that can't always be explained by differences in disease prevalence – for example, in the UK, the annual rate of requests for carbohydrate antigen 125 testing shows a nine-fold variation between practices! Creating recommendations to encourage the correct use of the test should potentially greatly lessen the number of tests ordered, therefore saving money, without adversely affecting patients.

How do lab specialists go about effecting change?

We must take on a continuous active advisory role, in order to improve clinician understanding of what tests to order, when to order them, and how they should be interpreted. The vast majority of lab-related diagnostic mistakes occur at the laboratory-clinical interface, and involve test demand (pre-pre-analytical phase) and result interpretation (post-post-analytical phase). Improving the way the lab and the clinician collaborate will help to reduce these errors.

When it comes to interpretation, there is also a need to make results clear so that the appropriate action can be taken. In a recent US survey, about 20 percent of primary care physicians reported experiencing challenges and uncertainty in interpreting different laboratory report formats – this translates into millions of patients every year who risk being adversely affected by unclear, or poorly understood, test results.

What challenges do you anticipate?

I have observed a general reluctance to get more involved in structuring tests and providing input on which tests are ordered, as I think lab professionals often assume that all tests the clinician requests must be necessary. The communication between the lab and the ward is sometimes very poor, and integration isn't easy. In order to play a central role in healthcare and improve the clinical impact of laboratory testing, we need to change our own attitude, become more outward looking and innovative, and create opportunities to demonstrate the value of our profession. We play a pivotal role in healthcare delivery, by providing clinicians with the information they need to provide the right care to patients, and we need to make our voices heard.

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