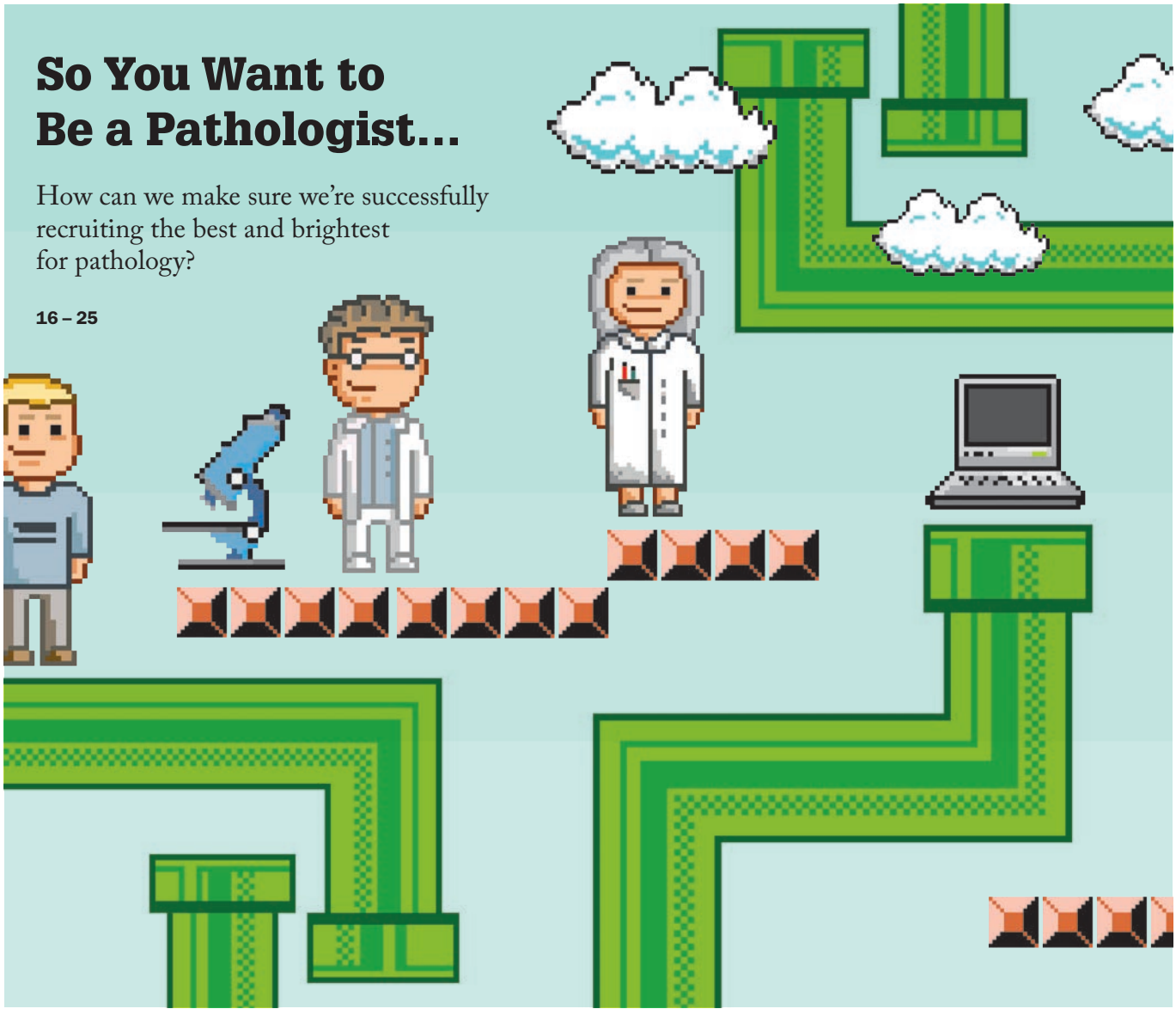
MAY 2018 # 42

the Pathologist™

So You Want to Be a Pathologist...

How can we make sure we're successfully recruiting the best and brightest for pathology?

16 – 25



Your Premier Partner to Implement Digital Pathology!

REGULATORY CLEARED END-TO-END SOLUTIONS ACROSS THE US, CANADA AND EUROPE

UNITED STATES

- Uses FDA-cleared scanner/pixel pipeline for Primary Diagnosis
- Scanner Agnostic
- On-Site Scan Center Staff

CANADA AND EUROPE

- Has Omnyx® CE Mark and Health Canada license for Primary Diagnosis

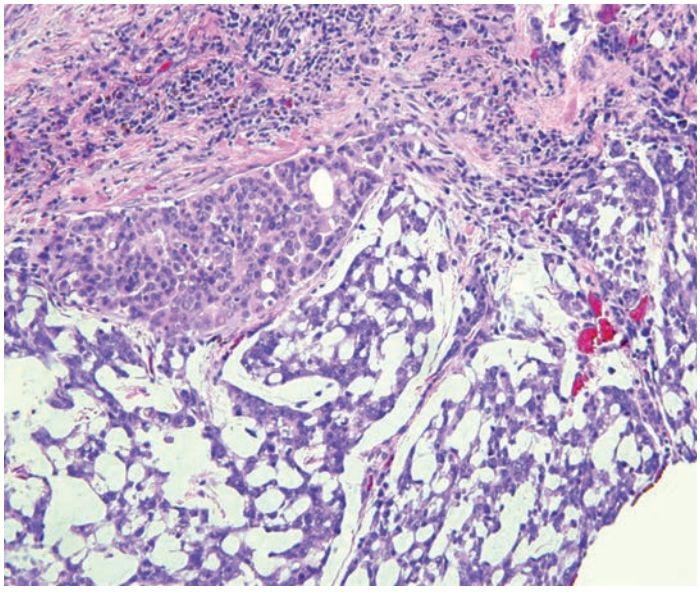
- Diagnostic Cockpit Software
- Integration Services

- Implementation Services
- Strategic CapEx to OpEx Model

To learn more about our device-agnostic platform and our novel solution-as-a-service model, call Tim Wing at +44 (0) 7785 375822.

www.inspirata.com

Case of the Month



A renal tumor was resected from a 30-year-old African-American woman. Several histologic patterns were identified, including a reticular and a solid pattern, both shown here.

What is the most likely diagnosis?

a Papillary renal cell carcinoma

b Tubulocystic carcinoma

c Medullary carcinoma

d Collecting duct carcinoma

To register your guess for this month's case, please go to http://tp.txp.to/0518/case-of-the-month
We will reveal the answer in next month's issue!

Answer to last issue's Case of the Month…

B. Silicosis-associated osteoporosis

This disease is an equine osteoporosis associated with pulmonary silicosis (1). Pathognomonic histologic features include:

- large, coalescing foci of osteolysis in the cortical and medullary compartments with disordered remodeling characterized by mosaic arrangement of cement lines
- replacement of compact bone with thin trabecular bone meshwork
- numerous large, hyperactive osteoclasts with supernumerary nuclei and hyperplastic osteoblasts lining many bone surfaces

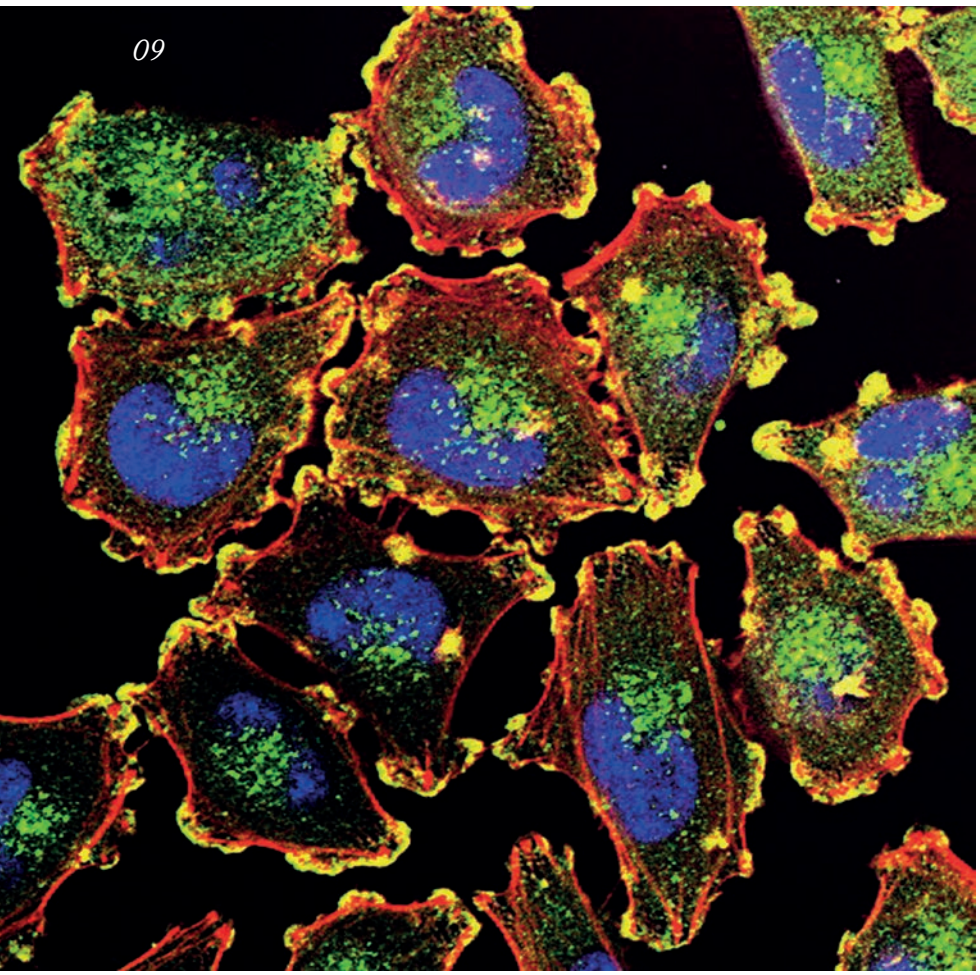
Bone lesions also often have depletion of hematopoietic bone marrow, congestion, hemorrhage and edema in the intertrabecular stroma.

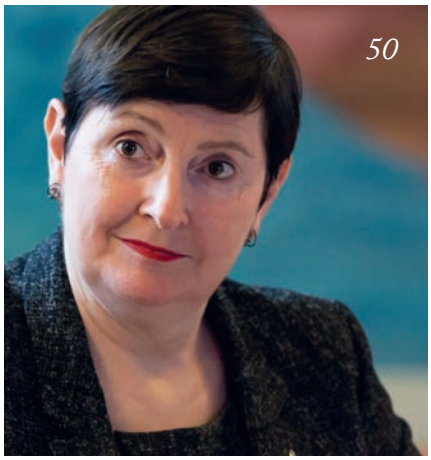
Submitted by Regina Zavodovskaya, PhD Student in the Integrative Pathobiology Graduate Group at the University of California, Davis School of Veterinary Medicine, USA.

Reference

1. *AM Arens et al., "Osteoporosis associated with pulmonary silicosis in an equine bone fragility syndrome", Vet Pathol, 48, 593–615 (2011). PMID: 21097716.*

Contents





On The Cover

A visual representation of the pathology recruitment and career pipeline in the style of an 8-bit video game.

Feature

In Practice

NextGen

Profession

Sitting Down With

the Pathologist

ISSUE 42 – MAY 2018

Change of address:
info@texerepublishing.com
Hayley Atiz, The Pathologist,
Texere Publishing, Haig House, Haig Road, Knutsford, Cheshire, WA16 8DX, UK

General enquiries:
www.texerepublishing.com
info@texerepublishing.com
+44 (0) 1565 745200
sales@texerepublishing.com

Distribution:
The Pathologist (ISSN 2055-8228), is published monthly by Texere Publishing, Haig House, Haig Road, Knutsford, Cheshire WA16 8DX, UK
Single copy sales £15 (plus postage, cost available on request info@texerepublishing.com)
Non-qualified annual subscription cost is £110 plus postage

texere publishing ltd

Available on the App Store

Simply insert the
primary EDTA tubes
and walk away!

iSED®

the *perfect* ESR System

USA MADE

- Results in 20 seconds
- No disposables
- Full random access
- 100uL sample size perfect for pediatrics

ALCOR SCIENTIFIC

WWW.ALCORSCIENTIFIC.COM

Toll Free 800.495.5270

Toward a Higher Profile

How can we ensure that we have a pathologist workforce when we need it?

When I had my first interview for a pathology training post 25 years ago, I was asked why I was wasting my time applying for a job that would soon be made redundant by advances such as immunohistochemistry and computerization. The same question is being asked now, although it's artificial intelligence and genomics that are being proposed as a threat to the specialty. My response remains the same: we should make the most of the new technologies available to us, adapting how we train and work as appropriate, but not worry that we might soon be unemployed. Pathologists and scientists remain a vital part of the healthcare workforce and it is essential that enough people are attracted to the specialty to meet present and future patient needs.

But how many is enough? Workforce planning is an almost impossible task in all medical specialties – and pathology is no exception. The lead time for training pathologists and senior scientists is so long that it is difficult to match the number of people entering training with the number of specialists that may be required at the end of it. With changes in test complexity, technology, working patterns, and service reconfigurations, it's hard to know exactly how many specialists are needed now, let alone in five or 10 years' time. What is clear is that pathologists will continue to be in demand – and that we won't be replaced by robots or computers in the foreseeable future.

Much is already being done to attract the next generation of pathologists – from talks in schools and short courses for medical students to university pathology clubs and placements for doctors in training. Social media has transformed the way pathologists communicate with each other and with the public. Initiatives such as National Pathology Week, International Pathology Day and Medical Laboratory Professionals Week help highlight the vital role of pathologists in healthcare. What all of these approaches have in common is that they increase the visibility of pathology. Being able to appreciate the contribution of the specialty, learn from inspirational role models, and feel welcome and valued as a trainee are all vital when it comes to overcoming the negative stereotype of pathologists (antisocial loners with no communication skills – who don't like patients).

Pathology is an exciting and rewarding specialty, never more so than in the current climate of rapid technological advances. We must share that excitement to inspire the pathologists and scientists of tomorrow. This issue's focus on encouraging pathology recruitment is important and timely, and gives much food for thought.

Suzy Lishman
CBE

Upfront

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

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

Email: edit@thepathologist.com

Quick Copy

Ligation-mediated PCR whole genome amplification speeds up detection of copy number alterations

The complexities of whole genome sequencing for single cells make it a time-consuming affair – not ideal for resource-stretched clinical laboratories. Now, a more streamlined protocol – ligation-mediated PCR whole genome amplification – aims to speed up low-pass sequencing and detection of copy number alterations (1). The European research team behind the method put it to the test by analyzing single circulating tumor cells (CTCs) and white blood cells – successfully, they say; the protocol detected copy number alterations in single tumor cells with as few as 200,000 reads. To learn more about the technique, we spoke with Nicolò Manaresi, CSO of Menarani Silicon Biosystems.

Why focus on detection of copy number alterations?

Copy number alterations (CNAs) are a hallmark of cancer, and further evidence has pointed to the importance of investigating CNAs in several settings. For example, researchers at the University of Manchester discovered CTC CNA profiles that predict chemoresistance/chemosensitivity in small cell lung carcinoma patients (2). Another hot topic is immune oncology; given the high cost of treatments and risk of severe adverse reactions, immunotherapies are in desperate need for better predictive biomarkers and companion diagnostic options – and copy number losses appear to be relevant. There are several other examples of the effect CNAs have on disease research.

What do your findings mean for tumor cell studies going forward?

As our new method streamlines the process of library preparation for genome-wide CNA profiling, we anticipate that investigation of CNA and their heterogeneity across CTCs from patients will become more and more affordable to researchers, and will drive new discoveries. Moreover, we anticipate the potential adoption of the workflow, which is currently for research use only, in the clinical setting after further investigation.

What's next?

To foster adoption in the clinic, actionability and clinical utility are key, and this is our current focus. We believe that our cell-based liquid biopsy workflow may play an important role in oncology precision medicine, by supplying longitudinal, accurate CTC molecular profile.

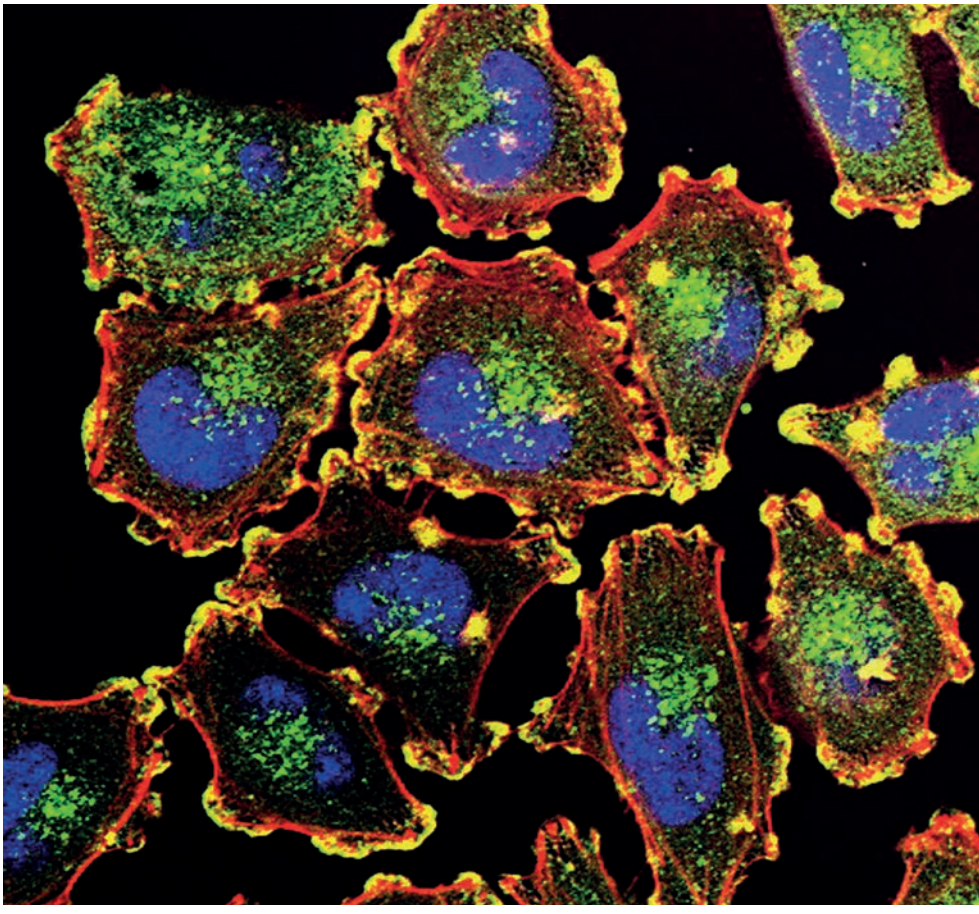
References

1. *A Ferrarini et al., "A streamlined workflow for single-cells genome-wide copy-number profiling by low-pass sequencing of LM-PCR whole-genome amplification products", PLoS One, 13 (2018). PMID: 29494651.*
2. *L Carter et al., "Molecular analysis of circulating tumor cells identifies distinct copy-number profiles in patients with chemosensitive and chemorefractory small-cell lung cancer", Nat Med, 23, 114–119 (2018). PMID: 27869802.*

Screen Test for Spec

How ATR-FTIR spectroscopy could lead to less invasive cancer prescreening

A team from Georgia State University are using Fourier transform infrared (FTIR) spectroscopy in attenuated total reflection (ATR) mode to develop a less invasive prescreening test for melanoma and lymphoma. Here, we talk to Regents' Professor of Physics Unil Perera about his hopes for the method.



What inspired you to develop a prescreen method?

The earlier we detect cancer, the better. Some screening methods, such as colonoscopies, are the gold standard, but are expensive and uncomfortable – to the point where patients avoid being tested. I wanted to devise a simple screening test that would be less invasive, less uncomfortable, and less costly – as well as capable of screening for more than one disease. One day, I want doctors to be able to screen patients annually; if they detect the markers for cancer, then the patient can be referred for further tests.

How far along is the work?

We have used ATR-FTIR to analyze biochemical changes in the blood serum of mouse models. We have shown in our previous work that we can identify colitis and diabetes – more recently, we were able to detect markers of lymphoma and melanoma and discriminate between healthy mice and those with tumors (1). Potentially, the technique could be applied to many different diseases – but it has yet to be proven on human samples.

What's your ultimate aim?

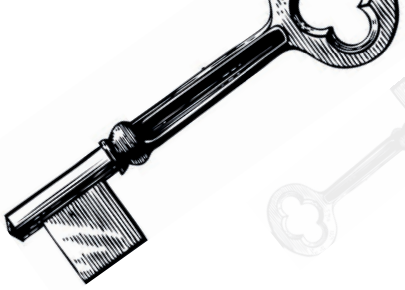
We want to come up with a portable device/detector that sits in a doctor's office. A patient gives blood, and the doctor checks for indications of a particular cancer. Our goal, ultimately, is that the doctor just needs to put in a drop of blood and get an answer – but that's obviously some years away. Our priority right now is to prove that this works in humans.

What keeps you motivated?

I'm happy to make some contribution to human health – even a minor one. After our cancer paper was published (1), I got an email from one of our faculty members, saying that as a survivor of cancer, she was happy to see that I was doing something on early detection. That was really special.

Reference

1. *H Ghimire et al., "ATR-FTIR spectral discrimination between normal and tumorous mouse models of lymphoma and melanoma from serum samples", Sci Rep, 7, 16993 (2017).*



Prostate Cancer Proteomics

How protein expression levels could unlock hidden insight into the disease

"There have been suggestions that proteomics studies reveal pathways and mechanisms in many cancers that genomics/transcriptomics do not," says Tapio Visakorpi, Professor of the Prostate Cancer Research Center at the University of Tampere, Finland. "However, the proteomics of clinical prostate cancer samples have not been previously analyzed." To tackle this gap in prostate cancer knowledge, Visakorpi led a research team to uncover the associated proteomic pathways, with the aim of further understanding genetic and transcriptomic aberrations in the disease (1).

The study, which used high-throughput mass spectrometry on benign and malignant prostate cancer samples, found that the disease was correlated with significant shifts in protein levels in aggressive prostate cancer. Visakorpi suggests that these are putative biomarkers. Evidently, research that focuses only on genetic or genomic aspects of disease is missing parts of the puzzle. Visakorpi says, "In the future, I believe that comprehensive discovery studies on cancer mechanisms will also include proteomics. And not just proteomics (as done here), but also screening of protein modifications."

Proteomics research is resource-intensive, so Visakorpi and his team have been focusing on two specific questions: why does a subset of prostate cancers (which, histologically, almost all men develop) progress to become a clinical disease? And, of that subset, why are some particularly aggressive? "If we identify the mechanisms for that aggressiveness, we may find new diagnostic tools, as well as therapies," he says.

"Currently, we are measuring the levels of identified proteins in a larger cohort of prostate tissues, as well as from blood. In the future, we will also test them from urine. These analyses hopefully will indicate whether any of these proteins could actually serve as a biomarker of aggressive prostate cancer."

At the same time, Visakorpi notes the need to improve methodologies related to sample acquisitions. "We need better tools to obtain samples from metastases, isolation of circulating tumor cells, more sensitive cfDNA analysis, better fixation and processing of tissue samples, more success in growing cells in vitro or in mouse (as patient-derived xenografts)," he says.

Reference

1. *L Latonen et al., "Integrative proteomics in prostate cancer uncovers robustness against genomic and transcriptomic aberrations during disease progression", Nat Commun, 9, 1176 (2018). PMID: 29563510.*

Hostile Predictions

Epigenetic analysis uncovers prognostic biomarkers for aggressive brain tumors

Assessing glioma by histomorphology and grade offers little predictive value when it comes to the later development of glioblastoma, but diving into the epigenetics may uncover useful biomarkers. A research group led by Houtan Noushmehr, Professor at the University of São Paolo, investigated the DNA methylation profile of 200 tumors from 77 patients, which revealed biomarkers of aggressive tumor recurrence (1).

"In 2010, we defined a subset of gliomas that harbored a unique epigenetic profile, which we termed G-CIMP (glioma - CpG Island Methylator Phenotype) (2). It was later shown that isocitrate dehydrogenase mutations can initiate this methylator phenotype, and our recent findings may provide additional diagnostic tools to aid oncologists in determining proper therapeutic avenues," says Noushmehr. Looking at the DNA methylation of high- and low-G-CIMP tumors, then identifying the intra-heterogeneity within primary high-G-CIMP tumors – which often carry worse prognoses – allowed the team to uncover predictive biomarker signatures comprising seven hypomethylated CpG sites in the tumors. "The biomarkers could potentially be used as an additional screening method during pathological review. Currently, histological and molecular features are evaluated during normal standard of care for patients with evidence of brain cancer," he says. "Our markers have the potential be included in this initial standard of care. However, further studies are needed to confirm and validate our discovery; specifically, a pre-clinical trial would need to be performed."

Looking forward, the investigators hope to use bioinformatics and advanced sequencing techniques to discover which genomic components play an important role in glioma tumor development. And they will continue to explore the intricacies of the relationship between the epigenome and genome within glioma subtypes. Noushmehr adds, "We are also working closely with oncologists, neuropathologists and neurosurgeons to hopefully translate some of our initial work into clinical applications."

References

1. *CF de Souza et al., "A distinct shift in a subset of glioma CpG island methylator phenotypes during tumor recurrence", Cell Rep, 23, 637 – 651 (2018). PMID: 29642018.*
2. *H Noushmehr et al., "Identification of a CpG island methylator phenotype that defines a distinct subgroup of glioma", Cancer Cell, 17, 510 – 522 (2010). PMID: 20399149.*

Progress on Pseudoprogression

Droplet digital PCR for circulating tumor DNA could distinguish pseudoprogression from true disease progression

Well known as the most aggressive skin cancer, melanoma has a high likelihood of spreading to other parts of the body. The American Cancer Society estimates that over 9,300 people in the United States will die of metastatic melanoma this year (1). The standard of care for treating patients with metastatic melanoma is immunotherapy; an antibody to the immune checkpoint protein PD-1 is administered alone or in combination with other immunotherapeutic drugs.

Approximately one in 10 patients who receive this treatment experience a phenomenon called pseudoprogression, wherein immune cells infiltrating the tumor cause an increase in its size, mimicking the appearance of true disease progression. Radiologically, pseudoprogression can be identified by tumor enlargement or the development of new lesions, followed by shrinkage as the patient responds to continued treatment. In contrast, true progression can be seen when the tumor continues to grow and the patient remains unresponsive to immunotherapy.

Physicians treating patients with advanced melanoma often find it challenging to identify pseudoprogression at the beginning of treatment. In large part, this is because of the limitations of tumor imaging, which can sometimes return ambiguous results. Now, a group of researchers from Australia have turned to cell-free circulating tumor DNA (ctDNA) in an attempt to identify pseudoprogression more rapidly.

Jenny Lee of Macquarie University and the Melanoma Institute Australia, along with collaborators from the University of Sydney, investigated whether ctDNA could be used to differentiate between true progression and pseudoprogression in patients undergoing immunotherapy to combat melanoma (3). Previously, the researchers analyzed ctDNA profiles from immunotherapy recipients using droplet digital PCR (ddPCR) technology and found that cell-free DNA could accurately predict tumor response, progression-free survival, and overall survival (4). Lee's work showed that elevated levels of ctDNA during the treatment period were typically tied to overall poor prognosis.

Wanting to build on these results, Lee and her team looked at specific mutations (such as *BRAF* and *NRAS* alterations) in the ctDNA profiles of 125 stage IV metastatic melanoma patients at the start of therapy and at regular intervals for up to 12 weeks. They were able to identify by serial imaging nine patients displaying classic signs of pseudoprogression. Using ddPCR, they found that the number of ctDNA copies was reduced by greater than 10-fold within 12 weeks of treatment, in all nine patients. Furthermore, the team were able to correlate these ctDNA patterns with overall survival. According to their work, the one-year survival rate for participating patients with progressive disease and declining (>10-fold) ctDNA profiles was 82 percent, compared to only 39 percent for patients with stable or increasing ctDNA profiles.

For cancer types in which pseudoprogression is prevalent and an identifiable mutation is present, a biomarker that is able to identify true progressive disease and accurately predict patient outcomes (independent of tumor imaging) would prevent physicians from prematurely discontinuing an effective treatment. If the work done by Jenny Lee and her colleagues holds true, ctDNA may be that biomarker.

References

1. *American Cancer Society, "Key Statistics for Melanoma Skin Cancer" (2018). Available at: https://bit.ly/2lMpQLl. Accessed April 17, 2018.*
2. *C Robert et al., "Pembrolizumab versus ipilimumab in advanced melanoma", N Engl J Med, 372, 2521–2532 (2015). PMID: 25891173.*
3. *JH Lee et al., "Association between circulating tumor DNA and pseudoprogression in patients with metastatic melanoma treated with anti–programmed cell death 1 antibodies", JAMA Oncol, [Epub ahead of print] (2018). PMID: 29423503.*
4. *JH Lee et al., "Circulating tumour DNA predicts response to anti-PD1 antibodies in metastatic melanoma", Ann Oncol, 228, 1130–1136 (2017). PMID: 28327969.*

In My View

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

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

Contact the editors at edit@thepathologist.com

Preparing for the Worst of Us

Patient prejudices do exist, but with the right preparation – for them and us – we can sidestep discrimination to do what we do best: save lives

By Malak Abedalthagafi, Assistant Research Professor of Genomics and Neuropathology at King Abdulaziz City for Science and Technology, Consultant Physician in Molecular and Neuropathology at King Fahad Medical City, Saudi Arabia, and part-time faculty member at Harvard Medical School, USA.

Should I start with the numbers?

Would it surprise you to know that 26 percent of practicing physicians in the United States were trained in other countries (1)? That foreign-born doctors, representing over 40 percent of our primary care workforce and over half of the doctors in elder care, are responsible for treating our most vulnerable citizens (2)? You may also be interested to know that patients are less likely to die within 30 days if their physician is from another country – either 0.5 or 5 percent less likely, depending on your source (3).

Or maybe you'd rather hear a story…

How about the time I was in residence in pathology at Georgetown University, at our fine needle aspiration clinic, treating a patient with a lump in her neck? After she found out that I was from Saudi Arabia and my attending was from Syria, she said, "Oh, great. I'm stuck between two people from terrorist countries."

The problem is that, although the numbers we deal with are rational and don't hold biases, our patients do. Although foreign-born and internationally trained doctors represent a large percentage of the US healthcare practitioners and perform at least as well as our domestic colleagues, we are often subjected to xenophobic comments and rejected by American patients because of their own background.

About 15 percent of pediatric residents report that they've heard prejudicial comments from patients (4). Doctors may be more likely to hear these comments in rural communities where these biases are common, but the problem is found in urban environments as well: roughly 40 percent of physicians at a New York-area hospital report having witnessed patients rejecting doctors based on race or ethnicity (4). So what does that mean for the huge population of people moving to the United States to work in medicine? Well, it means that they need to prepare for patients who – despite evidence; despite facts; despite rational thinking – are convinced that these doctors are less competent than their American counterparts. I think the best approach to address this challenge is through four main points:

- Discussion. In our residency teaching conferences, we focus a lot on sharing scientific knowledge – but perhaps not enough on how stereotyping affects interactions in the clinic and in the lab. This new era of precision medicine will require pathologists to face more patients, so we need to be ready.
- Simulations. Diversity training would be a valuable addition to any medical institution – not in the usual common-sense context, but instead training doctors in how to respond to patients who reject commonly held values of diversity and inclusion. To respond firmly – yet gracefully – to such patients, we'll have to practice.
- Formal introductions. These patients may react strongly in part because they are shocked when someone so different from them is thrust into

their personal space, especially while they are in a vulnerable position. If patients are informed beforehand that their doctor is from a different country, they may have more time to process this information and prepare for the interaction.

- Biographical statements. Patients in the United States need to be reminded that, no matter what country their doctor is from, he or she is a well-trained professional. A full biographical statement detailing the physician's training background may reinforce that their doctor is fully capable of treating them.

Perhaps we cannot change these patients' behavior – we certainly don't have enough time to change their deeply held prejudices – but we can help our physicians navigate these stressful situations better. And maybe, just maybe, we can help patients get out of their own way so we can save their lives.

References

1. *PD Ranasinghe, "International medical graduates in the US physician workforce", 115, 236–241 (2015).*
2. *The New York Times, "Why America needs foreign medical graduates", (2017). Available at: https://nyti.ms/2jFK6ev. Accessed May 8, 2018.*
3. *Reuters, "U.S. patients have lower mortality rates with foreign-trained doctors", (2017). Available at: https://reut.rs/2K2JHOx. Accessed May 8, 2018.*
4. *CNN, "Racism in medicine: an 'open secret'", (2016). Available at: https://cnn.it/2rst7kh. Accessed May 8, 2018.*

Surveying the Workforce Landscape

The medical laboratory field must intensify recruitment efforts to prepare for an upcoming dearth of applicants

By James L. Wisecarver, President of the American Society for Clinical Pathology.

The American Society for Clinical Pathology (ASCP) has been conducting its wage and vacancy surveys of non-physician laboratory professionals since 1988. Through the last 30 years, the laboratory workforce has experienced changes driven by expected challenges, such as hiring, recruitment and retention – but also by other factors, such as the economy, new technologies, and government regulation. The newly released ASCP 2016–2017 Vacancy Survey (1) suggests that US-based laboratories will need to redouble their efforts to develop and maintain a skilled workforce. Current survey data reveal that we can anticipate a massive increase in retirements of laboratory professionals over the next five years. Worse yet, the exodus is expected to be particularly acute for supervisory-level personnel.

With overall unemployment rates (4.1 percent) at their lowest levels since 2008, clinical laboratory work shifts that were difficult to fill during and after the recession – such as night, double, or weekend shifts – are proving to be so once again. On average, hiring staff takes three to six months for most departments, and it can take anywhere from three months to a full year to hire a supervisor. Data from the previous survey (conducted two years prior) indicated that it took laboratories only three to six months to fill supervisory vacancies at that time.

Across the nation, the overall vacancy rate was highest for LIS/QA/PI departments (10.98 percent) and lowest for anatomic pathology departments (4.7 percent). Survey data suggest, however, that vacancies in general are most problematic in rural areas and at small community hospitals, where they often take longer to fill and can leave laboratories with heavier workloads.

Survey respondents also indicated that workloads and automation have increased the need for lower-level staff to perform routine testing, which in turn enables upper-level laboratory staff (such as laboratory scientists or technologists) to concentrate more on running and verifying test results. As fewer staff perform more total testing, turnaround time becomes increasingly dependent on the staff's level of expertise and training. This, coupled with the loss of experienced laboratory supervisors, may be fueling employers' interest in recruiting certified technologists – a speculation borne out by comparisons between the new data and the previous survey's results.

Recently, the ASCP presented its wage and vacancy data to the Clinical Laboratory Improvement Advisory Committee (CLIAC), a federal government advisory panel. It prompted much concern from – and discussion by – the committee in terms of how best to tackle the shortage of qualified laboratory personnel. Unfortunately, that seems to be an issue with no easy answers. Anecdotal information suggests that existing laboratory training programs have difficulties in maintaining funding, which means that clinical laboratories may have to train their own staff to meet workforce needs – a potentially expensive and time-consuming process.

Reference

1. *E Garcia et al., "The American Society for Clinical Pathology's 2016–2017 vacancy survey of medical laboratories in the United States", Am J Clin Pathol, 149, 387–400 (2018). PMID: 29522068.*

Tissue Is Still the Issue

The need for adequate tumor samples hampers even state-of-the-art diagnostics such as NGS – but some technologies require less tissue, improving oncology biomarker testing for pathologists, clinicians and patients

David Moore discusses his experience and the results of a three-year, soon-to-be-published NSCLC molecular testing audit

As a histopathologist specializing in thoracic pathology, I work between a molecular diagnostics laboratory (which receives and tests samples of all cancer types from a large range of institutions, including both NHS and private laboratories), University College Hospital, where I report thoracic histopathology, and University College London, where I participate in non-small cell lung cancer (NSCLC) research.

Why is there so much discussion about NSCLC biomarker testing?

In NSCLC, the current standard biomarker tests are for *EGFR* driver mutations, *ALK* translocations and PD-L1 expression. There are additional biomarkers, such as BRAF, *ROS1*, and *HER2*, that are associated with approved or investigational treatments. So there are already multiple tests to be done – and with the rapid progress of precision oncology, it's likely that we will soon need to test for yet more biomarkers in yet more tumors.

In your opinion, what are the advantages of next generation sequencing (NGS) over other methods?

The majority of biomarkers in oncology are predictive; they forecast patients' response to therapy. For a number of cancer types, it's now standard of care to test for predictive genomic biomarkers – *EGFR* driver mutations in lung cancer, for instance. Using NGS technology, we can apply one test that covers a number of genes relevant to not just one, but a variety of cancers. Our 22-gene panel can be applied similarly to lung *(EGFR)*, melanoma (*BRAF* V600E), and colorectal (*KRAS*) cases, so they can all go through the same workflow. Secondly, and even more importantly, NGS allows us to generate analytical and potentially clinically useful information for many more patients.

Can you elaborate more on the clinical benefit?

In our lab, we're able to test cases with a limited amount of material or a relatively low tumor fraction; for example, endobronchial ultrasound biopsies (which are often 90 percent lymphocytes, 10 percent tumor) or 4–5 mm^2 lung biopsies. And that means we don't have to subject those patients to repeat biopsies (and that, as a result, they receive conclusive results faster), unlike other NGS assays that require more tissue or tumor material.

We can also apply NGS to samples with evidence of formalin fixation artifacts. A minority of cases exhibit a significant pattern of lower-level variants typical of formalin fixation effects, which can interfere with analysis, meaning that variants detected in clinically relevant gene regions may not be genuine mutations. Using a single-gene testing method like PCR, we would never be able to see these potential false positives – but, with NGS, we can see the "background effect" of overfixation and, based on that, recommend re-biopsy and retesting. The *EGFR* resistance mutation *EGFR* T790M is often a low-frequency "transition variant" like we see in formalin fixation artifacts, so the ability to exclude that possibility in a T790M-positive sample is crucial to ensure the patient receives the optimal therapy.

What about the difference in panel size – is bigger necessarily better?

I can't say that any one solution is "the best," because they are different. Some are large, multi-gene panels, whereas others – like our 22-gene test – are more focused. The advantage of a large panel is that you gain information on a much wider range of genes. On the other hand, there's the law of diminishing returns. The more data you generate, the less likely it is to be clinically relevant.

"Using this limited 22-gene panel, we're able to return some information on 83 percent of cases."

Importantly, not all NGS technologies are equally suited to each sample type. Our test, for example, requires a minimum of 5 percent tumor content and can be applied to very small biopsies; some others require more tissue and at least 20 percent tumor fraction, which is significant. For example, in our study cohort of nearly 3,000 samples from across the UK, we have a good, unbiased sample of lung cancer tissue specimens. Yet almost one-third of those cases would fall below the 20-percent threshold, making them impossible to analyze with some other panels. The result? Patients might miss opportunities to receive therapy that could benefit them.

So let's hear about your data audit…

We have audited all of the NSCLC cases

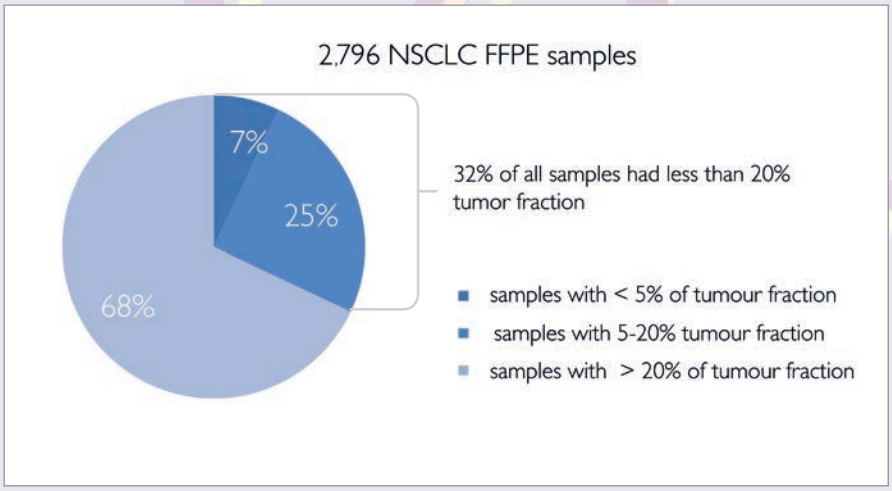
submitted to our laboratory over the three-year period from 2015 to 2017. Our starting sample pool included 2,976 cases, of which 7.8 percent were rejected (mainly due to <5 percent tumor cell fraction). Of those accepted, NGS analysis was successful in 94.9 percent (a 5.1 percent failure rate). Median turnaround time was seven days.

We have pulled quite a bit of interesting information from these data. We've divided the samples into categories by tumor cell fraction (5–20, 21–50, 51–75, and >75 percent tumor). We have also analyzed the reasons samples were rejected or failed analysis, and we have identified the number of cases with a recognized driver mutation in *KRAS, EGFR, BRAF, NRAS, PIK3CA*, or *ERBB2* (HER2). In a number of cases with no evidence of a driver mutation, there was evidence of amplification in another relevant gene that might account for a genomic driver event.

We performed additional analyses on the 2017 cases by looking at those negative for not only *EGFR, KRAS, BRAF, NRAS, PIK3CA,* and *ERBB2* driver mutations, but also amplification evidence – about 33 percent of all cases. We investigated how many of those cases had evidence of other somatic mutations that were likely to be cancer-specific. The most common in that cohort was *TP53*, found in half of that subset, which reduced the number of cases without any tumor-relevant mutation to only 17 percent. So, using this limited 22-gene panel, we're able to return some information on 83 percent of cases.

Are all of those variants clinically significant?

Not all of them. But there are a number of findings that might make those patients eligible for ongoing clinical trials, even though there is no approved therapy available.



Analysis of tumor fraction in 2,796 NSCLC samples received by Sarah Cannon Molecular Diagnostics Laboratory. 32 percent of samples had less than 20 percent tumor fraction.

There is also the additional benefit of excluding false negatives. In those 83 percent of cases, we can be sure that they contained detectable amounts of tumor DNA, and therefore the chance of our having missed any actionable mutations due to insufficient tumor DNA is very low. If only one marker is analyzed – let's say *EGFR* driver mutations, which have a prevalence of about 15 percent – then, in 85 percent of cases, we can't be sure that we have analyzed adequate tumor DNA, and therefore we can't exclude the possibility of a false negative result.

What is the usual cause of false negative or positive results?

Some samples just don't contain enough tumor tissue – specifically the actual tumor cells. In theory, these should be excluded from analysis based on sample acceptance criteria; however, some centers only send us pre-cut tissue "curls," so we are unable to verify that they have assessed the tumor content accurately. If the tumor content is lower than our threshold, it's a potential source of false negatives – and that's why we recommend that centers send us tissue blocks. Additionally, DNA can be degraded and over-fixed. Our technology is robust and sequencing is successful in 94.9 percent of cases, but there is always room for improvement in preanalytical handling procedures. We have identified some trends in our data that will be part of our upcoming publication, and we want that to contribute to awareness and education about this issue.

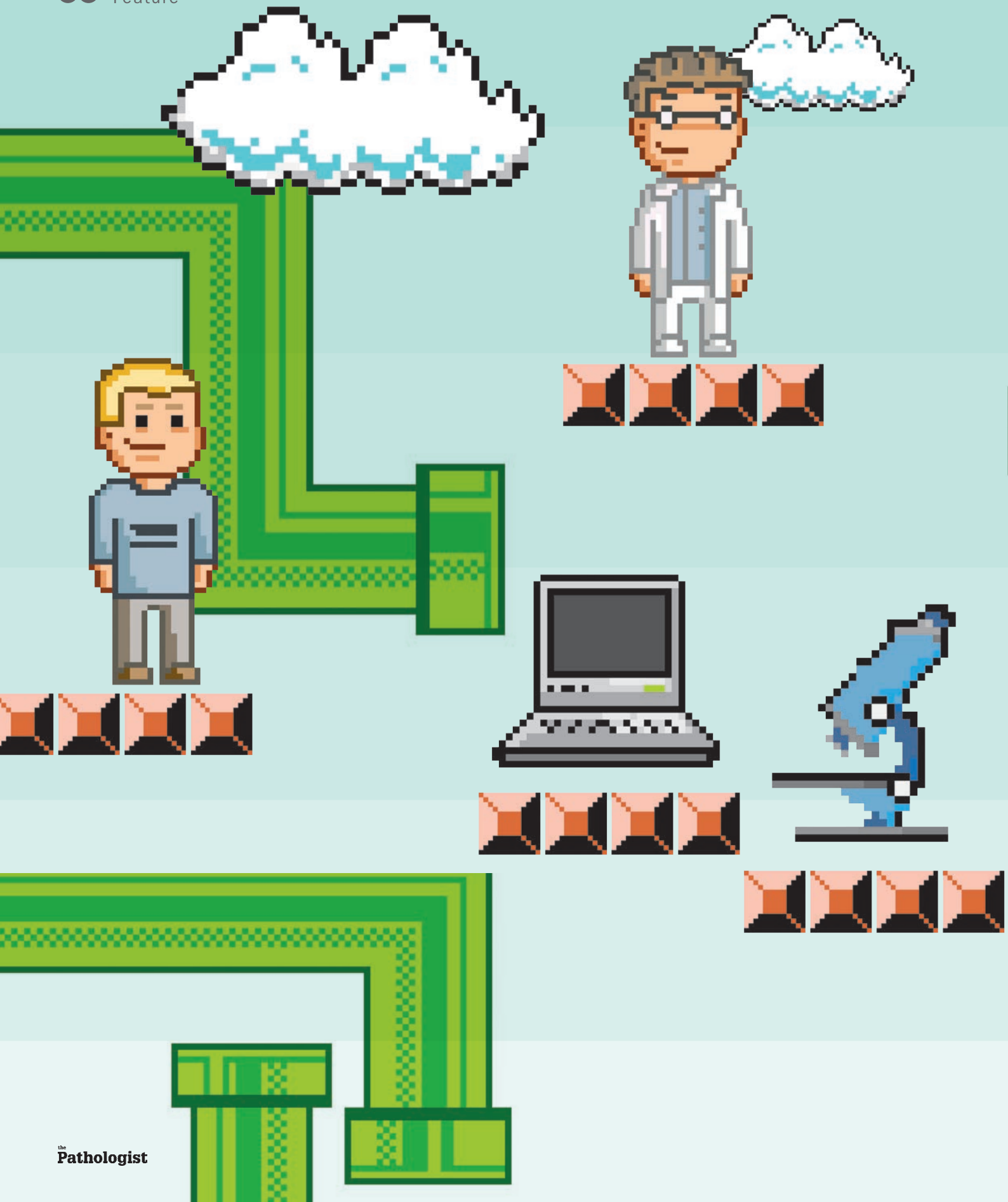
You mentioned acceptance criteria; what are those in your laboratory?

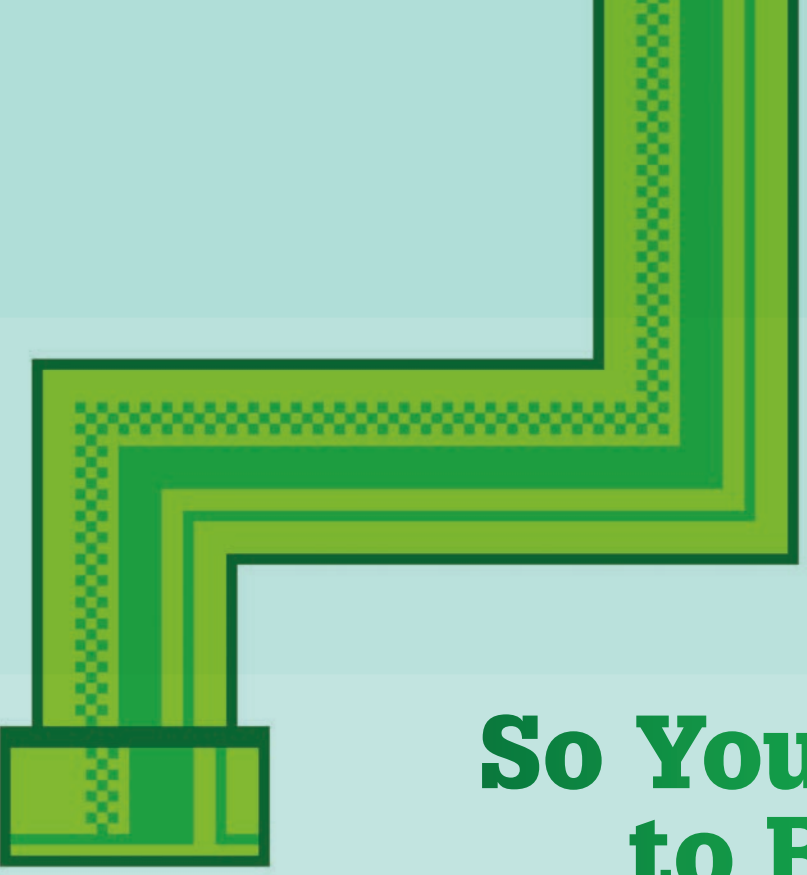
As a rule, we require 4 mm2 of tumor area and minimum 5 percent tumor fraction, but there is some flexibility. We can sometimes test samples below 4 mm2 or macrodissect tumor out from cases that are <5 percent. Ideally, of course, we get the whole block – but we often receive slides (we have no minimum required number), or tissue curls that come in a tube. Such samples are clearly suboptimal, because we can't perform a proper preanalytical review.

When can we expect to see the data published?

Hopefully soon! It's all finalized; it's just going through local pre-submission reviews at the moment

To learn more about the technology used, visit thermofisher.com/oncomine-solidtumour

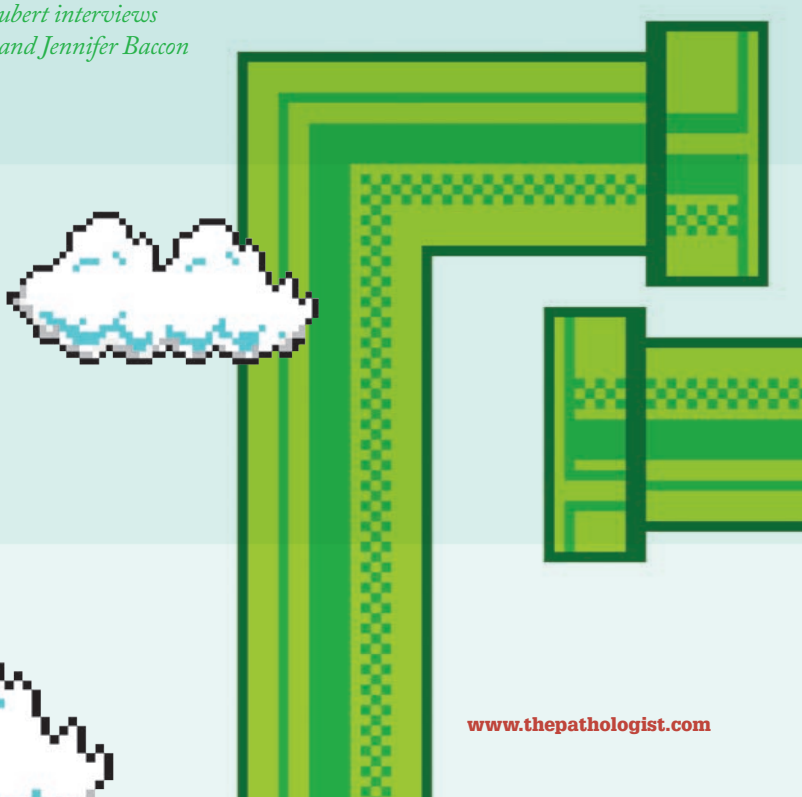




So You Want to Be a Pathologist...

Does pathology have a recruitment problem? And, if so, what can we do to correct it?

Michael Schubert interviews Nadeem Zafar and Jennifer Baccon



It's understandable that members of the public might not be sure who pathologists are or what they do. But when even medical students are asking, "What exactly is pathology?" then we know we have a problem – and it is costing us new recruits.

The "pipeline" is the educational and experiential track every aspiring pathologist must take before ending up in the laboratory. When does it begin? Many of us feel that, for students interested in a medical career, it should start in high school and be sustained throughout post-secondary education. Of course, it reaches its full extent in medical school – although it should continue throughout residency, fellowship, and even into the early years of a pathologist's career. But does it? And is it doing a good enough job of inviting new pathologists into the fold?

What factors positively impact this pipeline?

Nadeem Zafar: Pathologists offer a very broad array of services to virtually every aspect of clinical medicine – an attractive feature for physicians-in-training. Pathology is an intellectually endowed field that typically attracts thinkers and problem-solvers. Anatomic pathologists resolve diagnostic mysteries in a methodical and sequential manner, using a "keen eye" and expertise in pattern recognition. Cytopathologists have developed adept cognition through the third dimension; the trained mind reconstructs the lesion from which the sample is drawn by mentally recreating its spatial configuration, a more abstract approach to the diagnostic process. Clinical pathologists not only run highly sophisticated and quality-controlled laboratories, but also provide critical expertise to help run various hospital services through a broad array of testing and diagnostic procedures; for example, bone marrow and body fluid testing, electrophoresis, molecular pathology, and genetic studies. Every doctor – and every patient – has drawn on laboratory services. And it doesn't end there! There is a very strong component of basic and translational research that is an integral part of almost any academic pathology department. So I think there should be a lot of respect and appreciation for pathologists and for the work we do.

"Every doctor – and every patient – has drawn on laboratory services."

Jennifer Baccon: Pathologists who are visible to students and trainees are seen as role models. Many budding pathologists went into the field because they happened to meet a pathologist who inspired them. In addition, pathologists' frequent presence in all aspects of medical school training has a hugely positive impact on the pipeline. That's not all that matters, though. An optimistic forecast for job availability, lifestyle factors, and compensation are all key elements for medical students – and we can't forget the impact, like it or not, of popular television shows where forensic pathology portrayals reach young people and spark an interest in our field.

Which factors negatively impact the pipeline?

NZ: Although pathologists are direct care providers, most don't come into direct contact with their patients – or even many physicians or administrators – on a daily basis. The laboratory is a 24/7 operation, but we still have a major visibility issue. We seem to deliver our services from behind a wall, which makes us appear almost inconsequential. That's why we are not seen as the professionals who shape virtually every diagnosis (and treatment) through

> **"If students don't** have the opportunity to interact with pathologists in a clinical setting, **we graduate physicians who lack** a full understanding of the role of the pathologist on the patient care team."

one or more laboratory services. As medical laboratories become increasingly automated and many of the services once delivered by pathologists are gradually undertaken by non-MD diagnosticians in the clinical laboratory, our input into the world of medicine may become narrowed.

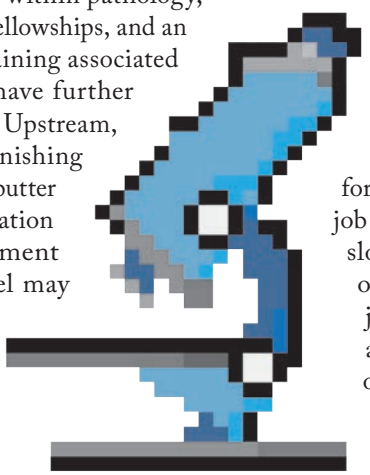
Significant restructuring of the medical school curriculum – making it more integrated using the "flipped classroom" model, with teachers as facilitators of self-learning – has further diminished pathology's visibility. Medical school curricula are not typically led by pathologists and, in most instances, pathology constitutes a very small – and not very visible – component of the curriculum. Anecdotally, I have heard that the success of these new curricula is mainly gauged by medical students' completion thereof, and by their performance on the United States Medical Licensing Exam, rather than by a true appreciation of the critical and seminal nature of pathology to the practice of medicine. Fewer opportunities for student electives within pathology, diminishing numbers of post-sophomore fellowships, and an inability to procure recognition of the training associated with post-sophomore fellowships may have further dampened students' interest in pathology. Upstream, bundled payments for patient care, diminishing reimbursement for biopsies (the bread and butter of anatomic pathology), continued automation of clinical pathology, and the replacement of pathologists with non-MD personnel may have had a negative impact on overall pathologist reimbursements – and thereby on medical students' interest in pathology as a career.

JB: I agree that we are not always visible to students, patients, and other practitioners. If students don't have the opportunity to interact with pathologists in a clinical setting, we graduate physicians who lack a full understanding of the role of the pathologist on the patient care team. With regard to the educational environment, I have a slightly different take. As an educator, I feel that the "flipped classroom" experience, where students prepare for a session, rather than coming in cold to hear me lecture, gives me the opportunity to use my time with them to actively engage them in discussion and thoughtful analysis. In my opinion, we should be taking every opportunity to volunteer to be more involved with education. The pedagogies are changing and our style of teaching needs to change with them. There's only one way we will be left out of the conversation in medical schools – and that's if we refuse to update our educational philosophies.

How many pathologists will we need over the next few decades?

NZ & JB: TThis is the key question. At the moment, we are seeing exciting new practice models implemented that integrate everything from digital pathology to deep neural networks (that is, artificial intelligence). The landscape is changing, and we need to do our best to accurately project what the future pathologist workforce should be, in terms of both numbers and composition. This will allow us to adjust the supply and demand relationship by tailoring the total number of available residency positions.

Published data back in 2008 projected a looming shortfall of pathologists, with a report from The Workforce Project Work Group five years later that suggested this shortfall would extend through the 2020s. The reasons presented in these predictive models included an aging population with imminent retirement from the pathology workforce (considered among the oldest in any field of medicine) and a large cohort of women with a preference for part-time practice.



On the other hand, there is also evidence – contradictory to some of the published job forecasts – to suggest that not only is the pathology job market not hot, but it may be warming up very slowly at best. Personal communications with our colleagues indicate that each advertised job in pathology attracts numerous applicants, and that many trainees are doing more than one fellowship simply because they are unable to find employment. Pathology also attracts a high number of international medical graduates,

many of whom are not eligible to work in the US unless they are recruited through special visas.

Unfortunately, we cannot know with any degree of certainty how many pathologists we will need in 2020 – or in 2025, 2030, 2035… We don't know what the composition of the future pathologist workforce will need to be – how many cytopathologists will we need? How many surgical pathologists, hematopathologists, neuropathologists, or any other type of laboratory medicine specialist? And what about the expanding roles for clinical microbiologists, chemists, bioinformaticians, or the as-yet undefined jobs with unknown skill requirements in the field of artificial intelligence (AI)? We need to be innovative and optimistic about our ability to recruit trainees and prepare them for whatever the future may hold.

What challenges does the world of pathology currently face?

NZ: I would not call them challenges; I prefer to think of them as opportunities. The future of pathology will look like nothing in its past. Personalized medicine will be the next big thing. The healthcare system will expect pathology to get a better handle on big data; we'll be expected to provide more, faster, and better-integrated information to allow earlier interventions and improved preventive care under predictive care models. For surgical pathology, a recent seminal event was the FDA approval of a proprietary digital pathology system for primary diagnosis. This will not only change the typical layout of the surgical pathology sign-out area, but also allow us to transfer images across borders and time zones (like radiology already does) for a quicker diagnostic turnaround time and a potentially lower management cost. Improved image compression and resolution will facilitate this process. Deep neural networks and cognitive computing are already beginning to show their value in surgical and cytopathology and, as they become more sophisticated and the neural network cloud continues to develop, AI will enhance our ability to provide more accurate information in a much shorter amount of time. One day soon, growing databases may even be able to identify new therapy options and clinical trials for patients before they have been widely publicized!

"We need to be innovative and optimistic about our ability to recruit trainees **and prepare** them for whatever the future may hold."

JB: Pathologists face the challenge of growing our field as rapidly as our technologies evolve. I would love to see us as drivers of technological development so that we can chart our own course, rather than just reacting to the presence of new technologies in the diagnostic medicine space. We also face the timeless challenge of demonstrating the value of pathology in clinical decision-making. The field is active in discussions about both emerging technologies and the role of pathologists in clinical care – but my personal feeling is that these conversations are still driven by only a small subset of our ranks, while many more pathologists are comfortable simply doing what they have always done (whether at the microscope or in the clinical laboratory).

I think it will be essential to attract trainees who both appreciate the traditional diagnostic aspects of their jobs and have the skillset to rapidly adopt new technologies into practice as they become available. I predict that we will see the repeated evolution of the role of the pathologist over the coming few decades.

How can we make pathology a more attractive career choice?

JB: Make it exciting! We need to frame pathology as a cutting-edge, technologically advanced field that will lead the practice of medicine in the future. We must aim to attract the best and the brightest – the future thought leaders of medicine. To show ourselves as leaders, we need

to get out into high schools and colleges, enhance our presence in medical schools, focus on genomics and personalized medicine when we "market" our field, engage in social media outlets, and create career trajectories where trainees are supported continuously from the time they start training through their first position.

NZ: The world of US pathology has always benefited from gifted pathologists who were educated in non-US institutions. This will not change – but how can we re-energize American medical students to consider the field of pathology as well? I don't think that cosmetic measures will bring about durable change. If we are committed to a long-term fix – and if we believe that this diminished interest is not cyclical – then we will work to change the future landscape of pathology. There are some milestones we must aim for, diligently and deliberately, with exceptional planning and execution and with a very broad buy-in. There are six vital points we must address:

1. *Reintroducing pathology to our high school and undergraduate students*
   Outreach into high schools and undergraduate institutions has become critical now that pathology has a smaller footprint in the medical school curriculum. Introducing pathology and pathologists through exhibits, sponsored projects, and summer electives can be very helpful. It's important that such events and activities are in sync with the contemporary adult style of learning – including being significantly technology-driven. The events must highlight the lives and contributions of pathologists to patient care, as well as the technology-heavy (future) nature of the field. Technology companies in Seattle and other tech-savvy cities are tapping into student interests through crowd-sourcing. Pathology needs to do the same. The world of US pathology needs to promote strong, communal outreach in a systematic way, driven by a unified institutional leadership.

2. *Improving the visibility of pathology at medical school*
   We must make learning pathology innovative and fun. Classroom didactics are quickly falling out of favor; in my opinion, pathologist-facilitated small group self-learning – vignettes with a rich admixture of media and progressive learning and testing – is where we all have to go. If we keep waiting for the entire educational system at our institutions to evolve, we will keep losing our own medical students' interest. Pathologists must be seen taking charge.

"Pathologists face the challenge of growing our field as rapidly as our technologies evolve."

We must copy those US institutions where medical students are paired with primary care physicians at the first-year level so that they may learn backwards (starting from patients and going back to texts). It would also be helpful to identify a model for post-sophomore fellowships that allows more streamlined training – and, ideally, even recognition through eligibility for the American Board of Pathology's diplomate status. I am currently working with a post-sophomore fellow and he is every bit as good as the PGY-1 (first post-graduate year) resident with whom I also work. We should also promote Pathology Interest Groups – especially ones that are action-based and innovative. And, finally, tapping into summer research grants could introduce those interested in pathology to the world of research in our field.

3. *Harnessing the resident workforce to attract more medical students*
   Harnessing residents and fellows is vital to encouraging US medical graduates to opt for pathology. If medical students interact with happy residents and fellows who are progressively achieving initial competency and have an optimistic view of their futures – and who give the impression of being facilitators and problem-solvers – then many more medical students will want to be a part of the pathology community. Every resident who does well in training should be able to convey to others the firm belief they have in their own future wellbeing: getting good fellowships and great jobs that pay well

and allow a well-rounded balance between professional and private life. Millennials want a clear work-life balance – something pathology should promote as a strength of its working style. Along with that balance, pathology already has strong representation from women and a very diverse work environment, but we must better showcase these positive attributes to attract more students to the field.

4. *Better connecting the pathologist workforce with the world of data*

(Of course, this is in addition to – not in place of – the diagnostic proficiency we maintain through continued medical education and recertification.)

Data is big and will only get bigger with time. A great deal of information flows through the laboratory, but it is raw, uncollated, and often deeply fragmented. The pathology team ensures the quality and validity of the test results in the clinical laboratory, but is not necessarily in a position to bring this information together, collate it, or organize it to help with the clinical management of the patient. The responsibility therefore fully shifts to the ordering physician to gather all of the information, make clinical sense of it, act on it, or gather still more information through additional testing to ensure optimal diagnosis and management. The newer molecular and genetic tests are producing a tremendous amount of raw data; at the moment, we don't even use all of it, but what we do not use may develop clinical value as more research unfolds. In other words, we are now collecting a huge amount of data, some of which we need immediately, and the rest of which we may need at some future point. This galaxy of information needs to be conscientiously archived and processed in real time as new information becomes available. The field is ripe for benefiting from AI to facilitate the work of diagnosticians, clinicians, administrators, and community thought leaders.

We are rapidly heading into a future when neural networks will prompt diagnoses, treatments and systemic improvements through much-improved data analysis, using a robust, cloud-based neural network and without losing data confidentiality. Pathology is one of the biggest data generators in the healthcare field, so it's logical that pathologists should assume significant leadership in the field of data mining. But without a better pipeline of new, well-trained recruits, we may not have the capacity to produce enough highly sophisticated informaticians, or to retrain the current workforce in this area. It's also past time for medical schools and computer science institutions to move much closer to one another, so that we can help to shape the evolution of medical data and technology. We need to start a robust, ongoing discourse on the impact of new technologies and their applications on the future pathologist workforce.

"The field is ripe for benefiting from AI to facilitate the work of diagnosticians, clinicians, **administrators,** and community **thought leaders."**

5. *Improving supply and demand in pathology*

Calculating the future demand for – and supply of – pathologists has been the single most important challenge to predicting the job market. Changes in healthcare delivery models, reimbursements, and the induction of technology make this task even more difficult. The time is ripe for us to meticulously survey pathology practices across the nation so that thought leaders may use those numbers to project workforce needs for the future. We know that healthcare costs are ballooning in a way that won't be sustainable for much longer. There will be cuts and streamlining of services with impact on reimbursements – not just limited to pathology, of course, but we will certainly have our share to bear. As more sophisticated technologies arise – molecular tests are increasingly inducted as first-line tests for certain cancers – and as our work embraces more automation and a greater input from deep neural networks (the "Alexa" of medicine) – there will be significant cost shifts between current and future reimbursement models.

But there is also room to open new reimbursement streams, such as diagnostic medical practice through clinical pathology consultations. On the anatomic pathology side, the use of digitized images for primary

“At the moment, our training is a combination of the **practical and the noble.”**

surgical pathology diagnosis could have a significant impact on the practice of surgical pathology itself, especially because the current workforce hasn’t had extensive digital pathology training or experience; such images could be moved around (just as radiology does) for consolidation and cost savings. In cytopathology, results from Papanicolaou smears are likely to be increasingly routed through deep neural networks simply because of the limited (and repetitive) nature of their findings, and the early maturation of the cloud-based neural network for gynecologic cytology. Human papillomavirus vaccination will also impact both gynecologic cytopathology and the incidence of HPV-associated lesions.

I also think we need to carefully study the impact of national and regional providers of pathology services, and of pathology practices owned by clinician specialists. Many of the jobs in pathology are still offered through word of mouth and never advertised, making it difficult to accurately calculate the job market for pathologists. It seems unlikely to me that there will be a big gap between supply and demand anytime soon; in fact, gauging by the trend among current trainees of opting for multiple pathology fellowships, there may actually be a shortage of jobs (or an overproduction of pathologists – some of whom may not be eligible to work within the US unless sponsored on special visas). This generous supply could potentially put pressure on pathologist salaries. A realistic question to ask is: should the number of pathology training slots be decreased to keep the supply and demand balanced, and to keep reimbursements at a desirable level? Or

should the training structure be significantly changed so that we produce pathologists with better leadership potential for the new technologies being unveiled in data management and AI?

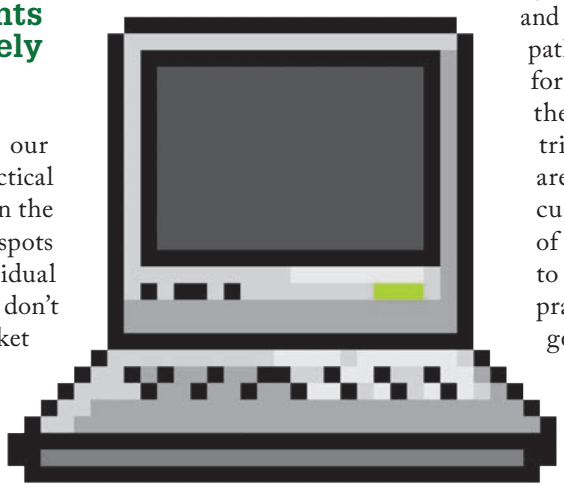
6. *Improving the efficiency of professional pathology organizations through consolidation and a shared vision and mission*

Professional pathology organizations are doing an exceptional job of lobbying for pathology and pathologists, maintaining proficiency and quality, allowing the sharing of ideas and research, and helping to develop academic medicine and private pathology. More recently, there has been an increased focus on "synergy" and the sharing of ideas and actions to promote the growth of pathology. It may not be possible to join every pathology professional organization, but consolidating pathology organizations may facilitate broader overall membership and help elevate our stature in the world of medicine.

Are we tailoring the training for our residents and fellows appropriately for the available jobs?

JB: Not entirely. At the moment, our training is a combination of the practical and the noble. We base it largely on the available residency and fellowship spots (practical), coupled with the individual trainee's interests (noble)… but we don't adjust based on the specific job market at a given time. Trainees today feel that they need to do two or even three fellowships to be able to find a job. Granted, some employers seek candidates who have training in multiple subspecialty areas, but many others post jobs that are focused on a single area. We could discuss the literature on the job market outlook for days – but suffice it to say that there are conflicting opinions as to whether there is undersupply or an overabundance of trainees in the pipeline. For me, the salient point is that there is a mismatch somewhere. Trainees feel that it is almost impossible to find a job, whereas the data suggest that the vast majority of them do land jobs. Similarly, some employers feel that there are abundant applicants for each position, while others feel that there aren't any people out there (particularly with extensive clinical pathology training) to fill their open position, and search for years for someone to fill the spot. Which perspective is true? If employers consistently have open positions, but trainees feel like there are none, then we need to find – and fix – the miscommunication. For instance, I'd like to see us get more involved in social media and other outlets that reach trainees, rather than having students and trainees alone enculturate the students in the early stages of the pipeline.

NZ: Our current training is based on the traditional model of pathology practice. Harnessing our new and still-developing role in the areas of personalized medicine, informatics, digital pathology, and artificial intelligence demands that – to appropriately prepare the new cadre of pathologists – we revisit the educational curriculum in medical school and residency. I believe that the most important areas to induct or expand into our educational curriculum in the very short term are informatics, molecular and genetic pathology, and the business of pathology. Our trainees are better wired for informatics than we, the mentors; they still need to learn to engage and triage big data, but the fundamentals are already there. What they need, but currently lack, is the art and science of traditional pathology and the skills to run cost-effective, patient-oriented practices. Only by equipping the next generation with a comprehensive set of skills and competencies can we ensure that we not only have enough pathologists to meet our needs, but also that they have the tools they need to cope with a constantly evolving specialty.



Nadeem Zafar is the Chief of Pathology at VA Puget Sound in Seattle, USA.
Jennifer Baccon is Chair of Pathology and Laboratory Medicine at Akron Children's Hospital, Akron, and Chair and Professor of Pathology at the Northeast Ohio Medical University, Rootstown, USA.

CELEBRATING THREE YEARS OF HUMANITY IN SCIENCE

The Humanity in Science Award recognizes and rewards scientific breakthroughs that aim to have a real impact on humankind's health and wellbeing.

HUMANITY IN SCIENCE AWARD

the Analytical Scientist

2015

Peter Seeberger & Andreas Seidel-Morgenstern, Directors at two collaborating Max Planck institutes in Germany, developed an innovative process to manufacture the most effective drugs to treat malaria from plant waste material, air and light.

2016

Waseem Asghar, Assistant Professor at Florida Atlantic University, developed flexible sensors for the rapid and cost-effective diagnosis of HIV – and other infectious diseases – in point-of-care settings.

2017

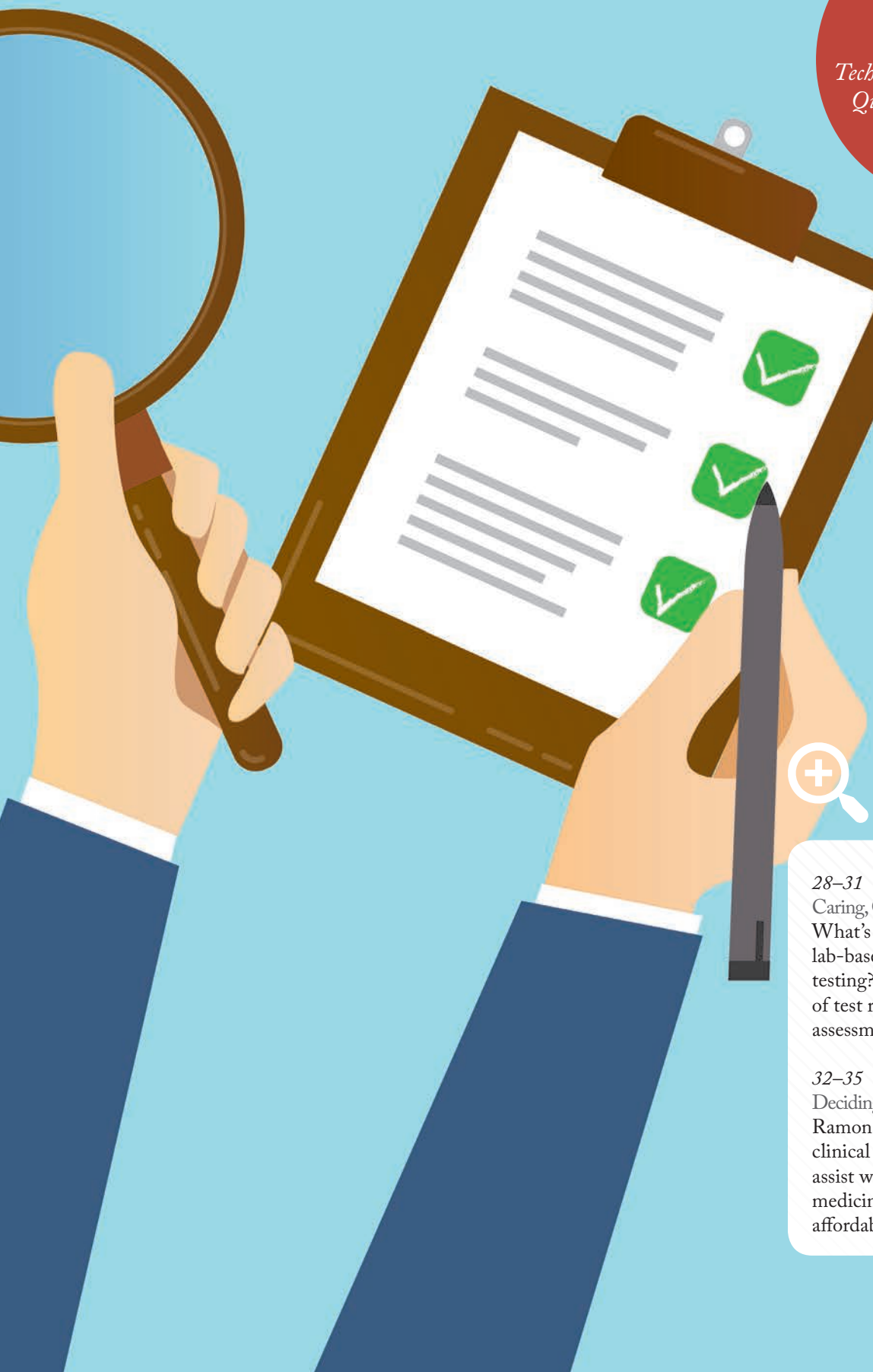
Richard Jähnke, Global Pharma Health Fund (GPHF), developed and continuously improved GPHF Minilab – a "lab in a suitcase," enabling resource poor countries to rapidly identify substandard and falsified medicines.

Nominations will open soon for the 2018/2019 Humanity in Science Award

www.humanityinscience.com

In Practice

Technologies and techniques
Quality and compliance
Workflow



Caring, Concern, and Consistency

Quality assurance processes are the lifeblood of laboratory-based and point-of-care testing

By Tim Woods

Quality control is a recurring – and vital – theme throughout pathology and laboratory medicine. It is particularly evident in the field of blood coagulation, a precision science that requires careful testing of samples, and equally careful testing of the tests themselves. And that's where quality assurance (QA) processes come in – both internal to the user or facility in question, and external to the test itself. As point-of-care testing (POCT) evolves and is increasingly adopted into healthcare practice, it becomes increasingly important for pathologists to understand the QA methods that go into ensuring that both laboratory-based and point-of-care tests are accurate, precise, and consistent.

At a Glance

- *Both internal quality control (IQC) and external quality assurance (EQA) are key to ensuring that laboratory-based and point-of-care tests yield reliable results*
- *The need for consistency is especially true in fields such as blood coagulation, which feature a wide variety of tests and sample types*
- *IQC and EQA should be seen as two sides of the same coin, and both should be considered indispensable to proper testing processes and accreditation*
- *The QA process may once have been seen as an "evaluation evil," but is now an important part of delivering the best possible patient care*

The resurgence of UK NEQAS for Blood Coagulation

Coagulation is a constantly developing field of work, a fact that was no less true during the dynamic decades of the 1980s and 1990s. In July 1988, I left my position as head of the coagulation laboratory at St Bartholomew's Teaching Hospital in London to move to the revitalized UK National External Quality Assessment Service for Blood Coagulation (UK NEQAS BC). The program had recently been revived under the guidance of Peter Kernoff, Director of the Katharine Dormandy Haemophilia Centre at the Royal Free Hospital in London, so was to be located there – but due to a lack of available space in the busy facility, a "NEQAS Portacabin" was installed and became a feature outside the entrance to the Haemophilia Centre.

In November 1993, my colleague Ian Jennings and I relocated UK NEQAS BC northward to work with Eric Preston and Steve Kitchen (hemophilia center director and laboratory scientist, respectively, at the Royal Hallamshire Hospital in Sheffield). Following the move, registration and participation in the laboratory program rapidly increased – not only within the UK, but also by cohorts of participating laboratories in Europe and further afield. In 1996, the Near Patient Testing (now known as Point of Care Testing) EQA program for oral anticoagulant control was piloted to 25 centers; this program alone grew to encompass over 5,000 registrations today, and additional POCT programs for activated clotting time (ACT) and D-dimer are now well-established and overseen by Dianne Kitchen, Lead Scientist for POCT programmes. Following Eric Preston's retirement, UK NEQAS BC has continued to grow under the guidance of the current Director, Isobel Walker.

Who we are

As part of the national network of 24 EQA centers (also known as proficiency testing centers) within the National Health Service that make up UK NEQAS, each constituent program offers not only test samples for an extensive array of evaluated analytes, but also advice and assistance for laboratory science, medical, pharmacy, and nursing healthcare professionals. Programs are operated on a not-for-profit basis, each being led by dedicated healthcare professionals with expertise in their respective specialties. Educational aspects are of paramount importance for UK NEQAS, and centers regularly hold scientific meetings for their participants.

"As POCT evolves and is increasingly adopted, it becomes increasingly important for pathologists to understand the QA methods that go into ensuring that tests are accurate, precise, and consistent."

"Unsurprisingly, there are often differences between the processes of laboratory testing and POCT, but one is certainly just as 'satisfactory' as the other."

EQA programs vary in their processes and types of sample that are distributed, according to their pathology specialty, but normally consist of a biological material (whole blood, plasma, serum, cerebrospinal, or other body fluid or solid) stabilized by buffers, fixatives, or freeze-drying. An aliquot of the same material is sent to the testing laboratory or clinic for analysis according to the facility's routine method of testing. The sample should be integrated into an existing run of patient samples wherever possible, rather than being accorded any special treatment.

Following testing, results are sent to the EQA provider for data and statistical analysis, comparing the participants' results against all others for the same sample using the same methodology. Normally, the provider issues an individual participant report soon after the closing date, followed later by a more comprehensive report based on all results received. Performance criteria are established prior to testing by steering committees with expertise in the relevant field of biomedical science, and each participant's results are compared with these criteria to determine compliance.

Participants experiencing performances outside the consensus from their peer group in any test may be offered assistance in the form of advice, together with repeat samples to check their results. Where persistent unsatisfactory or poor performance surfaces – thankfully a rare occurrence –participants will be offered further assistance, and those who are UK-based may ultimately be referred to the appropriate National Quality Assurance Advisory Panel for additional professional advice to improve performance.

Laboratory testing versus POCT

Unsurprisingly, there are often differences between the processes of laboratory testing and POCT, but – contrary to perceived ideas regarding performances within testing systems – one is certainly just as "satisfactory" as the other. In a number of cases, POCT precision in EQA surveys has been comparable to an equivalent laboratory method. This can be seen, for example, in the January 2018 UK NEQAS BC distributions for prothrombin time/INR testing. In the laboratory program exercise, the coefficient of variation (CV) for results from a sample with an overall INR of 3.4 returned by 914 participating centers was 6.4 percent, compared with a POCT program survey distribution (although not the same sample) with an overall INR of 5.7 returned by 4,166 participating centers, with a CV of 6.6 percent for the most widely used POCT system.

QA processes for laboratory testing and POCT are not only covered by EQA, but also internal quality control (IQC). IQC is generally purchased

from a commercial manufacturer – often, though not always, the producer of the testing device – and compares the result obtained on the IQC sample to a range. The range may be specific for the reagent or test kit used (in the case of a laboratory test), or a range for the POCT device, test strip or cartridge. It should provide an answer to the question, "Is my result the same today (or in this testing session) as it was yesterday (or in the previous testing session)?"

EQA is a service ideally provided by an organization independent from commercial entities, although some EQA programs are also available from equipment or reagent manufacturers. As noted, EQA compares a result from the provided sample for the laboratory or POCT process with results from other users of the same reagent, kit or POCT device. EQA provides an answer to the question, "Are my results the same as those obtained by other users of the same test?"

One of the major differences between laboratory-based and POCT analyses relates to the fact that POCT measurements are, more often than not, performed by members of a clinical team and not by laboratory-trained scientists. Healthcare professionals, not having received laboratory training, may lack an understanding of the importance of complete QA. POCT is an analytical process and, as such, the full testing process (from the preanalytical to the post-analytical phase) should be understood and carefully adhered to by all healthcare professionals using POCT systems.

The five Ws

Who should be responsible for POCT quality control?

Whoever is carrying out the testing: a biomedical or clinical scientist, a clinician, a nursing professional, or any other healthcare professional trained in the use of the POCT system.

What should the quality control process for POCT look like, and what information should be collected?

The operator of the POCT system should record IQC information including:

- the date and time of the test
- the batch of IQC used
- the range for that IQC batch
- the batch of test strips used
- the operator's identification.

It is the POCT system operator's responsibility to check IQC results before continuing to test patients and, if the IQC is out of range, to repeat. If it is then still out of range, the operator should suspend testing and contact the POCT system manufacturer or distributor for advice. The POCT system should, of course, always be enrolled in an accredited EQA program (where one exists for the analyte under test).

Where and when should quality assessment take place?

IQC should be tested wherever the POCT system is being used, be that near a patient on an inpatient ward, in an outpatient clinic, or in a phlebotomy or laboratory area. There are several time points at which IQC testing should take place:

- when starting a new batch of POCT system test strips or cartridges
- when maintenance has been carried out on the POCT device
- when there has been physical disruption to the system
- when there are unexpectedly high or low patient results
- at least once per clinic or testing session, with additional IQC tests carried out if a high number of patients are being tested
- if a POCT system is used infrequently or for only a small number of tests, IQC should be carried out for each batch of tests, even if it is a single patient test
- EQA should be performed whenever the provider schedules a distribution to be circulated to their participants, which is usually within a given time period before the closing date of the survey exercise, but may be specifically defined to have all participants test the EQA sample(s) on a set day.

When and how should the quality control processes themselves be evaluated?

EQA is a complementary tool to IQC in the QA toolbox, and results from both processes should be continuously monitored. National accreditation bodies, such as the United Kingdom Accreditation Service offer registration in a program of compliance with, and ongoing surveillance to, international standards (ISO 15189:2012 for

"EQA is a complementary tool to IQC in the QA toolbox, and results from both processes should be continuously monitored."

laboratories and ISO 22870:2016 for POCT-based registrations). EQA programs register to achieve accreditation to ISO 17043:2010, and I strongly recommend participation in an EQA program that has maintained its accreditation status.

Why are EQA and accreditation necessary, and how can laboratories access these services?

The many benefits of participating in an EQA program include:

- the comparison of performance against other participating sites, especially where using the same methodology
- the identification of problems - especially where systematic - that may be associated with reagents, kits or testing systems
- the flagging up of processes that require improvement.

EQA may also be used by participating centers to identify where there may be deficiencies in method practice. When such situations arise, the EQA provider may even offer corrective assistance in the form of advice and previously distributed samples to check on test systems. Participation in an EQA program is normally required for laboratory or POCT accreditation, with the EQA program itself having ideally been accredited against standards to ISO 17043:2010 with continuing surveillance by the accreditation body.

EQA services, including POCT programs, are available from UK NEQAS, with details available on the UK NEQAS website *(ukneqas.org.uk)*.

Questions and concerns

A number of qualitative POCT tests have raised concerns regarding their performances, and some semi-quantitative POCT methods have been known to fall short in their detection abilities. However, following discussion with – and intervention from – overseeing organizations, such as the UK's Medicines and Healthcare products Regulatory Agency (MHRA), these are under greater control, and standards for new tests are strictly maintained. If a particular POCT method is ever questioned and taken under investigation, a Europe-wide Field Safety Notice can be issued to ensure that users curtail testing with that system. An example of this situation is a recent a POCT D-dimer test (1). An investigation by MHRA resulted in the issuance of a Field Safety Notice and the withdrawal of the D-dimer rapid test from the market (2,3).

Pathologists' and laboratory scientists' concerns regarding the validity of results from POCT systems have now thankfully disappeared, along with the fear that POCT would diminish these professionals' working practices. POCT methods have been successfully integrated into many laboratories, and pathologists and lab scientists are often involved with the POCT coordinators and committees that many hospitals have established. Greater concerns in the UK now center on the conversion of the existing pathology system to a series of "networks" – hub-and-spoke models that centralize and reallocate laboratory services – and what role POCT methods can play in this process.

Quality assurance, and particularly EQA, was not too long ago seen as an "evaluation evil" – a blunt instrument with which to penalize users. Fortunately, we have seen the processes evolve to be embraced as a precision tool to assist healthcare professionals in obtaining the best test results for their patients. It's a trend that can only improve our work, and I hope it will be long-lived.

"We have seen [these] processes evolve to be embraced as a precision tool to assist healthcare professionals in obtaining the best test results for their patients."

Tim Woods is Chairman of the UK NEQAS POCT Working Group and Deputy Director of UK NEQAS for Blood Coagulation, UK.

References

1. *DP Kitchen et al., "Poor performance of a point of care D-dimer test: UK NEQAS BC investigation and reporting to Medicines and Healthcare products Regulatory Agency (MHRA)". Poster presented at the 57th Annual Scientific Meeting of the British Society for Haematology; March 27–29, 2017; Brighton, UK. Poster #PO-140.*
2. *Medicines and Healthcare products Regulatory Agency, "Field Safety Notices – 10-14 October 2016" (2016). Available at: https://bit.ly/2FA1FoE. Accessed May 2, 2018.*
3. *Medicines and Healthcare products Regulatory Agency, "Medical Devicec Recall of gabControl D-Dimer rapid test (M09DD02) from the market" (2016). Available at: https://bit.ly/2rdHM2i. Accessed May 2, 2018.*

Deciding Factors

How clinical decision support technology powers precision medicine

By Ramon Felciano

The adoption of precision medicine is happening at a pace that would have been difficult to imagine even just a few years ago. Hospitals and clinical labs have tremendous interest in delivering this kind of tailored care to patients – but implementing precision medicine as a new capability remains a major challenge. Nevertheless, the need to adopt is both clear and pressing, especially for healthcare organizations treating patients with cancer; precision medicine has remarkable value in diagnosing, treating, and monitoring the disease. So how can organizations transition to precision medicine in a cost-effective, scalable way?

The pursuit of precision

Precision medicine is built on a foundation of new sequencing technologies that generate massive amounts of patient-specific data – both a blessing and a curse for hospitals and clinical labs. On one hand, it is the sheer volume of genomic information and our ever-improving understanding of disease genetics that make it possible to provide an accurate, customized prognosis or select just the right treatment for a patient. On the other hand, without an army of PhD geneticists and bioinformaticians helping to make sense of it all, healthcare facilities who want to adopt precision medicine are often intimidated by the daunting task of keeping pace in such a rapidly advancing field.

In my opinion, the only way to solve this problem is through technology. In recent years, clinical decision support (CDS) tools have become increasingly available to laboratory staff and clinical care teams. Similar to the way Google Maps sifts through reams of data to help people choose the best routes to their destinations, CDS tools perform the "heavy lifting" of collecting and organizing all the relevant clinical information across lab data sources, electronic healthcare record (EHR) data, and the clinical literature that best captures our understanding of disease. Then, the information is fed into powerful integrated data analytics to offer healthcare professionals comprehensive, up-to-date, evidence-based interpretations that are tailored to the clinical profile of each patient.

Implementing precision medicine

Just a few years ago in the United States, precision medicine was only offered at pre-eminent academic medical centers. Today, an estimated 24 percent of hospitals will provide some form of precision medicine by the end of 2018 (1). But even though precision medicine is projected to spread and develop rapidly in the coming years, there is an urgent need to operationalize its clinical use right now.

The biggest challenge is keeping up with the speed of information growth and our constantly evolving understanding of the biology that underlies disease and treatment response. Though the cost of sequencing technologies continually decreases, the volume and frequency of new information that practitioners must integrate into their genomic analysis is only increasing – adding to the time, effort, and information complexity of solving patient cases using genomics. Elaine Mardis, now at Nationwide Children's Hospital, phrased this problem succinctly in the title of her article (2), "The $1,000 genome, the $100,000 analysis?"

For precision medicine to be effectively delivered to patients in clinical settings, practitioners must keep up with advances in treatments, disease biology, clinical trial availability, professional guidelines, and much more. Traditional approaches would mean that individual hospitals would need to hire dozens or even hundreds of MD/PhDs to wade through all of the

At a Glance

- *Precision medicine is being adopted at an increasingly rapid pace – but implementing it from scratch can be costly and difficult*
- *Clinical decision support (CDS) tools can pave the way to precision medicine for many hospitals and clinical laboratories*
- *Many CDS options are available, so users must be careful about selecting the most appropriate tool*
- *CDS tools can help make treatment decisions, manage liability risk, and ensure compliance with ever-changing data privacy regulations*

"Precision medicine is built on a foundation of new sequencing technologies that generate massive amounts of patient-specific data."

"The biggest challenge is keeping up with the speed of information growth and our constantly evolving understanding of the biology that underlies disease and treatment response."

information stemming from internal datasets, EHRs, external databases, and peer-reviewed literature – just to help pathologists, oncologists, and other healthcare team members apply that knowledge to each patient case. The operational, logistical, and financial implications of such a model make it a non-starter for the majority of today's clinical care settings.

A technological alternative

CDS tools offer a scalable, cost-effective way forward for medical centers that don't have access to a phalanx of dedicated data analysts. These tools incorporate advances in data mining, machine learning, predictive modeling, and other areas. The result? Technology that can process massive amounts of data and generate clinically actionable interpretations or recommendations for specific cases. There are many types of CDS tools; to select the right one for a particular set of needs, we need to understand the different options each tool provides.

CDS tools often start with some form of knowledge base – a vast collection of information fed into the platform at its foundation and then restructured and reorganized to make it easier for software algorithms to process. Some CDS tools may begin with specific datasets for narrowly defined clinical uses. Others are far more comprehensive, including carefully structured representations of peer-reviewed literature, as well as genomic, clinical, and therapeutic databases. Naturally, these tools can be applied to a broader range of health conditions. The most sophisticated of these approaches expand beyond even clinical literature and lab data to integrate many other types of information, such as best practice clinical diagnosis and treatment guidelines, detailed enrollment criteria for clinical trials, genetic and pharmacogenomics-related indications for available drug treatments, and collections of clinical case datasets that describe outcomes for biologically similar patients. Such technology provides pathologists, clinical geneticists, and other lab professionals with powerful computational engines to process,

integrate, and interpret the universe of information relevant to each patient. When implemented properly, these tools can provide the information needed to help inform a clinical decision at any given time.

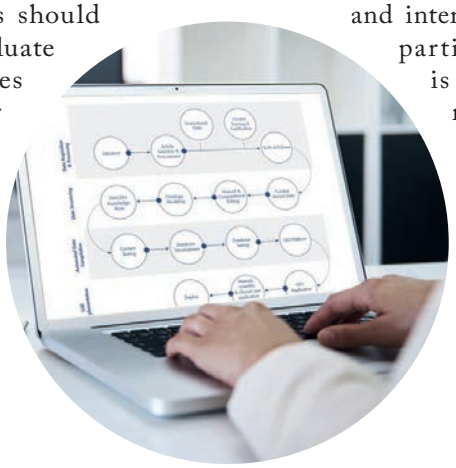
Consider how this kind of tool could work in a pipeline for reporting the results of a tumor genetic analysis. The tumor would be sequenced, leading to a list of potentially millions of variants spanning many types of genetic variation: single nucleotide variants, insertions and deletions, copy number variation, fusions, and more. When appropriate, a matched normal sample would also be sequenced so that germline variants could be quickly and automatically filtered out of the list. Variants deemed unique to the tumor would then be fed as a first data input into the CDS tool, which would crucially integrate the second data input: an algorithmic knowledge base that represents all known information about each variant – even if that variant's name, function, or clinical impact has changed over time. The tool could then apply some intelligent algorithms to determine what kind of downstream biological effect each variant might have, its possible corresponding impact on disease physiology, a differential clinical diagnosis, and potential responsiveness or resistance to an array of available therapeutic options. Some tools even automate variant classification according to professional guidelines, such as the American College of Medical Genetics and Genomics variant categories. All of these steps would be automated, running rapidly in the background, and the eventual output could provide a detailed explanation for the algorithmic reasoning that led to a given conclusion. Finally, the CDS tool would generate a short list of the variants most likely to be medically relevant – those that might be driving the cancer, as well as those that could be used to guide treatment selection or clinical trial enrollment.

Importantly, CDS tools are not intended to usher artificial intelligence into the medical establishment. The technology is designed to help experts make decisions, rather than to make decisions for them – and, as such, the strongest of these systems include a critical explanation component whereby physicians, oncologists, geneticists, and the rest of the care team can inspect and understand the evidence-based reasoning that led the system to suggest a particular course of action.

"The technology is designed to help experts make decisions, rather than to make decisions for them."

Key differentiators

When considering CDS technology, users should be careful to evaluate all of the features relevant to their laboratory's needs. For instance, some tools use the "black box" model, generating results without allowing the user to see the calculations and assumptions needed to arrive at that conclusion. This model introduces an element of risk to clinical teams, who cannot fully justify medical decisions, if they don't understand the evidence underlying the CDS-generated interpretations. For clinical lab purposes, tools that offer transparency are far more empowering. When these tools generate results, each one can be queried to reveal the specific data, filters, and processes that led to it. In the best-case scenario, users can even go back and adjust some of those elements – say, to exclude data deemed irrelevant for the case or tweak a filter to be slightly more stringent based on the user's expertise.



The need for a clear understanding of how patient data is processed and interpreted to reach a particular conclusion is becoming well-recognized. In some cases, it has even been the subject of regulatory oversight. In Europe, for instance, the recently enacted General Data

Protection Regulation (GDPR) includes provisions around providing consumers and patients a "right to explanation," including "the existence of automated decision-making and meaningful information about the logic involved, as well as the significance and the envisaged consequences of such processing for the data subject." Although GDPR is broad in scope and reaches far beyond healthcare applications, the emphasis on transparency and understandability of software system outputs used for decision-making is likely to make "black box" approaches a thing of the past.

Another differentiator is how data was processed to build the original knowledge base powering the CDS tool. Many options rely on machine learning, a fast and cheap method of churning through reams of data. Such artificial intelligence-based approaches have seen significant increases in adoption in recent years, but they remain limited by the size, quality, and "up-to-dateness" of the big data collections used to train the algorithms. Patient datasets are still too small for optimal clinical use (some experts estimate that one billion patient datasets will be needed for breakthrough algorithmic value). Another downside of the machine-learning approach is that when there are inconsistencies in the initial, smaller datasets, results will suffer. For example, two separate papers referring to the same gene by two different names will not be analyzed together – an issue that could lead to incomplete results and possibly an inaccurate interpretation or recommendation.

An alternative is CDS technology that incorporates both machine learning and expert-defined rules and algorithms, supported by well-curated input datasets – a hybrid computational approach that yields the best of both worlds. Critically, for this model to work, an organization must have the operational know-how, infrastructure, and expert staff to enable doctorate-level experts to create the baseline knowledge asset, review and assess the automated results, and adjust when needed before that information is entered into the knowledge base.

"When considering CDS technology, users should be careful to evaluate all of the features relevant to their laboratory's needs."

Finally, it is worth considering whether the CDS tool relies only upon its pre-loaded information. Some tools allow users to link internal data sources, such as the private knowledge bases many clinical labs are building from information about their own patient populations. Systems that make it possible to incorporate both internal and external data offer the most flexibility and value for hospital-based users, resulting in CDS technology that can be tailored to a particular institution's patient population by leveraging data from that population.

Looking ahead

CDS tools are following genomics and precision medicine into clinical use, starting with rare hereditary diseases and cancer. In the near future, I anticipate that these tools will be deployed globally – using patient privacy-sensitive approaches – for many more medical conditions. As that trend continues, healthcare organizations are likely to find that CDS tools are an important way to manage liability risk. Hospitals that lack a mechanism to ensure that decisions are based on the most up-to-date information and are being made in a reproducible, objective manner will not only be less likely to provide consistent, high-quality care, but also run a higher risk of lawsuits. CDS tools will allow organizations to make reproducible, accurate decisions for each patient – and in countries where frameworks are now being put into place to give consumers the legal right to an explanation for each medical decision, such tools will be essential for compliance.

When I look to the future, I see CDS technology paving the way for hospitals and labs with limited budgets to get into the realm of precision medicine, delivering better care for their patients in a cost-effective fashion.

Ramon Felciano is Chief Technology Officer of QIAGEN's bioinformatics unit. He was a founder of Ingenuity Systems, now a QIAGEN company.

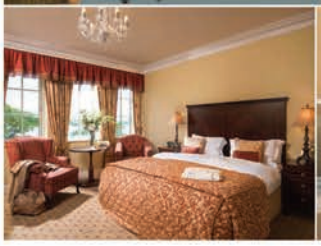
References

1. *N Versel, "Data requirements, money hold back growth of precision medicine among health systems" (2018). Available at: https://bit.ly/2qFSb60. Accessed April 18, 2018.*
2. *ER Mardis, "The $1,000 genome, the $100,000 analysis?", Genome Med, 2, 84 (2010). PMID: 21114804.*
3. *European Union General Data Protection Regulation, "Article 15, section 1(h): Right of access by the data subject" (2018). Available at: https://bit.ly/2vqMHBC. Accessed April 18, 2018.*

Pathology Horizons

13-15 September 2018 | Lough Erne Resort | N. Ireland






"It has been interesting to have people suggest the ways that they think pathology will travel in the next 10-15 years, but also to talk informally between sessions about emerging technologies and events. I'd really recommend Pathology Horizons going forward and look forward to the next meeting."

Dr. Anthony Gill, Pathology Horizons 2017

Pathology Horizons is an annual and open CPD conference organised by Cirdan to discuss what developments lie ahead in pathology.

Speakers & Presentations

A/Prof. Jane Armes | NSW Pathology | Australia
Title: Genome Sequencing as a Diagnostic Aid

Prof. Richard Kennedy | Almac Diagnostics | N.Ireland
Title: Development of Genomic Assays for Multi-Arm Clinical Trials in Cancer

Dr. Eric Glassy | Providence Little Company of Mary Medical Center | USA
Title: Extreme Makeover: Creating Pathology Reports that Make a Difference

Dr. Niamh Buckley | Queen's University Belfast | N.Ireland
Title: Application of Liquid Biopsy to the Detection and Treatment of Ovarian Cancer

Dr. Dean Wallace | UCLA | USA
Title: Opportunities Outweigh the Challenges of Radiology and Pathology Integration

Dr. Irene Regan | Academy of Clinical Science and Laboratory Medicine | Ireland
Title: Laboratory Medicine: The Times They Are A Changin

Dr. Laszlo Igalia | Norfolk and Norwich University Hospitals NHS Trust | England and Ferenc Igali | University of Lincoln | England
Title: Virtual and Augmented Reality in Digital Pathology

To view full list of speakers and the agenda, go to:
www.pathologyhorizons.com

RCPath CPD Approved

CPD CERTIFIED
The CPD Certification Service

Early Bird Tickets Available
Register at www.pathologyhorizons.com/register

CIRDAN
Improving Wellbeing Through Innovation

NextGen

Research advances
New technologies
Future practice

Stromal Secrets

Stromal cells present in menstrual effluent may offer a noninvasive way to test for endometriosis

By Peter K. Gregersen

When patients present with pelvic pain or infertility, it's not often that a doctor's first thought is endometriosis. It can be even more difficult to have such symptoms taken seriously when the level of pain seems so disproportionate to the disease – and when the gold standard for diagnosis is laparoscopy or uterine biopsy, many physicians hesitate to suggest such invasive interventions for what is frequently perceived as a minor issue. But endometriosis is, in fact, anything but – and, with menstrual effluent providing a potential new, noninvasive approach to testing, patients with the condition may soon receive the diagnosis and treatment they so desperately seek.

From HLA to *WNT4*

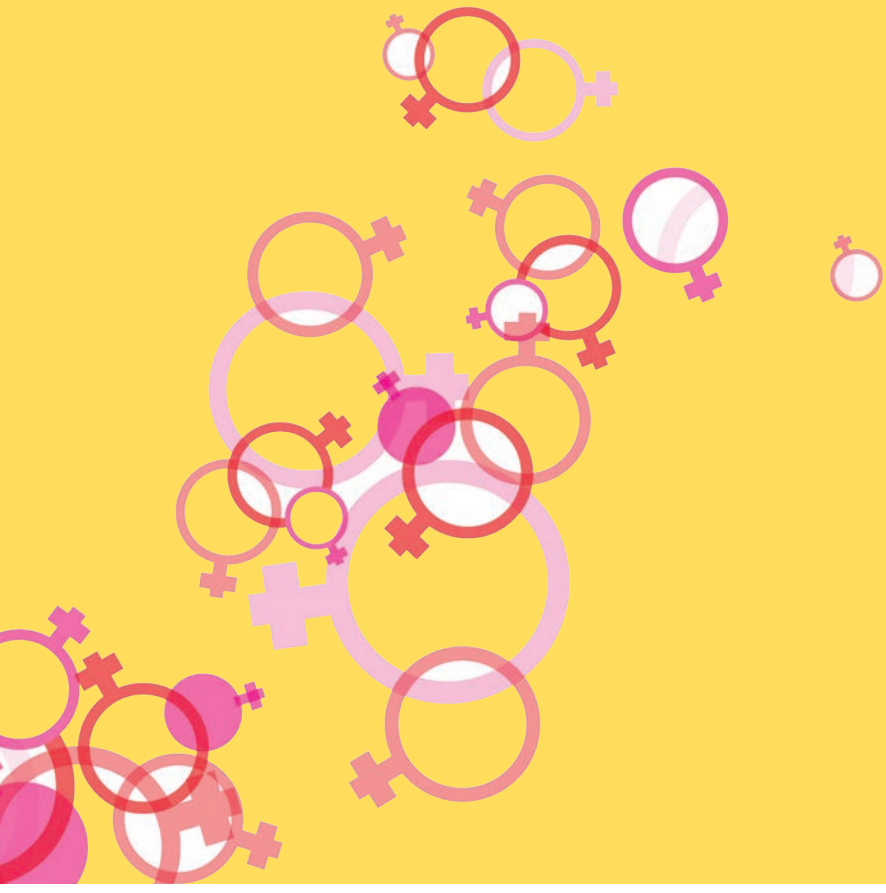
I have been interested in genetics for a long time. I originally trained as a rheumatologist here in New York, studying at Columbia and New York University, and did my early work cloning human leukocyte antigen (HLA) genes involved in rheumatoid arthritis. This was in the early 1980s, so it was just at the beginning of the cloning revolution. My colleagues and I cloned the major HLA genes for rheumatoid arthritis and developed a hypothesis – called the "shared epitope hypothesis" – for how those genes worked. From there I thought, "Well, we've got big HLA effects – maybe there's something going on in T cells?" I spent some time working on T cell repertoires, to explore the possibility further, but by the 1990s I was back to my first love: genetics.

I formed the Northern Rheumatoid Arthritis Consortium – the first consortium for genetic analysis of the disease – and, since then, we have produced 100 hits and become an international group, the Rheumatoid Arthritis Consortium International. As you can see, most of my life has been focused on mapping genes and autoimmunity, and – more recently – on analyzing the functions of those genes.

Of course, there are many complexities: most diseases have lots of genes involved, each with a very low individual effect. A lot of those involved in autoimmunity seem to impact T cells, B cells, and other immune functions. Over the last five years, we have focused on studying those same variants in individuals who neither have the autoimmune disease of interest nor are on medications, so that we can really tease apart the functions of those variants in the absence of all those complications. We have published a lot in recent years on T and B cell genes – the ones that regulate how quickly a B cell will respond to a stimulus, or how high T cells will jump if you stimulate them

At a Glance

- *Endometriosis is a common condition – but few researchers are focusing heavily on its diagnosis or treatment*
- *Currently, the only definitive endometriosis diagnostic is laparoscopic observation of lesions*
- *Stromal and natural killer cells present in menstrual blood may offer a new, noninvasive way of identifying patients with the disease*
- *In the future, cell characteristics may also help personalize treatment for these patients*



in standard ways. A lot of these genes can influence endophenotypes, so I think the current focus is on trying to understand endophenotypes in the context of these risk alleles. It's something I have done with lupus, arthritis, multiple sclerosis, myasthenia gravis, and others over the years – but then, about five years ago, some colleagues who suffer from endometriosis came to talk to me about it.

I didn't know anything about endometriosis at the time – but I found some interesting genetic research on loci associated with low odds ratios. *WNT4*, the top endometriosis gene, is directly involved in the decidual response, which is disrupted in the condition.

Defects in decidualization

Rheumatoid arthritis is a common disorder that has captured many researchers' attention. Endometriosis is even more common – but very few people worldwide are seriously working on it or its genetics. The focus of the work so far has been on trying to stage the disorder, because it features variable types and degrees of severity: there are adhesions around the perineum that bleed and cycle with the periods; there are chocolate cysts that engulf the ovary and impair ovulation; and there is invasive, often debilitating lower pelvic floor disease (perforation of the vaginal wall, bowel, or bladder). Having spoken to a lot of people with endometriosis, I've learned that the level of pain does not always follow the severity of the disease – but we don't yet know why.

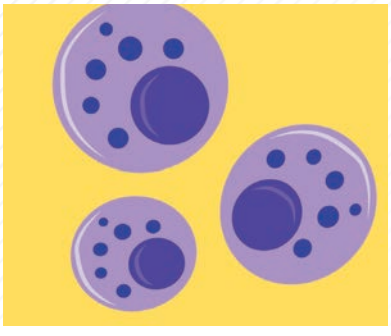
Aside from not really understanding how endometriosis works, there are two main issues with the condition. One is the delay in diagnosis – up to a decade! A typical story would be a high school or college-aged woman coming to a school nurse or doctor with these

Natural Killer Cells

Many of the endometriosis patients my colleagues and I studied exhibited very low levels of natural killer (NK) cells, particularly in the uterus. Uterine NK cells are part of the decidualization process, which in these patients is defective. It's possible that they have either insufficient NK cells, or that there's an abnormality in the cells' function that results in poor decidualization.

The cells are also important for placental implantation and placentation; uterine NK cells prevent placental trophoblast invasion from going too far. Inadequate placentation results in insufficient engagement with the uterine wall (and thus a lack of blood supply to the fetus); excessive placentation, on the other hand, can result in penetration of the uterine wall.

Phenotypic findings like NK cell levels have biological meaning in terms of understanding disease. They are both interesting and important because we can use them for large population studies. Better yet, their presence in menstrual effluent means we can conduct these studies without the need for uterine biopsies or other invasive procedures.



symptoms; they don't get recognized as being endometriosis – "Oh, just suck it up; this is what menstruation is all about; we'll put you on a nonsteroidal anti-inflammatory or 'the pill'" – which can sometimes be effective, but many people ultimately need surgery. Worldwide, surgeries are performed by a few well-trained surgeons. Although there haven't been controlled trials, it seems clear that stem cells drive these lesions, so removing the entire lesion – including the stem cells – is really important. If the surgeon just cauterizes the lesions, they will come back. It's common for women to have had multiple operations, because they saw a temporary improvement after each one, but then had to go back in because the lesions weren't fully removed.

Many endometriosis patients come to the attention of physicians because they have pain (though they are often dismissed because the intensity of the pain seems so unlikely) – but with others, we come to the second issue: infertility. About 30 to 40 percent of people who present with female infertility have endometriosis, and if you treat that, you often restore fertility – possibly because the disease interferes with ovarian function or with decidualization (which is important for implantation). Unfortunately, the only way to conclusively diagnose endometriosis is by laparoscopy to see the lesions; there are no noninvasive tests. That's what initially made me think we needed to stop focusing on the immune system or the lesions themselves; instead, we needed to look at the source of the cells causing the lesions – the menstrual blood. Almost all women experience retrograde menstruation at every cycle, and yet only five to 10 percent get endometriosis. Why is that? One possibility is that there are cell differences that cause the condition – and that's something we can study by collecting menstrual blood from women with endometriosis.

The first thing we learned was that, if you put menstrual blood into culture, stromal cells grow out of it like crazy. These are fibroblast cells that have some pluripotent ability. They grow very rapidly, and they exhibit decidualization defects that can be observed on uterine biopsies of people who should otherwise be in the late luteal phase.

"What we need is a biologically relevant diagnostic, and these stromal cells may be exactly that."

We decided to see whether these cells could be induced to decidualize; standard approaches to decidualization use cyclic AMP and combinations of progesterone and estrogen, so we took that approach and, lo and behold, stromal cells from people with endoscopically confirmed endometriosis do not decidualize well, whereas normal cells do. Great news – because what we need is a biologically relevant diagnostic, and these stromal cells may be exactly that. At the moment, we still need a visual examination to document endometriosis, so women who present with symptoms of the condition must undergo laparoscopy. It's my hope that, eventually, we can examine the stromal cells of such patients to determine whether or not they are likely to need a more invasive procedure.

Diversity and heterogeneity

Obviously, this work is still in its early stages. One criticism we've heard of our method is that we haven't staged the disease. We're going to get there! First, we need to apply the test to a large number of people with well-staged endometriosis and see if it correlates with severity. We have yet to establish the test's sensitivity and specificity. And we're currently collecting menstrual effluent from people who present with infertility to see whether or not it might be useful in that setting. Finally, we'd like to establish how the test results change after a patient's lesions are removed – is it a genetic defect that remains, or is it (as previous data suggest) a phenotypic outcome of the lesions that resolves?

To find out, I set up a normal control registry about 10 years ago. It contains data from about 5,000 people with no symptoms of endometriosis – but some of them carry risk genes like *WNT4*. We're now asking them for menstrual samples so that we can see whether or not those who carry the *WNT4* risk haplotype (which includes an abnormality in the gene's estrogen-binding site) also exhibit decidualization changes. Work like this might help us understand the biology of decidualization without having to perform uterine biopsies to gather data. We could perform blood-based genetic tests on populations and ask specific phenotypic questions – or vice versa. I suspect that there are multiple paths to a decidualization defect; GWAS revealed a number of genes in the pathway. There is clearly heterogeneity in terms of severity (for instance, *WNT4* is more associated with invasive pelvic floor disease), but the factors influencing it are not yet clear. There's a broad diversity of endometriosis phenotypes, so I expect we'll see similar diversity in our molecular investigations.

"There's a broad diversity of endometriosis phenotypes, so I expect we'll see similar diversity in our molecular investigations."

A need for further study

Conditions like endometriosis are often understudied. This is partly because there's not much funding available and partly because – in my opinion – women's diseases in general are underappreciated and underdiagnosed. The awareness of endometriosis has been very low until recently; after all, I myself am a well-trained physician who attended a highly ranked medical school, and yet I was completely unaware of it until it was called to my attention.

My approach is also unusual. This field is driven by surgeons, but even those I know and respect were skeptical of working on menstrual blood. "Why don't you work on understanding the lesions? Get the cells out, find out what types are involved and what cytokines they are making…" It makes sense, of course, but it requires getting surgical specimens. And the lesions are incredibly diverse, so it's hard to decide which are truly representative.

Finally, it's difficult to determine which cases of endometriosis have a genetic basis, and what distinguishes them from spontaneous disease. The heritability of the condition is estimated at about 50 percent, so many people with endometriosis will have a relative with the condition. I suspect that, as with autoimmune disorders, there's a genetic subset of the disease. Families with heritable endometriosis probably have much more highly penetrant genes than those that have been mapped by GWAS – and those may be incredibly important to find, even if uncommon, because they may give us insight into disease pathogenesis. To find out more, we'll need to recruit large families, perform genetic testing, and see how the results correlate with disease phenotypes.

Developing a diagnostic

I think this test could become a diagnostic that could help drive the selection of therapy. There are some people who do respond quite well to progesterone therapy, the endocrinology approach to endometriosis. Others need more intensive intervention; for instance, we put some patients into menopause or perform surgery to remove the lesions or even the entire uterus. Of course, these are treatments we'd like to avoid if at all possible – so if we can identify patients who might succeed with less aggressive therapy, we can ensure we're adhering to the basic principle of medicine: "first, do no harm."

I also think that testing stromal cells in menstrual blood has applications beyond just endometriosis – for instance, perhaps in adenomyosis or fibroid tumors. We have considered developing new collection methods for menstrual blood, such as single-use cups or specialized tampons, but for the moment, patients seem most comfortable with the reusable cup. Some patients are hesitant to perform the collections (and some physicians are hesitant to ask their patients to do that!), but with problems as life-affecting as endometriosis or infertility, many women are happy to undertake the task if it carries the potential for answers.

The next step for my own research is to miniaturize this process and make it more efficient. We can now grow cells from fresh menstrual effluent for 48 hours and get a decidualization assay from 3,000 cells (or even fewer) – it's amazing! I think we can miniaturize that assay so that it can be performed on a 96-well plate and still take only 48 hours to complete. We are also looking into gene expression data. The cells actually appear to be different at the single-cell level, but it's work we've only done on cultured cells thus far; fresh effluent is our next step. We may also try freezing samples (which doesn't change cell distribution) for later culturing and analysis. And, finally, we're collaborating with colleagues at Cold Spring Harbor Laboratories to look at possible proteomic changes. Very little is known about the signaling pathways in terms of possible phosphorylation changes after decidualization; my guess is there may be defects in that pathway that we could capture just by stimulating the cells and looking at the phosphorylated proteome. That way, we can see where the potential defects lie.

Ultimately, I'd like us to be better able to help at-risk populations who present to infertility or pelvic pain clinics. The prevalence of endometriosis in those patients is probably going to be quite high, and if we're going to help them, we need to pay this condition the attention it deserves.

Peter K. Gregersen is Professor and Director of the Robert S. Boas Center for Genomics and human Genetics at the Feinstein Institute for Medical Research, and Professor of Molecular Medicine at the Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Manhasset, USA.

the Pathologist™

Register now at

www.thepathologist.com/register

It is quick and easy and completely FREE

As a fully registered user you will benefit from:

- Unlimited access to ALL articles
- Full access to digital and archived copies of every issue of The Pathologist
- Print (and PDF) copies delivered direct to you
- Email news alerts
- Networking opportunities
- Application Notes and Product Profiles

There are many good reasons to register to The Pathologist. Here are just a few:

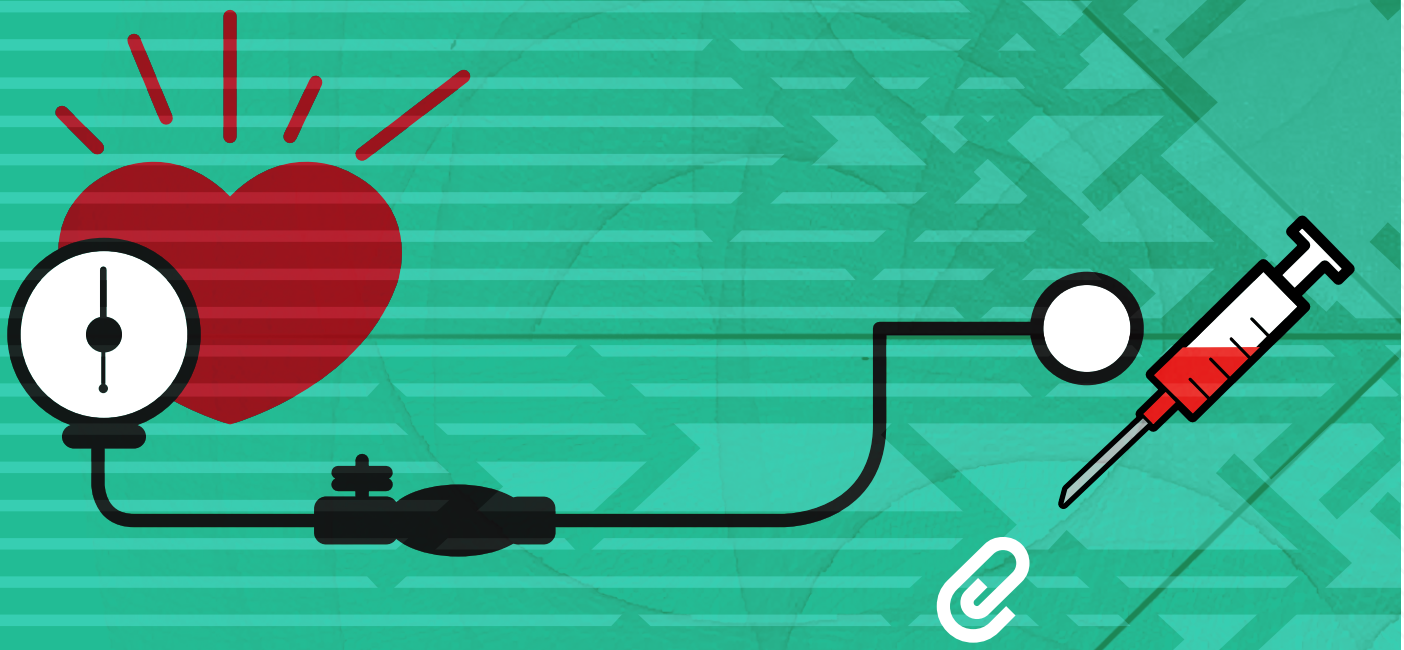
- You can access expert opinions and commentaries from across the globe on the most pressing issues in pathology
- We provide a platform to discuss pathology, its advances and advantages, and the changing face of medicine and medical education
- The conversational tone of The Pathologist makes it accessible to laboratory medicine professionals in any specialty, at any stage of their careers

Empowering pathologists to build a better future for pathology

Register now at **www.thepathologist.com/register**

Profession

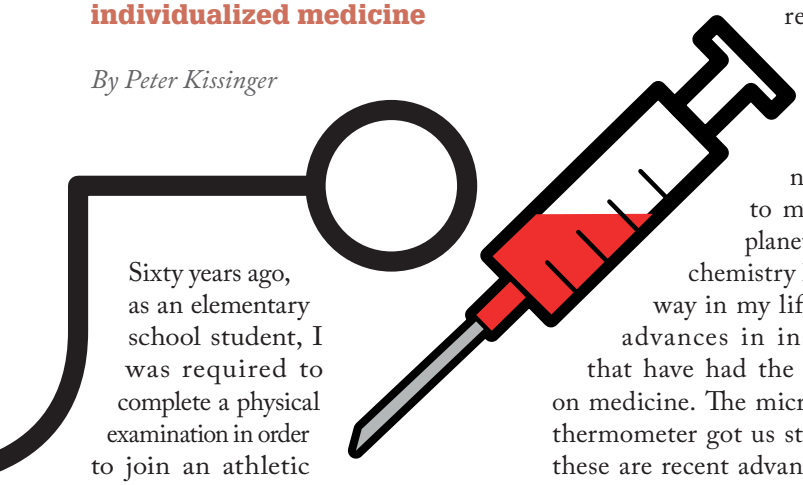
Your career
Your business
Your life



Clinical Chemistry: The Road to N=1

Why we need more chemistry in the clinic if we're going to reach the goal of individualized medicine

By Peter Kissinger



Sixty years ago, as an elementary school student, I was required to complete a physical examination in order to join an athletic team or participate in summer camp. At the time, such exams were fully in the domain of physics. The available tools measured height and weight, and included a chilly stethoscope, a blood pressure cuff, a rubber hammer, and a mercury thermometer. There was a little device with a bright light used to peer into my ears, nose, and throat. Virtually no chemical measurements were made beyond looking at the clarity of urine and a semi-quantitative test for sugar therein.

Following a recent morning encounter with my physician, I told a class of premeds that I'd just had a "pchem" exam. I related how a "physical" had become a "physical chemistry" exam, with the doctor showing me tables of numbers on a tablet computer, enabling comparisons with reference ranges and my own longitudinal data. Those same data are now available to me anywhere on planet Earth. Clinical chemistry has come a long way in my lifetime, and it is advances in instrumentation that have had the biggest impact on medicine. The microscope and the thermometer got us started, but even these are recent advances considering our history of several hundred millennia.

At a Glance

- *A lot of medicine focuses on physical statistics and not enough on chemistry statistics*
- *Chemistry has been a part of medicine for a long time, but ihas only recently become part of critical care*
- *It could help us further personalize care to better serve patients*
- *Combining as many variables and statistics as possible will build a better personalized picture*

Where it all began

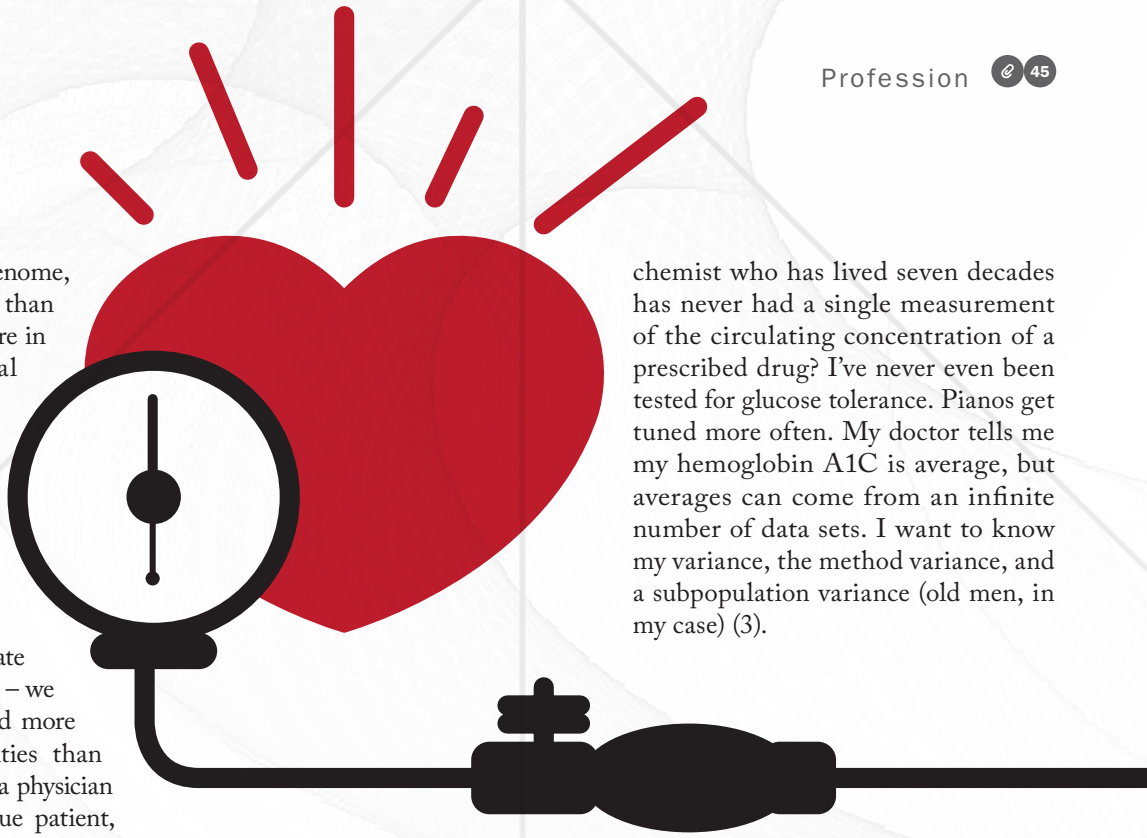
Clinical chemistry is a relatively new component of critical care and the community hospital setting, and even newer in routine diagnostics. The history of the field began with some fabulous pioneers, such as Donald Dexter Van Slyke (1883-1971), Joseph J. Kleiner (1897–1974), Arnold Orville Beckman (1900-2004), Wallace H. Coulter (1913-1998), Leland C. Clark (1918-2005), Solomon Aaron Berson (1918-1972), Lenard Tucker Skeggs, Jr. (1918-2002), Rosalind Sussman Yalow (1921-2011), and John Wendell Severinghaus (b. 1922). These great minds were tinkerers – they did not follow a strategic plan, create PowerPoint slides or speak of reimbursement codes or third party payers. There is no room here to dig deep into the history of clinical chemistry, but a great place to start learning more is a short review by Larry Kricka and John Savory, published in 2011 (1). My point: clinical chemistry is largely a post-WWII phenomenon which in many respects did not accelerate until the 1970s. Diabetics had no means to monitor glucose at home even modestly well until 1980, 50 years after insulin became a drug. The American Association of Clinical Chemists began in 1948 and about thirty years later, just as I joined, the name was changed to the American Association for Clinical Chemistry, implying advocacy and welcoming a wider demographic.

"When one doctor sits with one patient, more often than not, intuition based on experience matters most."

The age of complexity

With the human genome project, we were thought to be on the cusp of a great advance in diagnostics, but we now know that knowledge of genes alone are not enough. Next, at the turn of the millennium, we thought that the proteome would be the answer. The terms "biomarker" and "molecular diagnostics" were invented, but once again, the new dawn of diagnostics failed to materialize. Now, we are moving onto metabolomics – will it deliver? Only time will tell. All of these areas have potential to develop further, but it will require more investigative effort than was initially thought.

Each person is unique and defined by



much more than their genome, which itself is less stable than we thought. Our proteins are in constant post-translational flux, depending on the time of day, the time we last ate, and the time a drug entered the body. What we consume, the variability of our microbiome, and the state of various organs are not reliably programmed at birth. Yet we largely operate with the tyranny of averages – we chase p-values (2), and find more correlations and probabilities than we do mechanisms. When a physician is confronted with a unique patient, averages aren't much help. While some analytes are reliably fixed in a homeostatic fashion, these appear to be very scarce. When one doctor sits with one patient, more often than not, intuition based on experience matters most.

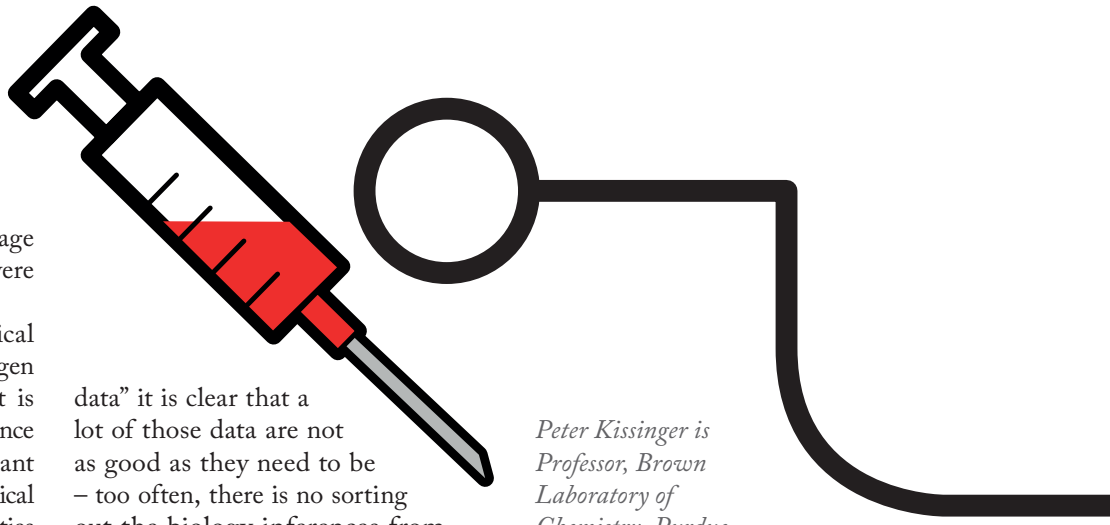
"Shouldn't drug monitoring be the most common companion diagnostic, especially in critical care where drug–drug interactions and organ system deficiencies are likely?"

Measurement matters

Clearly, we need to explore the virtue of more chemistry measures versus time. In the ICU, displays still mainly focus on physical metrics. The only routine chemical measure is oxygen saturation. But physical measures of temperature, blood pressure and heart rate are all responding to chemistry. When they wander too far, we take a blood sample, but could the problem have been anticipated? We dose a drug based on such crude notions as 10 mg for all or mg/kg or mg/m^2. Shouldn't we be dosing to achieve a measured exposure? Isn't concentration in circulation a better concept of dose than a pill swallowed or a bolus infused? Shouldn't drug monitoring be the most common companion diagnostic, especially in critical care where drug–drug interactions and organ system deficiencies are likely? Getting the right drug at the right dose at the right time is not often a genomics problem. Likewise, every child matures biochemically and physiologically in a way that does not follow a consistent timeline – shouldn't we be measuring more? Is it not odd that a bioanalytical chemist who has lived seven decades has never had a single measurement of the circulating concentration of a prescribed drug? I've never even been tested for glucose tolerance. Pianos get tuned more often. My doctor tells me my hemoglobin A1C is average, but averages can come from an infinite number of data sets. I want to know my variance, the method variance, and a subpopulation variance (old men, in my case) (3).

Testing, testing…

So much for venting. Things are improving – we are doing more point-of-care testing, although it is still limited. We are getting closer to N=1 personal reference ranges and we have access to our own electronic health data. We can make measurements in smaller volumes of blood than ever before and can now do a lot of tests with 0.1 mL, a few with 0.01 mL, and some with less than 0.001 mL. However, we still frequently take far more blood than we need. There have been several reports of anemia resulting from too many blood draws with cardiac patients (4,5) and we've all heard of excessive ordering of diagnostic tests. I suspect that most of the volume of those blood draws was thrown away, and this can be confirmed by a visit to your local clinical chemistry laboratory – more than one major lab has told me "all of our automation is based on sample tubes large enough to hold a bar code". The patients are waiting for bioanalytical chemists, clinical chemists, and pathologists to improve this situation. The tools are getting better, and among them are mass spectrometers, which in

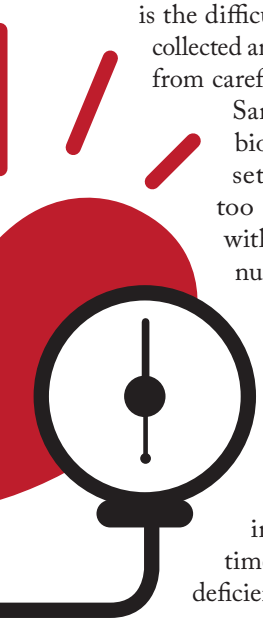


the clinical world are now at the stage where the Skeggs' AutoAnalyzers were in the 1960s.

Mass spectrometry as an analytical resource is older than pH meters, oxygen electrodes, and immunoassays, but is relatively new to diagnostics. Performance is good, but there remain significant challenges for quantitative work in clinical chemistry, including many nonlinearities whereby variable matrix components influence the response for the desired analyte(s). Many do not fully understand this matrix effect and its impact on method validation. Mass spectrometry technology is not yet economically competitive for random access, allowing for rapid examination of different analytes in each of a series of samples using a single instrument. This is especially impactful for intensive care clinical applications where rapid turnaround time can be critical. On the other hand, when samples are numerous for a single analyte or panel, and time is not critical, there is no better performance for the price.

Sample quality

A major worry in clinical chemistry today is the difficulty in finding properly collected and characterized samples from carefully controlled biology. Sampling matters – every bio sample comes with a set of attributes, which too often are incomplete, with time (chronobiology), nutrition, polypharmacy, and comorbidities rarely available in any detail. Understanding of the problem, the will to do better, and the money to improve are generally in short supply, but the time has come to fix these deficiencies. In the age of "big data" it is clear that a lot of those data are not as good as they need to be – too often, there is no sorting out the biology inferences from sampling errors and analytical variances, and a reproducibility crisis has been widely described.



"I'd certainly prefer a quarterly chemical examination, but I want reliable numbers."

Some suggest that the traditional annual physical examination is not very helpful (6). I'd certainly prefer a quarterly chemical examination, but I want reliable numbers. Some have advocated building facilities for chemical examination at local pharmacies or even grocery stores (7), but the recent scandal involving Theranos and their founder suggests that the proposed enabling technology is not what was promised (8). The resulting book and movie will bring bioanalysis into view for a wider audience than ever before (9) – we can only hope that the negative publicity will not derail the efforts of the wider clinical chemistry community to make blood tests more comfortable, affordable, and efficient.

Peter Kissinger is Professor, Brown Laboratory of Chemistry, Purdue University, and a founder of Bioanalytical Systems, Inc. (BASi), Prosolia, Inc., and Phlebotics, Inc. Indiana, USA.

References

1. *L Kricka, J Savory, "A guide to the history of clinical chemistry", Clin Chem, 57,1118–1126 (2011).*
2. *TM Annesley, JC Boyd, "The P value: probable does not mean practical", Clin Chem, 60, 1021–1023 (2014).*
3. *E Lenters-Westra et al., "Biological variation of hemoglobin A1c: consequences for diagnosing diabetes mellitus", Clin Chem, 60, 1570–1572 (2014).*
4. *A Salisbury et al., "Diagnostic blood loss from phlebotomy and hospital-acquired anemia during acute myocardial infarction", Arch Intern Med, 171, 1646–1653 (2011).*
5. *C Koch et al., "Contemporary bloodletting in cardiac surgical care", Ann Thorac Surg, 99, 779–784 (2015).*
6. *Medscape Multispecialty. WebMD Health Professional Network. Ritual, not science, keeps the annual physical alive. Available at: https://wb.md/2r0WybU . Accessed April 26, 2018.*
7. *Theranos Inc., "Theranos", (2018). Available at: https://bit.ly/1Gwh5DO. Accessed April 26, 2018.*
8. *DDN News, "Theranos: lessons learned", (2018). Available at: https://bit.ly/2r0LPPG. Accessed April 26, 2018.*
9. *J Carreyrou. "Bad Blood: Secrets and Lies in Silicon Valley", Knopf: 2018.*

The Feedback Loop

Pathologists never stop learning. Giving and receiving effective feedback is a vital, but often overlooked, aspect of our education

By Xiaoyin "Sara" Jiang, Sarah Bean, and Rachel Jug

It's often said that medicine is a lifelong learning process – that medical education never ends, and that there's always more to discover. Although most pathologists would agree with this statement – particularly in our own field of specialty – one key aspect of learning is frequently overlooked: feedback. Do you know how to give effective feedback? Do you know how to receive it and put it to work for you? Do you know how best to use feedback to improve your work and expand your knowledge? Many pathologists have not put that much thought into feedback, and yet it's one of the most important skills you can develop.

What sparked your interest in feedback?

Sara Jiang: I've spent time at Duke University as a medical student, a resident, and now as a faculty member – so I've had the opportunity to see many different feedback styles. And let me say: not all feedback is equal! Some people are very thorough in their responses and evaluations, whereas some do not give much information at all. I've been in situations where I've asked for feedback and the answer has been a generic, "Oh, you're doing great! Keep up the good work. We love having you." That may feel good to hear (and of course, it's a nice thing to be able to say, too), but it's not helpful for someone whose goal is to improve their skills.

When I joined the faculty at Duke as an attending, I wanted to make a real effort to ensure that I was effectively meeting the needs of my trainees. I work closely with Sarah Bean in cytopathology, so I had the opportunity to hear her speak about feedback – a subject in which she has extensive experience. Since then, we have been able to work together on developing some feedback education – and have worked together to teach it to others.

Rachel Jug: As a current trainee, I recognize the importance of receiving feedback. It's valuable because I can use it to improve my performance. But during my training, I also get to act as a teacher to a variety of learners – for example, medical students in lectures or rotating through our department. It's when the tables are turned and it's my job to give feedback that I can see how difficult it is, if you haven't had much experience with feedback exchanges. Like any other skill, you have to develop it by practicing! I'm very interested in helping people to become more familiar with – and comfortable with – feedback, because I think it helps all learners and educators better themselves.

What makes feedback so important for professional development in pathology?

SJ: No matter what your career stage, we are all learners in medicine. Our chosen field is a process of lifetime learning – and learning is at the core of feedback.

The idea of feedback in medical education goes back to 1983, when Jack Ende published his seminal paper on the subject (1). He wrote, "Without feedback, mistakes go uncorrected, good performance is not reinforced, and clinical competence is achieved empirically or not at all." I quote this regularly because I think it really gets to the heart of the matter. Feedback is a good opportunity to correct mistakes. It's a good opportunity to reinforce the things learners and teachers are doing well. And if you don't have feedback, you're basically flying by the seat of your pants – something I don't think is acceptable in a field as critical as medicine. The point of feedback is to improve our ability as doctors to deliver safe and effective patient care.

RJ: Feedback is crucial in medicine

At a Glance

- *Feedback is a key component of learning in any field of medicine – and no less so in pathology*
- *Giving feedback can be difficult because there is little training for it and many teachers fear emotional responses from learners*
- *Receiving feedback can be equally challenging when trying to decide how to react, what advice to take on board, and what may not be useful*
- *Only by practicing and being intentional can we improve at both giving and receiving feedback*

because it's an ever-evolving field. Continuous education is vital to ensure the safety of our patients and the quality of our work. When people hesitate to give or receive feedback, bad habits go unchecked and learning opportunities are missed.

What are the main barriers to giving and receiving feedback?

SJ: I think a lot of the barriers are skill-based. People aren't necessarily trained in how to deliver feedback – something we're trying to help with – so they may not feel like they have the skills or the knowledge to give effective, sensitive feedback. People who are still in training may also feel like they aren't in a position where they're empowered to give feedback; medicine is very hierarchical and it can be difficult to get into the mindset of "critiquing" a "superior."

I think there are logistical factors as well. For instance, we're all extremely busy – and people often think that feedback takes a long time, so they're afraid they don't have time to do it. It may not always be convenient to give feedback; for instance, you might be in a room with a patient, and most people would prefer not to give (or receive) feedback in front of third parties – especially when you're commenting on their medical treatment!

There's also fear of the emotional aspect, and that comes from both above and below. Trainees may be afraid to give feedback to those higher up in the hierarchy because they don't want to offend anyone. But the same is true for those of us who have climbed up through the hierarchy. We're often afraid that the feedback we give with the intention of improving performance will instead be taken as a personal criticism. We're all very conscious of wanting to nurture and encourage our staff and younger colleagues, which creates a fear that constructive feedback might be taken personally and trigger a negative emotional response.

RJ: Lacking an established feedback culture in your workplace can be a barrier, because feedback isn't exclusive to the domain of residents and attendings. It should be exchanged between all members of the pathology department – physicians, scientists, techs, couriers, administrative assistants – to ensure the proper working of the department. Of course, not everyone may feel comfortable giving feedback to others whom they perceive as being higher up in the departmental hierarchy or having more or different expertise. That's why we need to encourage the idea of "feedback culture" – because if you establish something as being "normal," then everyone becomes comfortable with accepting commentary from everyone else. It helps to break down potential barriers to feedback exchange.

Do you have any advice on improving feedback skills?

SJ: I think you can start with small steps. One really easy way to create a feedback culture is to label feedback as such. It sounds simple – but when you ask residents whether they're getting feedback, they often say they aren't… whereas, if you ask the teachers, they'll tell you they give feedback all the time. The problem is that they're not necessarily calling it that. Even something as simple as saying, "this is feedback" gets the receiver in the right mindset. You want them to think, "Okay, I'm getting feedback. It's time for me to listen and get myself into a receptive frame of mind."

When I'm on service with a resident, I like to let them know I'll be giving them feedback ahead of time. At the beginning of the week, I say, "We're going to establish some goals now, and at the end of the week, we're going to have a very brief instant-feedback time." So at the end of the week when I say it's time for feedback, their response is not, "Oh, my gosh, I'm getting feedback – it must be bad," but rather, "This is what always happens at the end of the week; it's an opportunity to learn."

But how do you acquire feedback skills? That's not something we teach in medical school – but it is something that is now part of the residency competency requirements, at least for pathology residents in the US. There's a professionalism competency for "gives and receives feedback," so it's actually something residents are expected to achieve. And there are a number of tools out there to help: published articles, courses (like the ones Dr. Bean and I give), and even web-based resources (we're developing a podcast and we created an American Society of Cytopathology Cell Talk on feedback). For those who are anxious at the idea of giving feedback, my advice is: find one small thing to say – one piece of feedback for your residents. Once you've done that, look for another. The more you do it, the more natural it becomes, and the more everybody begins to expect the feedback process.

RJ: My general advice would be to practice giving feedback on a regular basis. It helps to be self-reflective; consider the times you have received feedback and think about the way that people gave it to you. Try to recall the teachers you've had over the course of your education, their different feedback styles, and what worked well – and then try to use the best of them as role models for framing your own feedback delivery.

Do you have any tips for receiving feedback well?

SJ: Most people tend to think about receiving feedback less often. As individuals, we need to be more mindful about the way we receive feedback. Sarah Bean has a wonderful way of approaching it – she says, "Feedback is a gift. There are a few different ways to react to a gift." In other words, you can choose what to do with it. For some feedback, you may think, "This is wonderful; it's exactly what I needed to hear, and I'm going to put it to use immediately." To other comments, you might say, "You know what? This is not useful to me." And to others still, you might think, "This is kind of okay; maybe I'll store it away, reflect upon it more, and

use it later." Approaching feedback as a gift is really helpful – not only because it gives you control over what you do with it, but also because it reinforces the fact that the person who is giving you the feedback is giving it to you with good intentions.

RJ: It's important to consider that the optimal exchange of feedback is bidirectional. There should never be just one person giving feedback and the other receiving it. It should be an ongoing conversation. And I think that those on the receiving end should be mindful of what they're being told, ask questions and get clarification if necessary, and reflect on it afterward. That's how they can benefit most from it and implement constructive criticism into their practice.

How do you prefer to give feedback yourself?

SJ: A lot of us are familiar with the "feedback sandwich," wherein one piece of negative feedback is sandwiched between two instances of positive commentary. We prefer the "ask-tell-ask" approach, which takes that sandwich model and tweaks it to make it more effective. To create true bidirectional feedback, there needs to be a learning partnership between the giver and the receiver. The "ask-tell-ask" method facilitates that by allowing an opportunity for the learner to give input:

- *Ask:* Here, the learner performs a self-assessment. The teacher might ask, "What do you think went well in that fine needle aspiration?" The question prompts the learner to evaluate their own performance. "I think I was able to make the patient feel really comfortable with the procedure."
- *Tell:* At this point, the feedback giver reflects on what the learner has said. For instance, "I agree that you did a wonderful job of making the patient feel at ease." It allows the teacher to reinforce the things they agree with from the learner's self-assessment. This is also the point at which you tell them the additional components they might not have identified. "You put too much gel on the patient's neck."
- *Ask:* The second ask is to check understanding and develop a plan to act on the feedback. You might say, "Does that make sense? How can we fix this moving forward?"

Have you had any particularly good (or bad) feedback experiences?

RJ: I recall a time when I was given really good feedback. It was in the fine needle aspiration (FNA) clinic. I was doing an FNA on a patient and didn't use a supporting hand to keep my needle steady. My attending was watching me during the consultation. As soon as we had finished with the patient and were alone in a separate room, he gave me feedback. He started by telling me the things that I had done well; then, he told me that an area of improvement would be to use my other hand as a support to keep the hand with the needle steady, and he showed me how to do it. Throughout the interaction, he was positive, friendly and respectful of me.

The next time we saw a patient together, he observed my practice again, and I used the method he had taught me. He made a point of commenting afterward on how well I had done at implementing his feedback! Ever since, I've thought of that as a really good example of how to give high-quality feedback. It felt like a team approach – a bidirectional conversation – and it made me, as a learner, feel like he wanted to provide me with the best possible education.

In contrast, one of the least effective pieces of feedback I have ever received was actually secondhand. An attending gave me a written evaluation and, in the comment section, they quoted another attending – someone who was commenting on my performance without ever having seen me perform my clinical duties! It was much harder for me to take that feedback seriously and to implement it, because I felt that it wasn't really speaking to me and my abilities – and it definitely wasn't a bidirectional exchange.

SJ: Feedback needs to be timely, non-judgmental, based on direct observation, and focused on behaviors that can be changed. I think the previous two examples illustrate this perfectly. When you're giving feedback, it cannot be based on hearsay, because the learner is more able to trust something the teacher has seen for themselves. The attending in the first example did a wonderful job of implementing all of the components of effective feedback; the second not so much.

We often perceive feedback as part of medical education – and it's true that much of the research on feedback has been in the context of teaching medical students and residents. But I think, no matter whether you're in a teaching hospital or a private practice; whether you work with residents or lab staff; whether you're just beginning your medical career or running an entire department, feedback is vital to ensure that everyone performs to the best of their ability and is able to continue lifelong learning.

Even if you don't think you're giving feedback, you probably are – one way or another. By being mindful of it and making an effort to do it the right way will help you at every stage of your career.

Xiaoyin "Sara" Jiang is a Pathologist at Duke Cancer Center and Assistant Professor of Pathology at Duke University. Sarah Bean is an Associate Professor of Pathology at Duke Health, Pathology Medical Director of the Derm/Path Clinical Research Uni, and Program Director for the Cytopathology and Surgical Pathology Fellowship. Rachel Jug is a third-year resident in pathology at Duke University, Durham, USA.

Reference

1. *J Ende, "Feedback in clinical medical education", JAMA, 250, 777–781 (1983). PMID: 6876333.*

Power to the Pathologists

Sitting Down With… Jo Martin,
President of the Royal College of Pathologists, Professor of Pathology at Queen Mary University of London, and Director of Academic Health Sciences at Barts Health NHS Trust

How did your journey into pathology begin?

I studied preclinical medicine at Cambridge University and did the clinical aspects of the course at the London Hospital. Subsequently, I did general medical and surgical jobs, then worked in accident and emergency, and subsequently medicine for the elderly at Guy's and St. Thomas' NHS Foundation Trust. I think a memorable moment that helped solidify my path involved Professor Sir Colin Berry, who was then head of the pathology department at the London Hospital. He introduced the department by saying that they had produced approximately 30 Professors of Pathology and he expected me to follow suit. At the time (and at that stage of my career), I was inspired by the fact that someone would encourage me not to limit my expectations!

What key moments prepared you to be President of the Royal College of Pathologists?

In terms of skills and experience, I think the broad scope of my career helped. I did the general Part 1 exam, covering the basics of all pathology disciplines. I became a histopathologist and a professor of neuropathology – although I was a general pathologist, my PhD was in neuropathology; I've been head of pathology and learnt lots about all the various areas; head of a clinical support division; and I was clinical advisor to Ian Barnes during the Barnes review period, which introduced me to the national side of medicine. And although you clearly need to bring skills and expertise to the role, I also think you need to bring a lot of who you are as a person. My drive has always been to make things better – or at least to try! I want to have a positive impact wherever I go, by leaving things in a better state than I found them.

What do you hope to achieve as President?

I have a two-pronged approach: I want patients to have really good pathology services, and I want pathologists to feel better about themselves and their profession. Everyone is under a great deal of pressure at the moment, so anything we can do to make their lives better is really important.

I want patients and the general public to know just what an astonishing level of expertise they have supporting them through their screening, disease prevention, diagnosis, and treatment. I don't think the public are entirely aware of the kinds of experts who support them behind the scenes. To encourage better understanding, the College has been doing a lot of public engagement with charities and schools to help raise the profile of pathologists in the public's mind. We've got phenomenally clever individuals in every department who have trained for 12 or more years, and they deserve recognition.

It's also something we want to tell the next generation of medical students. To that end, we've got some exciting programs to support the medical school curriculum with pathology resources. We want to ensure that the path to our specialty has a higher profile and we need medical students to be fully aware of the impact they could have as pathologists.

What is currently the most exciting area of pathology?

There's massively exciting stuff going on all over the field – computational pathology, gene therapies, interconnectivity – so it's difficult to pick just one. That said, an area that sticks out to me at the moment is the prospect of scanning mass spectrometry combined with morphology and data from the 100,000 Genomes Project. Such a combination of technology gives a complete morphological, genetic, and protein map of tissues, and it's coming down the line very fast. All medicine is personalized, of course, but giving doctors the potential to make decisions based on personal data on a patient's genome, metabolome, epigenetic status, and biochemical condition is very exciting.

"I want patients and the general public to know just what an astonishing level of expertise they have supporting them."

If you could change one thing about the field, what would it be?

I think I would double the workforce. We can buy things like new equipment – which is undoubtedly needed – but the enormous strength and capability behind pathology lies in the brains and skills of the people. They want to do what's best for the patient, and because they serve all areas of healthcare, across all settings, they know how things work and how things could be better. With a little more leeway, they can bring new tests and therapies into play faster, but could also use their experience, as well as analytical and innovative approaches to improve the whole patient pathway.

Pathologists are more than capable of making massive changes to our profession. On many occasions pathology has undergone total transformations that people haven't really been aware of – adopting liquid-based cytology, molecular transformations in microbiology, virology, and genetics. When new technology is brought in, we retrain every single member of the workforce, all of whom adapt to it seamlessly. There aren't many fields where that holds true! I think, above all else, the people behind pathology are the most valuable assets in the discipline. Given a little bit of time, pathologists are capable of astonishing things.