

the Pathologist™

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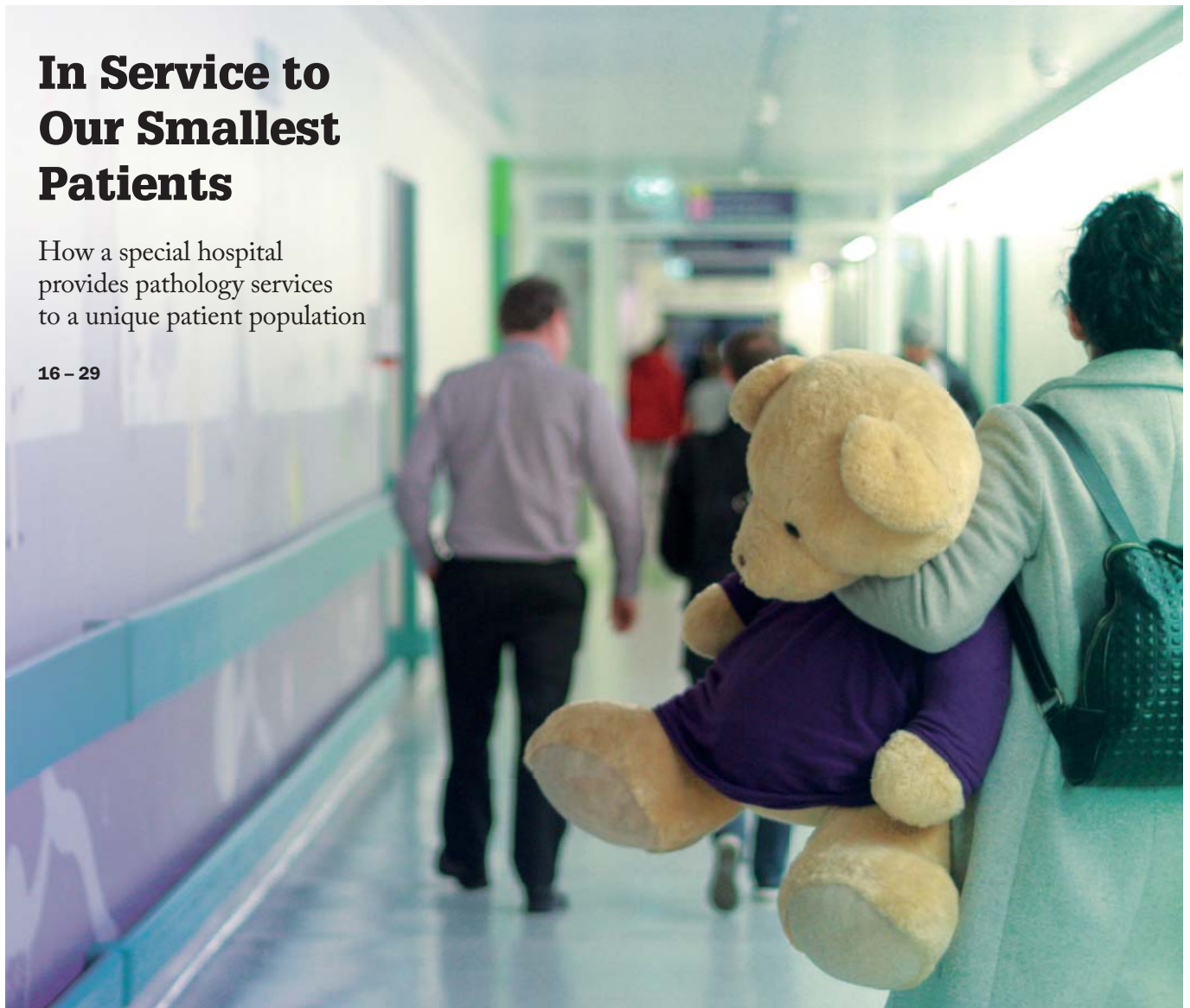
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WHEN YOU PUT
COMPLEXITY INTO CONTEXT

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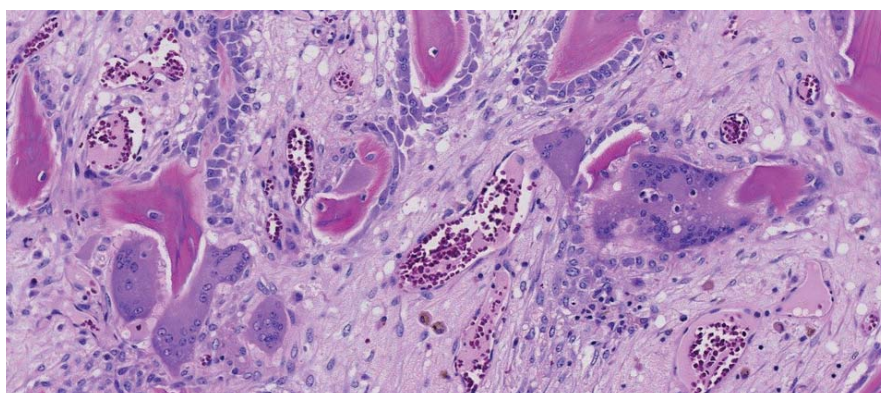
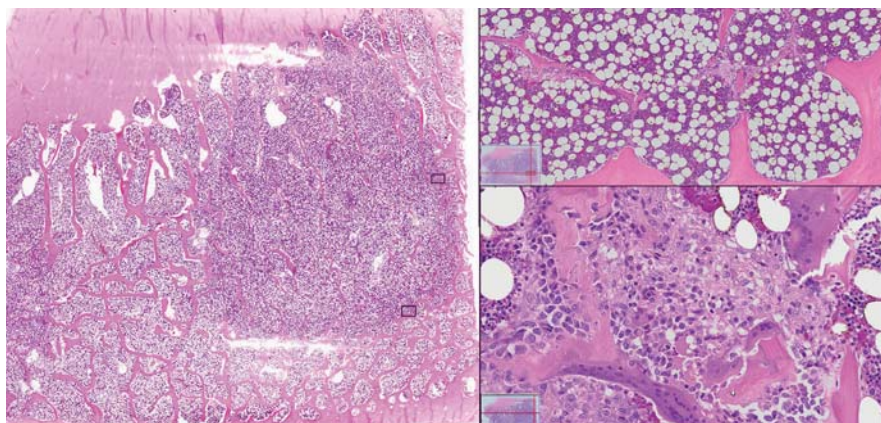
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Case of the Month



The patient was a normothermic, adult, castrated male horse with a six-month history of progressive lameness and pain upon palpation of the scapulae and bones of the neck and spine. Widespread, sharply delineated, radiolucent bone lesions were identified on radiographs of the vertebrae, scapulae, ribs, mandibles, and pelvis. Diffuse bronchointerstitial lung pattern was noted on thoracic radiographs. Complete blood cell count, serum chemistry, serum electrophoresis were unremarkable with the exception of mild microcytic normochromic anemia. The primary differential included metastatic neoplasia.

What is the most likely diagnosis?

- a Fibrous osteodystrophy
- b Silicosis-associated osteoporosis
- c Multiple myeloma
- d Fibrous dysplasia

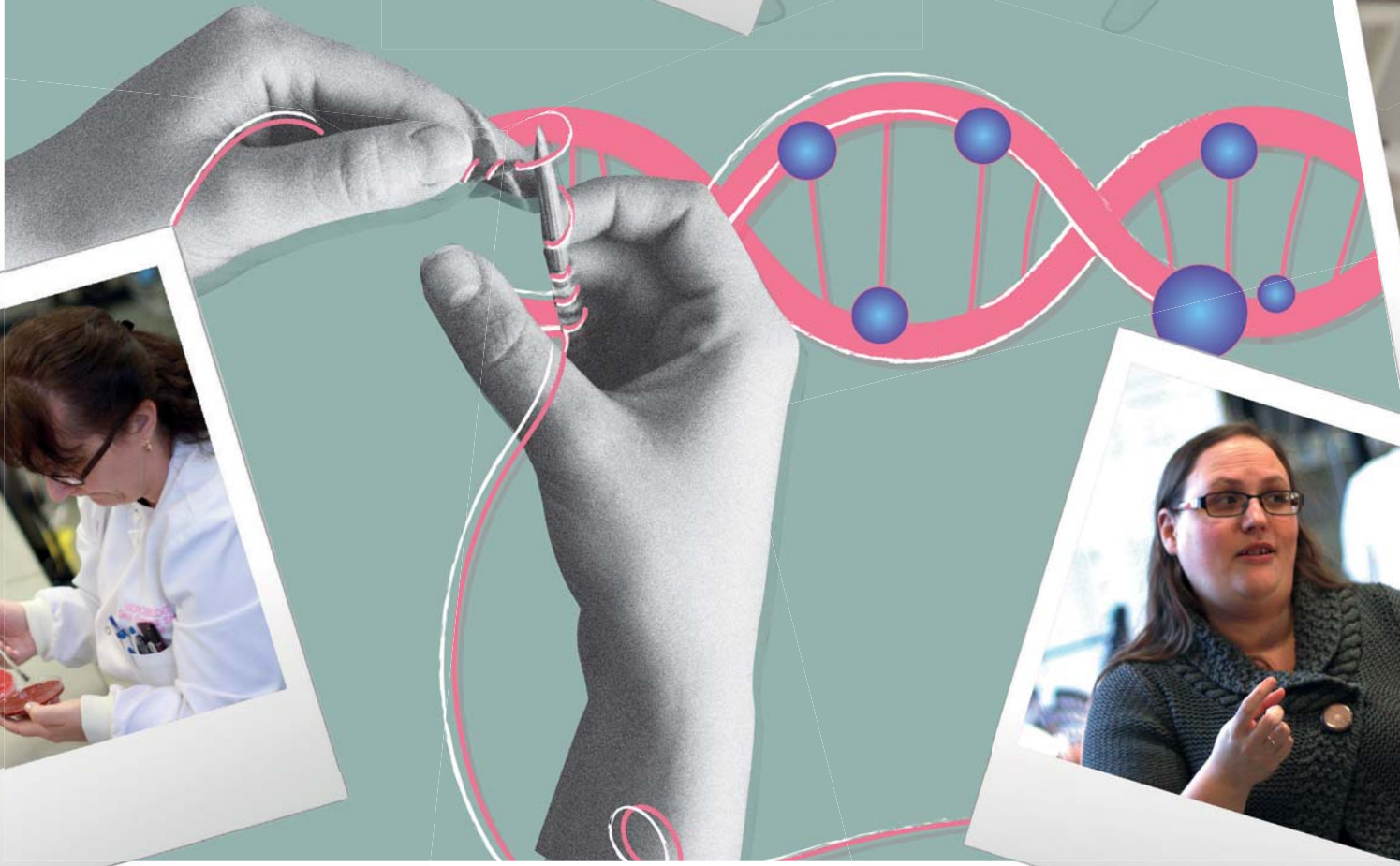
To register your guess, please go to <http://tp.txp.to/0418/case-of-the-month>
We will reveal the answer in next month's issue!

Answer to last issue's Case of the Month...

A. Succinate dehydrogenase

Last month's images showed a paraganglioma, a rare tumor arising from the paraganglia that form the sympathetic or parasympathetic tissue and the adrenal medulla. In people who have germline mutations of genes encoding one of several components of the succinate dehydrogenase enzyme

(such as SDHB, SDHC, SDHD, or SDH5), the incidence of paragangliomas is 30 percent by the age of 30 (1). SDH gene mutations can be found in in 10 percent of sporadic paragangliomas, which typically occur as multiple tumors in younger patients. SDHB mutations are the most ominous; they are associated with malignancy of tumors in about 50 percent of cases. The absence of immunohistochemical staining with the antibody to the SDHB protein is considered sufficient evidence of an underlying SDH germline mutation.



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Sharing the Salt,
by Michael Schubert

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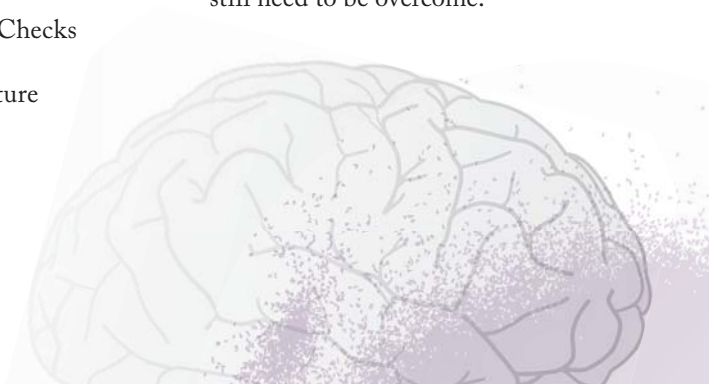
*Visitors pass through
the corridors at Great
Ormond Street Hospital.*

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Editor - Michael Schubert
michael.schubert@texerepublishing.com

Associate Editor - William Aryitey
william.aryitey@texerepublishing.com

Content Director - Rich Whitworth
rich.whitworth@texerepublishing.com

Publisher - Lee Noyes
lee.noyes@texerepublishing.com

Business Development Executive - Sally Loftus
sally.loftus@texerepublishing.com

Head of Design - Marc Bird
marc.bird@texerepublishing.com

Designer - Hannah Ennis
hannah.ennis@texerepublishing.com

Digital Team Lead - David Roberts
david.roberts@texerepublishing.com

Digital Producer Web/Email - Peter Bartley
peter.bartley@texerepublishing.com

Digital Producer Web/App - Abygail Bradley
abygail.bradley@texerepublishing.com

Audience Insight Manager - Tracey Nicholls
tracey.nicholls@texerepublishing.com

Traffic & Audience Database Coordinator -
Hayley Atiz
hayley.atiz@texerepublishing.com

Traffic and Audience Associate - Lindsey Vickers
lindsey.vickers@texerepublishing.com

Traffic Manager - Jody Fryett
jody.fryett@texerepublishing.com

Traffic Assistant - Dan Marr
dan.marr@texerepublishing.com

Events Manager - Alice Daniels-Wright
alice.danielswright@texerepublishing.com

Marketing Manager - Katy Pearson
katy.pearson@texerepublishing.com

Financial Controller - Phil Dale
phil.dale@texerepublishing.com

Accounts Assistant - Kerri Benson
kerri.benson@texerepublishing.com

Chief Executive Officer - Andy Davies
andy.davies@texerepublishing.com

Chief Operating Officer - Tracey Peers
tracey.peers@texerepublishing.com

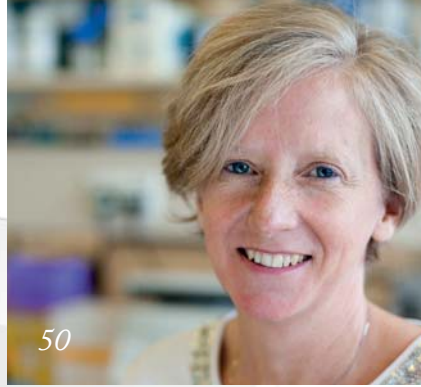
Senior Vice President, North America
- Fedra Pavlou
fedra.pavlou@texerepublishing.com

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

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NextGen

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Detecting methylation signatures in peripheral blood could be an important diagnostic indicator – and, when combined with AI, epigenomics may allow us to identify pathogenic variants of (previously) unknown significance.

Profession

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How can we ensure that we're finding and encouraging the medical students most likely to take an interest in pathology?
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Ayesha Azam analyzes the difference in support and guidance for medical students in a developing and a developed country, and how this may alter career paths.

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- 50 **Sarah Coupland, Professor and George Holt Chair of Pathology at the University of Liverpool, and Honorary Consultant Histopathologist at Royal Liverpool and Broadgreen University Hospitals NHS Trust, UK.**

Feature

- 16 **In Service to Our Smallest Patients**
Pediatrics is one of the most delicate arms of medicine in terms of patient care. This month, we visit Great Ormond Street Hospital, one of the world's leading pediatric hospitals, to learn about the complexities of serving these patients and the key factors to keeping ahead of the curve.

In Practice

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Is it time to update molecular tests for lung cancer? New genetic and biomarker findings have led to a guideline revision to make sure all patients are appropriately treated.



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Sharing the Salt

*Starting conversations with colleagues
and patients can have unexpected benefits*

Editorial



After a fascinating visit to a central London pathology laboratory (see our feature on page 16), The Pathologist's content director and I dined in a train station restaurant before our respective journeys home. Evidently, our table had been hastily separated from the one next to it; we shared a number, a napkin holder, and salt and pepper grinders – all of which sat on the other table.

“Excuse me... Could I please borrow the salt?”

Over the course of the evening, we shared the single salt and pepper grinders back and forth across the tables a couple of times, growing somewhat well-acquainted with our neighbors. By the end of the meal, they were fans of *The Pathologist*, despite never having read a single word of its content. We had learned more about their lives, too; they had spent the day at a hospital just around the corner from – and with close pathology ties to – Great Ormond Street. For all we knew, the laboratory medicine professionals who had spent that day speaking to us might have spent the next looking at samples from the couple at the other table.

Who knows what you might learn if you strike up a conversation – or what you might receive if you're open to sharing? For us, it was a pleasant conversation and some seasoning for our food. For a healthcare professional, it could be a crucial piece of medical history or evidence that might otherwise have gone unnoticed. And for a patient, it could be comfort, reassurance, or the ability to make a more informed decision about their own treatment.

The lines of communication have to be open. It's something we hear again and again – so why, if it's such a universally acknowledged fact, is it difficult for people to share information? Pathologists are perhaps concerned that every minute spent away from the laboratory is another diagnosis that must be delayed. Clinicians may be unaware of the benefits pathologist contact can provide. And patients could be hesitant to request to speak to a pathologist – they might not even be aware that it's an option.

So what can we do to help pave the way to better interaction and engagement? It might be as simple as opening your office door (1), or as involved as publishing a regular newsletter about your work (2). It might mean adding your telephone number or email address to patient reports so that you can be contacted directly. It might mean something no one has thought of yet – an innovative way of starting the conversation.

Do you have a suggestion? If so, please do get in touch (edit@thepathologist.com) and tell us more about it. Let's share some salt and start a conversation of our own...

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2. M Prystowsky, “Collaboration Through Communication”, *The Pathologist*, 38, 14–15 (2018). Available at: <http://bit.ly/2GAgQ2Q>.

Michael Schubert
Editor

Upfront

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

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

Email: edit@thepathologist.com



Adding to the CNS Tumor Toolbox

DNA methylation finds another role – this time, in classifying central nervous system cancers

To appropriately diagnose and treat a tumor, it's essential to understand its origins – particularly when it comes to central nervous system (CNS) tumors, says Stefan Pfister, Director of the preclinical program at NCT Heidelberg's Hopp Children's Cancer Center. "The reason I wanted to focus on CNS tumor classification is the notion that a substantial proportion of diagnostic reports are ambiguous and can leave the neuro-oncologist in a guessing situation when making treatment decisions. We think this affects about 10-15 percent of patients, with an enrichment in the pediatric population."

Treating one in every 10 brain tumor patients using guesswork is far from ideal, so Pfister led a large, multi-institutional research group in creating a DNA methylation-based approach to classifying CNS tumors. They used specific DNA methylation signatures found in different cell types to determine in which cells the tumor originated. Next, they developed an algorithm to sort 82

different CNS tumors based on their methylation signatures (1).

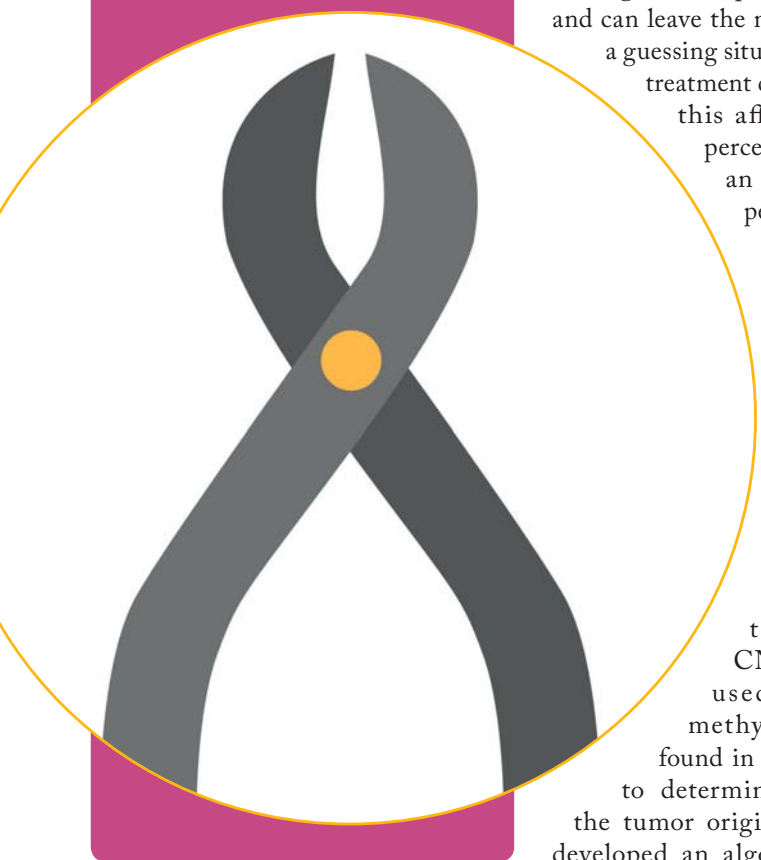
Pfister says, "[The algorithm] adds an additional, highly powerful tool to the neuropathologists' toolbox. It is robust, can be done from very small amounts of FFPE tissue (even previously stained sections), and gives a confidence score. It's not meant to replace the neuropathologist by any means, but rather to improve diagnostic accuracy."

The researchers have also created an online portal (moleculareuropathology.org); with it, they hope to grow the number of tumors they can help diagnose by crowdsourcing datasets from fellow neurologists. The more data the algorithm has, the smarter it will become. So far, the interface has over 10,000 datasets uploaded, with 75 percent of participants agreeing to use the classification for further refinement of their samples. Pfister says, "I think this is a great example of community-based learning!"

Algorithms – and their implementation – will continue to evolve, and Pfister believes that DNA methylation analysis will become a "general and universal tool that could one day replace many gene-specific tests."

Reference

1. D Capper et al., "DNA methylation-based classification of central nervous system tumours", *Nature*, 555, 469 – 474 (2018). PMID: 29539639.



A Protein Probe for Progeria

Biomarkers could help track the progression of the syndrome and its treatments

Hutchinson-Gilford progeria syndrome (HGPS) is a rare genetic disorder characterized by phenotypic traits that mimic the appearance of rapid aging. The condition presents in early childhood and causes diseases such as atherosclerosis and stroke, often resulting in mortality by the time patients reach adolescence. Treatment options for HGPS are limited, but a recent study has identified novel protein biomarkers that may help monitor the syndrome's progression and the effect of therapeutics (1). To learn more about the research and its implications, we spoke with Leslie Gordon, Professor of Pediatrics Research at Hasbro Children's Hospital and the Alpert Medical School of Brown University, and Medical Director at The Progeria Research Foundation.

How did you identify relevant biomarkers? For many years, we had been studying various hematologic tests to better characterize disease in children with HGPS. These tests were chosen based on clinical disease characteristics (for example, leptin due to lipodystrophy, lipid panel due to cardiac disease) and relevant questions about organ function. These were usually available as standard clinical tests and did tell us something about disease. However, we knew that there were hundreds of blood proteins that might or might not be obvious indicators of health and disease in HGPS. The development of technology that allows assessment of many proteins in a single test sample at low sample volume was immensely attractive because we cannot presume to know which proteins are causally tied to crucial disease

characteristics, such as heart disease in children with HGPS. I was surprised at the pure number of proteins that were different from non-HGPS control children. Many of the proteins we have tested clinically are normal, so I really didn't know what would happen in the multiplex assay.

Was the study particularly challenging, given the rarity of HGPS and its pediatric nature?

Because children with HGPS are so small, the amount of blood they can safely donate is very low. Because the prevalence is so rare (one in 20 million), the testing platform must be reliable because these blood samples are precious.

Once a child begins a trial treatment, there is no way to obtain an "untreated" sample again. Because a test for a single protein can require 100 or more microliters of plasma, we are always extremely conservative with the tests we perform. We chose a multiplex study because it allowed us to assess a large number of proteins using a small amount of plasma, while still being both sensitive and specific for any given protein.

Is enough research being done on rare diseases such as HGPS?

There can never be enough research; we need to race as fast as possible to a cure. And that means a lot of basic and clinical science – so we need as many researchers

as possible to have the opportunity and the funding to test their brilliant new ideas and help these children. However, it's always a challenge to obtain sufficient resources and interest to fund further research into rare diseases.

Although HGPS is one of the rarest diseases on earth, studies have confirmed a link between HGPS, heart disease, and the general aging process that affects us all. We all make a little bit of progerin, the toxic, disease-causing protein in HGPS. We make much less progerin than children with HGPS, but the protein builds up over a lifetime and may be partly responsible for aspects of normal aging, such as atherosclerosis.

Our study on biomarkers used samples obtained from The Progeria Research Foundation (PRF) Cell & Tissue Bank, along with samples from our PRF-funded clinical treatment trial at Boston Children's Hospital. All of PRF's programs collectively provide the resources needed not only to advance the field of HGPS, but also to discover what the condition can tell us about heart disease and aging (progeriaresearch.org).

Reference

1. LB Gordon et al., "Survey of plasma proteins in children with progeria pre-therapy and on-therapy with lonafarnib", *Pediatr Res*, [Epub ahead of print] (2018). PMID: 29342131.



Cost-effective Cancer Checks

How population testing of breast and ovarian gene mutations may be the way forward

Is screening the entire population a cost-effective way to detect breast cancer mutations? The answer, according to a study by a multi-institutional team of researchers, is yes. “I have been working in the area of population testing for the last 10 years, and there are few interventions in medicine that save both money and lives,” says Ranjit Manchanda, Clinical Senior Lecturer, and Consultant Gynecological Oncologist at Barts Cancer Institute. “We have previously shown in a randomized trial that population-based BRCA testing in a Jewish population is effective, acceptable, does not have detrimental effects on psychological well-being or quality of life, and is cost-effective. In fact, in most scenarios, it is cost-saving.”

Manchanda and his fellow investigators looked into the cost-effectiveness of bringing this type of testing to the general population in the US and the UK. This step of their research covered *BRCA1*, *BRCA2*, *RAD51C*, *RAD51D*, *BRIP1*, and *PALB2* gene mutations – all associated with ovarian or breast cancers in women – and found that it was cost-effective to screen these, compared with the willingness-to-pay threshold established by the National Institute for Health and Care Excellence (1; see Figure 1). The study used an incremental cost-effectiveness ratio (ICER) per quality-adjusted life year (QALY).

Most importantly, the researchers’ findings showed that population-based

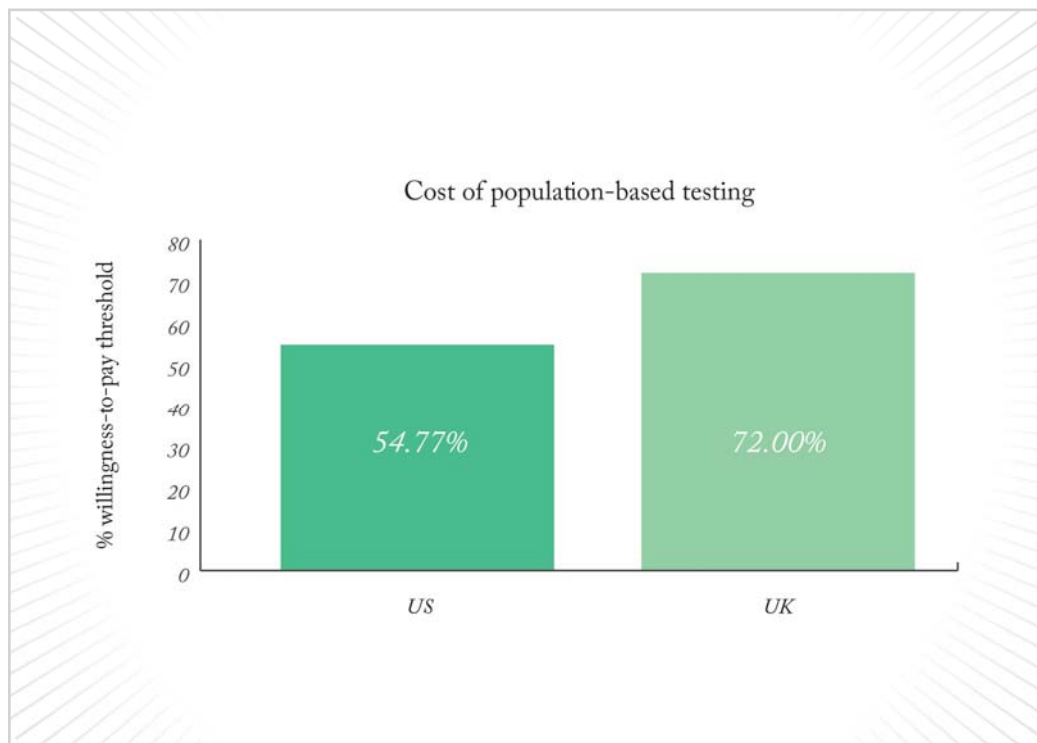


Figure 1. The US willingness-to-pay threshold is \$100,000/QALY; population-based testing cost equaled \$54,769.78/QALY. The UK willingness-to-pay threshold is £30,000/QALY; population-based testing cost equaled £21,599.96/QALY.

testing could prevent 1.91 percent of breast cancers and 4.88 percent of ovarian cancers in US women, and 1.86 percent of breast cancers and 3.2 percent of ovarian cancers in UK women.

Although the results are positive, it does not represent all the evidence needed. “We need to do implementation studies in the general population to generate further scientific evidence and demonstrate to policymakers that an appropriate number of women undergo preventive interventions to reduce their risk of cancer (as we find in women tested through high-risk clinics),” Manchanda says.

The researchers are also investigating the most effective and cost-efficient method of making such widespread population testing a reality, whilst investigating the overall impact of population testing on patient

lifestyle, quality of life, and psychological wellbeing.

Despite more research being needed, Manchanda feels strongly about the importance of breast and ovarian cancer screenings: “The current system is not efficient at maximizing identification of people at risk. We are currently not exploiting our current technical knowledge and ability to the fullest effect to maximize prevention and save lives. Evaluating new approaches and mechanisms, like population testing, is essential.”

Reference

1. R Manchanda et al., “Cost-effectiveness of population-based BRCA1, BRCA2, RAD51D, PALB2 mutation testing in unselected general population women”, *J Natl Cancer Inst*, [Epub ahead of print] (2018). PMID: 29361001.

Controlling CTC Capture

New approaches boost our ability to detect circulating tumor cells

Despite the new diagnostic potential afforded by liquid biopsies and circulating tumor cells (CTC), many such assays – even FDA-approved ones – suffer from low sensitivity, which has restricted their usefulness as prognostic indicators and limited their widespread adoption. A group

of researchers wanted to boost CTC detection by improving the capture step (1). “First, we identified two strategies – cell rolling and multivalent binding – that can improve CTC capture,” says Andrew Wang (pictured), study author and Associate Professor in the University of North Carolina School of Medicine’s Department of Radiation Oncology. “Second, we showed that higher CTC capture sensitivity may enable CTC as a predictive biomarker and a biomarker for disease surveillance.”

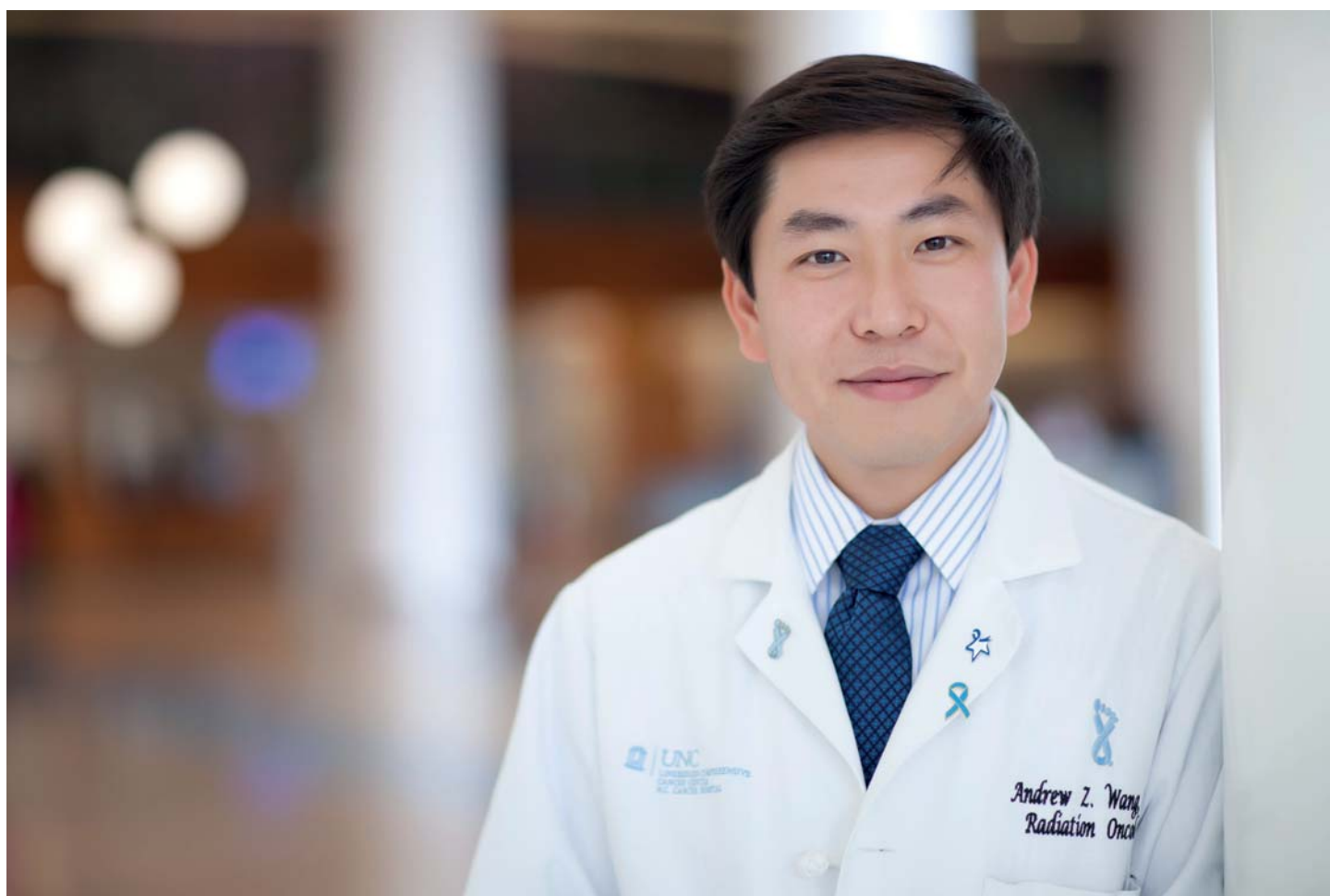
Using a nanotechnology-based assay called CapioCyte, they discovered that cell rolling and multivalent binding could increase CTC capture by up to 38

percent. The assay enabled the researchers to detect CTCs in all patients in their study, and to detect CTC increases and decreases among patients.

Now, Wang says the team is working to develop cancer-specific CTC detection chips. “In addition, we are exploring clinical indications for CTC. We have formed a company and are working to commercialize the detection chip and instrument.”

Reference

1. JH Myung et al., “Multivalent binding and biomimetic cell rolling improves the sensitivity and specificity of circulating tumor cell capture”, *Clin Cancer Res*, [Epub ahead of print] (2018). PMID: 29545463.



Sensitive Joints

Nanopore sensors give an osteoarthritis biomarker high sensitivity

Over 30 million US adults and nearly nine million UK adults over the age of 45 suffer from osteoarthritis (1,2). The molecule hyaluronan, also known as hyaluronic acid, plays an essential role in joint physiological functions, giving rise to its use as a biomarker for osteoarthritis. The downside, however, is that the molecule offers neither high sensitivity nor a high dynamic range; consequently, the results it provides are only semiquantitative. Now, researchers from Wake Forest School of Medicine, Cornell University, and the University of Oklahoma Health Sciences Center are looking to boost sensitivity for more quantitative measurements with a solid-state nanopore sensor (3). To find out more about the technique, we spoke with Adam Hall, lead researcher and Assistant Professor of Biomedical Engineering at the Wake Forest School of Biomedical Engineering and Sciences.

How did the investigation come about? My lab has a strong interest in applying nanopore technology to biomarkers, but we had only ever focused on nucleic acids. This particular project started when my colleague Ellie Rahbar and I were looking into possible ways to collaborate. She had prior experience working with hyaluronan as a biomarker of trauma and, knowing the mechanism of our technology, she recognized that nanopores might be able to measure it. We gave it a try – at first, just to see if it would work. To our delight, the signals were very clear! With the help of Paul DeAngelis, our collaborator at the University of Oklahoma College of Medicine, we eventually determined that we could identify the size of the hyaluronan very accurately on a molecule-by-molecule



basis. The final piece of the puzzle came when I was giving a seminar at Cornell University and happened to meet Heidi Reesink, a veterinary scientist who was using conventional technology to study hyaluronan in the knee joints of osteoarthritic horses. The fit was too perfect to ignore, so we initiated a collaboration that allowed us to apply our technology to an ideal *in vivo* system.

How easy would it be to fit this testing into a pathologist's workflow?

The technology itself is well-positioned for translation. We and others have developed advanced technology to increase affordability, make the results relatively easy to collect, and keep the measurement system compact. In fact, we believe the entire apparatus could be attached to, and powered by, a smartphone at some point.

There is clear evidence that osteoarthritis strongly affects hyaluronan, but definitive linkages between the disease's molecular characteristics and its grading and progression remain to be determined. This is mostly because of limitations in the technologies available for studying it; we believe our technology will fill that gap. A key advantage of our platform is its sensitivity: by using extremely small amounts of hyaluronan, we may be able to test blood or urine (instead of synovial fluid drawn directly from the knee joint) – letting us make analysis less invasive.

How does your approach compare with current osteoarthritis analyses?

Our approach will rival the precision and resolution of existing techniques that tend to be much more expensive and time-consuming – as well as requiring significant expertise and infrastructure. As with any new technology, it will take time for people to accept – but as our system becomes more accessible, and as we continue to show how our results compare with – or even exceed – those of conventional techniques, we think its advantages will become clear.

What's next?

We are pushing hyaluronan analysis further with more physiological testing as well as expanding to other possible diseases in which it may be important. We are also extending to other related molecules to diversify the utility of the platform, including our continued development of nucleic acid biomarker analysis.

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2. Arthritis Research UK, "State of musculoskeletal health 2017", (2017). Available at: <https://bit.ly/2IbZE3M>. Accessed March 29, 2018.
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H&E's IR Upgrade

New technology based on mid-infrared spectroscopy aims to increase the accuracy of biopsy grading

A mainstay of pathology – the trusty H&E stain – may have found a new digital companion through infrared light. “I was collaborating with cancer scientists in a spectroscopic imaging program and, over a period of four or so years, I learned that H&E staining was, for all intents and purposes, the only method they had for diagnosing cancer,” says Chris Philips, Head of the Optoelectronics Section at Imperial College London. “I also learned that it was very unreliable, which generated a huge unmet need in pathology. After a while, I realized that we could adapt our spectroscopic techniques to solve this.” The realization prompted Philips to lead a research team to investigate an H&E alternative that could offer histopathologists an objective way to measure biopsy sections. Their

creation: Digistain (1).

Digistain technology uses mid-infrared light to highlight the concentration of nucleic acids in sectioned FFPE biopsies, before calculating a score based on nuclear-to-cytoplasmic ratio (NCR). According to its creators, Digistain is able to grant an objective, quantitative measurement that removes the “chance” from biopsy grading; their paper states that practitioners agree only 70 percent of the time on the results of gradings carried out by eye. Philips adds, “The Digistain test can be performed in parallel with the standard H&E stain and is quicker overall, so it adds no delay.” The downside to the technology is – of course – the extra cost, but the researchers believe balance will be provided by savings made in unnecessary treatment plans based on inaccurate grading.

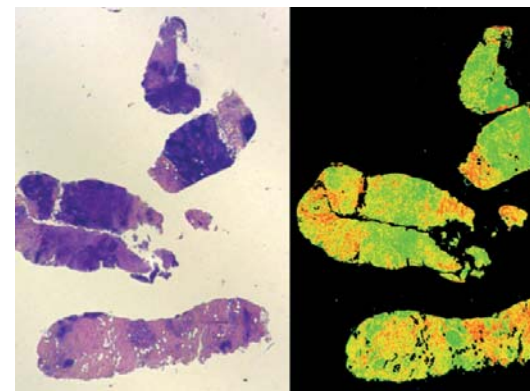
Philips also offers comfort to pathologists fearful of being supplanted by a machine: “We would never propose to replace pathologists. We recognize the critical importance of having a tried and tested protocol when approaching a medical problem as serious as cancer,” he says. “We propose only that this method is used to augment and inform the

biopsy grading process, and to put it on a quantitative footing. In time, we hope that the pathology profession themselves will find ways of using it that will result in the ability to make much more secure grading decisions.”

The investigators are currently testing the technology in breast cancer biopsies, but because Digistain works with biomarkers, they say that it could one day be applicable across a range of cancers.

Reference

1. H Amrania et al., “Mid-infrared imaging in breast cancer tissue: an objective measure of grading breast cancer biopsies”, *Converg Sci Phys Oncol*, 4 (2018).



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

New Horizons in Histopathology Training

Sudan moves forward with an improved educational system for its histopathologists – but big challenges remain



By Azza Zulfu, Doctor at the National Health Laboratory, Khartoum, Sudan

No matter where in the world you live, histopathology training is demanding. It requires high-quality laboratory machines with regular maintenance and replacement, regular deliveries of quality laboratory supplies, thousands of specimens (ideally showing a wide variety of disease processes in detail), a carefully constructed curriculum with well-defined competencies, an adequate number of competent educators with subspecialty training, hospital settings with multidisciplinary team meetings, and satisfactory salaries for all working personnel. Histopathology training bodies in countries with limited resources face huge challenges in providing and improving training despite the frequent inadequacy of their settings.

The Kitchener School of Medicine was established in Khartoum, Sudan, in 1924. Thirty years later, it was renamed the Faculty of Medicine and became part of the University of Khartoum (U of K). In 1976, the Medical Graduate Board (MGB) was established under the

umbrella of the Faculty of Medicine and, four years later, the school saw its first pathology training offering – a Master’s degree in the field. The four disciplines (yes – at that time, pathology had only four branches!) were studied in two years. Later on, training was extended to three years and, finally, to four.

“Histopathology training bodies in countries with limited resources face huge challenges in providing and improving training.”

Today, that degree program grants its students a full MD. Trainees study the four branches of pathology during the first two years. For the final two years, students narrow their studies down to only two subjects. But even that can sometimes be too much, and it has become increasingly clear that single-discipline pathology training is essential. Many times, the pathology training board at the U of K has proposed a pathology training program with a single specialty taught over four years. It’s a move that mirrors international trends, and one that follows the recommendations of the Royal College of Pathologists team that visited Sudan in 2006.

By the year 2002, a new training body for medical specialties had been established:

the Sudan Medical Specialization Board (SMSB). All of the clinical specialty programs joined the new body – or rather, all but one. Pathology, with the dual identity of being both a basic science and a clinical speciality, had its training confined to the Faculty of Medicine, along with other medical basic sciences. Despite the relegation, rapid global development of pathology as a clinical specialty with many subspecialties has prompted pathologists in Sudan to favor their clinical identity over basic science.

“It has become increasingly clear that single-discipline pathology training is essential.”

The year 2017 was a landmark for Sudanese histopathology training. On August 24th, by a decree from SMSB, the Histopathology Training Board was established: the first time Sudan had ever had a unidisciplinary program for histopathology alone. The draft curriculum was prepared by experts in pathology training and medical education, and David Bailey – Vice President for Communications at the Royal College of Pathologists – was invited to visit Sudan to supervise the curriculum revision workshop and conduct inspection visits to the proposed histopathology training centers. The final curriculum for the histopathology MD program was approved by the SMSB on 15 March 2018, and the

first batch of histopathology trainees will sit the entry exam on 30 June 2018!

A good situational analysis of the country’s previous histopathology training systems will provide a strong start for the new program. And there are plenty of positives: Sudan has 38 years of pathology training experience at both the U of K and Gezira University (which established a similar training program in 1993). Dozens of practicing histopathologists have graduated and are providing good service within the country and abroad. Senior pathologists who have worked in the rich Gulf countries have now returned home and are contributing to training that meets international standards. Efficient inter-institutional cooperations have been set up between medical schools, private laboratories, and the government, so that trainees can benefit from being exposed to a wide variety of experiences. We also have good international collaborations, gained through our participation in histopathology events. The Conference of the Arab Division of the International Academy of Pathology was held in Khartoum in 2012; even then, the international guests were impressed by the activity and eagerness of Sudanese pathology residents. Meeting with pathology educators and trainees from different countries opened new horizons for improving our own training. Sudanese pathologists trained abroad are now also providing services and training at home, allowing us to benefit from other countries’ experiences.

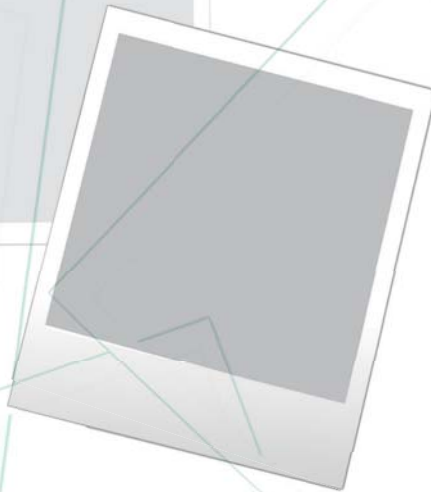
Moreover, we can also gain knowledge without the need for far-ranging travel. The availability of online histopathology resources – especially virtual microscopy – has brought practicing histopathologists living in areas with limited resources up to date with most new developments (in histology, immunohistochemistry, molecular pathology, and more).

On the other hand, the new histopathology training program faces

great challenges: limited laboratory infrastructure, limited centers for immunohistochemistry and molecular diagnosis, limited scientific research activities, the urgent need to train the educators themselves, the lack of subspecialists in the field, the lack of autopsies, and – possibly most worrying of all – the absence of quality control measures and auditing in most Sudanese histopathology laboratories. No institution is involved in any form of accreditation program. Tumor boards and multidisciplinary team meetings are scattered and irregular.

“The availability of online histopathology resources has brought practicing histopathologists living in areas with limited resources up to date with most new developments.”

It’s clear that there’s a lot of work yet to be done. After all, the new Sudanese histopathology MD program is just the first step on a long road to better training and, ultimately, better services for our patients.



IN SERVICE TO OUR SMALLEST PATIENTS

A hospital specializing in complex pediatric cases shines a light on the value of collaborative medicine and integrated pathology

With Simon Heales

In early 2018, Rich Whitworth and I were delighted to follow up on an invitation to tour the famous Great Ormond Street Hospital with Simon Heales, Head of Clinical Service for Pediatric Laboratory Medicine. Over the course of a day, we were introduced to the pathologists and lab medicine professionals responsible for the health and healing of some of the smallest – and most medically complex – patients to enter the hospital system. With new equipment and old, new approaches and trusted methods, we learned not only about the way children’s health is safeguarded, but also about how passionate those professionals are about their work and the families it serves. Here, we share the interviews and photos from a special day at a special hospital.

When you work at one of the foremost hospitals in the world, there’s an expectation that you’re always moving forward. Nowhere is this truer than at Great Ormond Street Hospital (GOSH) – a facility that serves an exclusively pediatric population, and one that provides the most difficult diagnostic and treatment challenges its staff have ever encountered. How do the pathologists and laboratory medicine professionals at GOSH tackle these medical mysteries?

By recognizing the unique needs of their patient population – and by working together across disciplines and specialties.

STILL A HOSPITAL FOR SICK CHILDREN

As pediatric pathologists, we provide the voice that children don’t have. Children can’t tell doctors what’s wrong with them, so the doctors rely on pathology services to provide that information – even more so than in any other setting. What makes GOSH unique is that our doctors receive tertiary and quaternary referrals – and that means the whole team must take on the most complex of medical problems. And that’s why I often say that there is no “routine” in our routine service. In fact, I try to avoid the word altogether. Instead, we call ourselves Pediatric Laboratory Medicine – emphasizing our focus on children’s health.

I believe the doctors here understand that they would be somewhat at a loss without pathology services – so we’re lucky to have the scope to host a range of different specialties. For instance, we have a center for lysosomal storage disorders and other enzyme deficiencies; we have areas to deal with hematology,



immunology, microbiology, histopathology, and much more, all at a highly specialized level. And though it's certainly specialist work from an outside perspective, it doesn't always seem like that to us – unusual is our normal!

That said, it's not all esoteric – and we actively avoid change purely for the sake of change. Not everything needs to be updated just because it can be; if something already works really well – an enzyme assay, for instance – there's no point in spending months trying to automate it; some assays work better manually, and we use quite a lot of them. But, at the same time, we're investing significantly in mass spectrometry, because we can use that technology to analyze a wide range of metabolites in a single sample and get a very fast response. We feel very strongly about embracing state-of-the-art technology, but it must be adopted appropriately.

We also focus heavily on translational research here; I'm a biochemist by background, but as Head of Clinical Service for Laboratory Medicine, I also oversee hematology, immunology, microbiology, histology, and every other diagnostic specialty. I can see how closely they work together, and how much they

might benefit from working even more closely. And that's what drives our desire for a “combined omics” approach to diagnostics and monitoring.

DEFINING COMBINED OMICS

Right now, in most hospitals, laboratory specialties are somewhat in silos. There is certainly crosstalk, but at GOSH, we're pushing for a completely integrated service. Instead of individual specialties, we want to develop our labs by technology – enzyme assays here, flow cytometry there, mass spectrometry over there – and share those technologies among all disciplines. We also want to have a unified specimen reception; at the moment, laboratories tend to have different specimen receptions depending on their disciplines, but a single receiving site would give us better control over preanalytical conditions. We want all of our specialists to have carefully controlled samples and unfettered access to tests and devices – but, even more importantly, we want to make sure that we're sharing our knowledge base as well as our tools, so that we can begin talking to – and understanding! – one another more effectively.

With the rise of genetics in the laboratory, we've found that our workload has only increased. When genetic analysis first came on the scene, my colleagues said things like, "We'll have to retrain as geneticists, because biochemists won't be needed." That couldn't be further from the truth! We need functional assays more than ever. Each time we find a new variant of unknown significance (VUS), we have to ask – is it functional? Answering that question requires enzyme assays, metabolite profiling, and other biochemical tests. It's the crux of "combined omics" – the integration of genomics, proteomics, metabolomics, and other –omic disciplines.

The Trust is investing heavily in electronic patient record systems; we no longer want just a chemistry report, a microbiology report, a pathology report... Instead, reporting scientists will be able to pull results from different areas to develop an integrated report. In my opinion, such integration is the most comprehensive – and therefore best – option for our patients, and everything we do here, we do for them.

**"IF WE DO NOT CONTINUE
TO MOVE FORWARD,
WE'RE DOING OUR PATIENTS
A DISSERVICE BY LOOKING
AT EVERY RESULT
IN ISOLATION."**

TRANSITIONING TO COMBINED OMICS

Pathology services across England are moving to a standardized hub-and-spoke model. We are currently in discussion with our network partners to explore closer working opportunities but pediatric pathology is a specialist service, so we need to ensure that the model works for our patient population and does not compromise patient safety. If you have a 120 µL blood sample from a newborn baby, you have to do all of your testing on that volume; the last thing you want to do is have to request a second blood draw. When dealing with a very sick neonate, you can't start sending samples off-site to non-specialist laboratories because that's not what's right for the patient.

We're very fortunate here because the hospital, as a whole

organization, is actively engaged with the lab. Not every hospital is like GOSH; when I talk to colleagues in similar positions, they often appear quite worn down by their roles – as if they're fighting a never-ending battle. On the other hand, I often feel like I'm being actively pushed to make positive changes for the lab. GOSH is a research-led hospital where scientific advancement is embedded into the working lives of our staff and the patients and families we treat and see. We're looking into implementing measures like generic consent, which would allow us to use excess tissue and blood samples for future research. It's especially valuable because we have the opportunity to use samples from a patient, conduct research, and then potentially take the results of that research directly back to benefit the same patient. I think that's what lies ahead for us – and hopefully for other institutions, too.

It's really important to get buy-in from all staff. In science, it can be hard to get people working together across the bench – let alone across the building. It's not the only challenge, though; once you have your staff on board, you have to work out how to implement change without compromising service; and how to ensure that everything is not only fit for purpose, but kept to an ISO standard as well. I think aspects of our work here make it easier to move to combined omics and to provide greater opportunities for our staff group. If we do not continue to move forward, we're doing our patients a disservice by looking at every result in isolation. Our highly specialized pediatric investigations will certainly benefit from a more integrated approach.

COLLABORATING TO IMPROVE CARE

I'm the Head of Laboratory Medicine at GOSH, but I'm also the Head of the Neurometabolic Unit at the National Hospital next door – so we've been working in partnership for quite a while, with a number of joint contracts and other arrangements that allow free movement between the two organizations. We're scientists at heart – and scientists are often good at networking and collaborating!

Here at GOSH, we compare ourselves to institutions like the Mayo Clinic, the Children's Hospital of Philadelphia, and Toronto's Hospital for Sick Children. Like them, we're hoping to become a sort of pediatric laboratory medicine supermarket, offering a broad range of specialist tests to other providers who may lack the facilities themselves. We have a great network with those institutions; we're constantly in touch with them for consultations, second opinions, and advice. What we haven't done yet is share operational details – aspects such as funding, organizational structure, and increasing efficiency – but it's something I hope to investigate in the future.

I never hesitate to raise the profile of laboratory medicine to the

wider Trust to highlight why we exist and our essential role in patient care. The training of the next generation is also embedded within our strategic plan. It will be news to no one that pathology is struggling to recruit new graduates. With limited resources for recruitment and retention, we need to come up with new ways to attract new graduates and train them in our highly specialized areas. At the moment, there's a traditional training route to which all new NHS scientists must conform – but we've got to look at ways to customize training to suit different educational and career needs.

Industry partnerships also help us move forward. In my own interest area, metabolic disorders, we have healthy relationships with the companies that produce treatments – enzyme replacement therapies for lysosomal storage disorders, for instance. We collaborate with those companies to develop new assays in the laboratory, and the collaboration benefits the companies because it means that more patients are diagnosed faster and progress to the treatments they provide. More importantly, because the longer diagnosis is delayed, the worse the outcome in metabolic disorders, the collaborations allow us to identify patients in need of treatment so that we can improve or even save their lives.

PREVENTING PREANALYTICAL VARIATION

Preventing preanalytical variation is a key priority here at GOSH, and one I think is under-recognized in pathology and laboratory medicine – Carolyn Compton raised the issue wonderfully in “Garbage In, Garbage Out” in *The Pathologist* last month. We're working on a number of initiatives to prevent preanalytical error; for instance, the Trust invested in a dedicated member of staff for one year initially to reduce preanalytical error.

The staff member will focus on the development of practice, policy and procedures to reduce preanalytical error rates for clinical samples. They will be an integral part of the laboratory quality management team and, within this structure, will oversee the implementation, development and coordination of improved preanalytical quality processes.

They will provide leadership and direction on quality improvement processes linked to the collection and delivery of samples and will advise on sample quality issues, developing a team approach and encouraging sharing of best practice to meet the requirements of a patient-focused service, which is vital for our children and their families.

Getting the right samples to the right place at the right time isn't as “sexy” as new tests and fancy machines, but getting the basics right is truly important. The last thing any hospital, parent or child wants is for their sample to end up in the wrong department. Eliminating preanalytical variation is very dear to our hearts, so we're working hard to achieve that goal.

A MOVE TO MASS SPECTROMETRY

At GOSH, what we have right now is a virtual facility – with machines distributed around the department. We have just acquired a new system, and we're planning to acquire more as we increase our test volume and move toward more quantitative assays.

We use mass spectrometry a lot – newborn screening, vitamin D assays, metabolic analyses – which is why we are so eager to expand and improve those facilities. Mass spectrometry is powerful and relatively cheap (aside from the initial system purchase), so we want to move as many tests as possible onto that platform – appropriately. As I mentioned, not every assay needs to be conducted via mass spec – but many can and should be. For instance, we measure glycosaminoglycans in urine to diagnose and monitor lysosomal storage disorders. At the moment, we use two-dimensional electrophoresis, which takes quite a long time; with a mass spectrometer, you can do it all in a single run, and it becomes fully quantitative instead of just semi-quantitative.

**“WE’VE GOT TO
LOOK AT WAYS TO
CUSTOMIZE TRAINING TO
SUIT DIFFERENT
EDUCATIONAL AND
CAREER NEEDS.”**

We're also running more enzyme assays on the mass spec. Instead of running one long assay that yields a rate of change, we can perform up to 10 different enzyme assays on a single dried blood spot – we add all the different substrates, incubate, and then have the mass spectrometrist separate out the products. It's a great way of doing lots of enzyme assays at once – and it uses the skills of the scientist in new ways. I anticipate that mass spec will develop in many other areas – histopathology (where they're already looking at proteins from embedded blocks), immunology (for instance, by looking at cytokines), microbiology... For these applications, I consider the use of mass spec a no-brainer.



A WHISTLE-STOP TOUR OF GOSH PATHOLOGY

ENZYMOLOGY

Derek Burke

In this laboratory, industry-funded posts complement our research. One of our staff members, Jonathan Lambert, has just finished a PhD on Fabry disease – both the diagnosis and the disease mechanism – that was funded jointly by his academic institution and by an industry partner. Now, another industry organization has provided two years of

funding for him to set up an enzyme assay for asparaginase, which will be used in leukemia for treatment efficacy monitoring. We never expected this laboratory to be working on leukemia – but because we do enzymology so well, the company wanted to recruit one of our enzymologists. And we benefit as well: when Jonathan's grant finishes next year, his assay may be rolled out into the NHS as a diagnostic or monitoring test for leukemia patients. It's a good relationship.

We strongly emphasize the importance of translational research at GOSH; you might set up a new enzyme assay to use as a diagnostic tool – and, if it works, it will be in clinical use very quickly. Everything we do here, we do for our patients and our doctors, so the impact is immediately visible.

You can't talk about GOSH – and especially about the enzymology lab – without talking about newborn screening. Our program is the biggest in the country, screening about 130,000 babies each year.



MICROBIOLOGY

Elaine Cloutman-Green

We have quite an interesting way of approaching microbiology here at GOSH. We're trying to incorporate new rapid diagnostics, while simultaneously looking at new combined omics approaches to aid clinical interpretation. When we began to look at bacterial whole genome sequencing, for instance, we quickly realized that we couldn't look at that data in isolation. Genetically, the profiles were showing antimicrobial resistance (AMR) – but, when we conducted sensitivity testing, that's not what we saw. To clear up the confusion, we sent our samples for LC-MS/MS to look at proteomic expression profiles, and compared that data with our sequences to see what additional information we could glean and how essential it might be. What did we find? It turned out to be key, which is why we're now exploring how to use tools like MALDI-TOF MS for

rapid CRE expression diagnostics. It's easy to miss things by looking at either DNA markers or expression profiles alone, so we are always trying to pair the two together. We really need to know what's functional to make reliable clinical decisions about patient treatment.

The AMR work is just one example of why it's important to have different tools and disciplines working together. I might sequence a viral genome alone – but then I go to immunology and ask what they've learned about the patient, because it definitely affects my interpretation. You can't do the clinical interpretation without understanding the overall disease process. With all of the data now available to us, interpretation is more complicated than ever. When you're designing clinical decision-making algorithms to handle big data, it's important to make sure that the final report can be fully understood by the clinical teams on the ward. From five million base pairs to a single page – that involves quite a bit of skill!

NEWBORN SCREENING

Tejswurree (Preetee) Ramgoolam and Helen Aitkenhead

The dried blood spot assay is a very simple test – just a pinprick for a drop of blood, and then we can perform nine different assays. It's normally done at day five of age; a midwife takes the sample, puts it through the post, and we receive it within a day via a special registered address. Upon receipt, we label the sample and put it into the Panthera blood spot punching machine, which automatically evaluates the quality of the spot – and, if it's good enough, punches it in four different places for the nine assays. One of the punches is for the five inherited metabolic diseases (medium-chain acyl-CoA dehydrogenase deficiency, phenylketonuria, maple syrup urine disease, glutaric aciduria 1, isovaleric aciduria, and homocystinuria); the other three are for cystic fibrosis, congenital hypothyroidism, and sickle cell anemia. We perform our cystic fibrosis and hypothyroidism testing via automated immunoassay, which takes 1–3 minutes per sample. Because of the length of time per sample, we prepare and load all of the samples during the day, and run the assays overnight. When we come in the next morning, we can check all the results.

We also have three tandem mass spectrometers – two for metabolic disease testing and one for sickle cell anemia. Using tandem mass spec for screening is very reliable and has the advantage of avoiding the detection of asymptomatic sickle cell disease carriers. With HPLC, the detection of such carriers is unavoidable and leads to unnecessary follow-up testing and referral for genetic counseling.



One thing that helps is to speak with the clinicians themselves. I ask, “What is it that you need from me? What information will change your management of the patient?” I can give them 101 different pieces of information, but that isn't helpful (and can even get in the way); all they really need are the few pieces that will affect the patient's diagnosis, treatment, and ongoing care. Best of all, we have everything we need on-site – so if a patient needs a test immediately, we can all pull together to optimize our use of a tiny sample and deliver rapid results in time to provide crucial treatment.





HISTOPATHOLOGY

Toby Hunt

Histopathology is the study of changes in tissue, which can have immunological, metabolic, oncological, or infection-based causes. We deal with a pediatric population – from fetal to about 16 years of age – and there are nuances to the pathology of those patients that you wouldn't necessarily see in an adult. To give you an example – consider the development of a kidney. A fetus may have a kidney, but because it has not completely finished its growth phase, there will be differences

PROTEOMICS

Our MALDI mass spec system – called Bonnie Tyler(!) – has made a massive difference to our protocols. For instance, whenever we received a new blood isolate, we used to take up to three days to identify the pathogen(s) involved and get an antibiogram – a summary of antibiotic susceptibilities. With Bonnie, we can take a positive blood culture, spin it down to get a pellet, identify the pathogen(s) in four hours or less, and begin treating the patient with more appropriate antibiotics based on species identification immediately, rather than just providing general recommendations based on a Gram stain.

We received a lot of support from our colleagues in biochemistry for this first venture into using proteomics – it was a very new thing for microbiology, after all. Our experienced biochemists helped us to understand what our results meant and what we could do with our new tools. Now, we've expanded to other types of analyses.

Currently, if we want to test for carbapenem-resistant Enterobacteriaceae, we have to take a sample, plate it, look at the pathogen's antibiogram, and then, if it looks resistant, perform follow-up testing in infection control. Final confirmation can take three weeks! And during that time, the affected patient must be isolated, receive special cleaning, go last on the list for investigations and operating theaters; in general, it really impacts on clinical care. To avoid that, we're introducing a new method that uses proteomics to look at enzyme cleavage of the antibiotic. In only two hours, we'll be able to get that confirmed result – sparing the patient weeks of disruption. I think it's clear how important that rapid proteomic result is to improving patient care!





in its appearance to that of an adult kidney. To the average pathologist, it might look unusual or even pathological – but actually, for patients at that stage of development, it is the norm. Another classic example is the thymus; in a fetus or newborn, there’s a prominent thymus to permit T cell maturation – but in adults, the thymus is atrophied or even completely absent, because it’s no longer required. If you have a specialty service, you need specialty support. And there are a number of subtleties that our pathologists need to be aware of to best serve a specialty population like ours.

In the Department of Histopathology here at GOSH, we

take in two types of samples: neuropathology and “surgical pathology” (almost anything other than neurological). In short, we accept everything – brain, heart, lung, renal, tumor biopsies of all sorts... Because we are a tertiary referral center, our patients will have seen a general practitioner; the GP will have referred them to a hospital; the hospital will have undertaken its own investigations and then, if the issue is too obscure or too complex, the patient comes to us. In other words, we have to try to make a diagnosis where others could not – likely because they didn’t have the same level of exposure to the condition or tumor, or to pediatric pathology as a whole.




HIGH-SPEED PCR

Tanja Rockenbach

We are trialing a new point-of-care PCR machine. It's very exciting because this piece of equipment will give us a result for urgent respiratory viruses in less than two hours – whereas, at the moment, routine real-time PCR takes six to eight (albeit for 24 samples). The faster turnaround has real benefits both in terms of providing the correct antiviral treatment to the patient, but also when it comes to infection control and bed flow on a ward- or hospital-wide scale.

A major advantage to this device is that it can be run out of hours; if a patient is admitted at midnight, we won't add them to the routine setup. On this machine, we can run a single sample and test for a full panel of viruses, as well as some of the important bacteria that cause respiratory infections, very quickly – allowing us to provide rapid results that make a real difference to patient management.



In histopathology, we use a machine called a microtome to cut thin section of tissue. We then use these slices to visualize the cells that make up that tissue so that we can understand and report on a disease process. Unlike many other hospitals, when a sample comes to us, we use almost 100 percent of what we get; because our patients are so young, our samples are often very small. Much of the material we receive is fresh, not fixed, because of the investigations we undertake. If an adult hospital receives a tumor biopsy (for instance, from a breast tumor or prostate core), they put it into formalin, the formalin goes off with the sample in it, it's given its individual accession number, popped into a processor, cut, stained, and the resulting images interpreted. When we receive a tumor biopsy, we take a portion of that fresh tissue, immediately produce imprints (by dabbing the tissue onto a slide so that cells adhere to the glass), and send the slides for cytogenetic testing. If the sample comes from the brain, we may also do a brain smear, which involves producing a monolayer of cells on a slide for interpretation – something that we turn around very quickly so that we can offer surgical guidance. Are tumor cells present in the sample? Is it an aggressive tumor type? What form of resection or other treatment would be best?

**“IT’S CLEAR THAT NONE
OF US CAN DO OUR
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FIGURE OUT WHAT IS
GOING ON.”**

We then subdivide the remaining material into pieces and freeze some of them prospectively, in case a future test is able to give us an answer that our current ones cannot. Many of the tumors we see are rare – some come into the laboratory only once every few years – so we always try to retain some material for future investigations. Every sample is a new challenge, so we prepare ourselves to run every test that is currently

HISTORICAL INVESTIGATIONS

The histopathology department here at GOSH has records going back to post-mortems in the 1850s and archived material dating from about 1900. It's all FFPE, which means it's stable and safe indefinitely at room temperature. Recently, we went back to the archival material, cut fixed sections, removed the wax, and put it through mass spectrometry to see what proteins were present – and what anomalies existed in them (1).

Because our tissue archive is so huge, we can look back and see how disease has changed through time. So if you look through our records in 1900, a large number of children were affected by infectious diseases, such as tuberculosis – and, with the advent of antibiotics, we see a huge reduction in the number of children affected by infectious disease. And as children then began to live longer, cancer and chronic illnesses became more prominent.





available – and those that may become available one day...

Finally, we fix the remaining tissue to run what adult pathologists might consider more “routine” histopathology. The gold standard for looking at tissue is, of course, hematoxylin and eosin staining – a pattern that is recognized by all trained pathologists. Beyond that, we also do special stains. For instance, we have a special stain for acid-fast bacilli (like those that cause tuberculosis). We can tell you whether or not a patient has the disease – but what we can’t tell you is whether or not that pathogen exhibits drug resistance. And that’s when we need to communicate with microbiology, who can add the next piece of the puzzle and tell us (and the clinician looking after the patient) which antibiotics are most likely to be effective.

Neurometabolic disorders are a good example of our approach to testing. When we receive a skin or muscle biopsy to test for metabolic disorders, we conduct a batch of tests; most of those must be performed on fresh or snap-frozen tissue because the techniques we use are dependent upon the enzymes present. As soon as you take that material away from the body, it begins to break down. So we perform enzyme histochemistry, which indicates whether or not an enzyme of interest is present in the tissue. We send some material to other laboratories for biochemistry or other analyses (such as enzymology). We section some material and send it for electron microscopy. Why? Because no one test can stand in isolation. Microscopy might reveal enlarged mitochondria or

BONE MARROW CHARACTERIZATION

There is little published data on normal pediatric bone marrow maturation across multiple lineage and maturation markers. It has mostly been characterized in murine models, so we have needed to establish our own pediatric libraries to map hematopoiesis in different pediatric age groups. To characterize bone marrow, we look at the maturation of myeloid, monocytic, NK, T, and B cells – from the youngest cells to full maturation. This knowledge allows for greater confidence in detecting very low-level aberrant populations that do not fit typical maturation patterns.

When we're hunting for minimal residual disease or low-level malignancy, we're looking for something that doesn't quite express as it should – aberrantly, or asynchronously. Our flow cytometer essentially comes with “empty” software – and we build each experiment in accordance with our needs. Basically, we use an antibody that attaches to an antigen site on a cell specific to a lineage or a maturation point. The antibody has an attached fluorochrome that

excites and emits energy at a particular spectrum. When the cell goes through the flow cytometer, different lasers excite the various fluorochromes according to their individual emission spectra. We can currently look at up to 18 different antibodies with attached fluorochromes on a single cell type. Once we've completed our analysis, we map the results into lineage and maturation hierarchies. And that's how we build the software; we tell it what we want to look at, and then we start mapping the outcomes of our experiments.

Now that we've established each lineage and its maturation patterns, we can characterize blood and bone marrow samples. Which markers are expressed? Are they all expressing normally? We look for even the smallest anomaly – two cells in a million that aren't right – because it helps us diagnose patients, stratify them according to their risk of treatment resistance or relapse, and monitor them during and after treatment. I know that our work makes a huge difference to the patients; it allows them to receive the customized treatment they need for their specific disease. And that's very important to us.

storage granules in the tissue – but why are the mitochondria enlarged? What's in those storage granules? We need enzyme histochemistry to reveal the actual biochemical deficiency. But what causes that deficiency? Is it a genetic condition? Our colleagues in the genetics department can tell us that – either by finding the genes for a known disorder, or by examining the entire exome or genome to identify a new genetic condition. It's clear that none of us can do our jobs without the others; we all have to work together to figure out what is going on.

We are also involved with evaluating “new” histopathology techniques, such as micro-CT for visualizing small specimens, mass spectroscopy to evidence the presence of particular proteins within formalin-fixed, paraffin-embedded (FFPE) material, and DNA sequencing of historical archival material (see “Historical investigations”).

FLOW CYTOMETRY

Sarah Inglott

Our flow cytometry laboratory performs diagnostic and monitoring analyses as well as translational research and

academic collaborations. On the diagnostic and monitoring side, we analyze peripheral blood and bone marrow, solid tumor, and spinal fluid samples. We assess children with suspected hematologic malignancies for leukemia-associated phenotype (LAP) markers. We can then monitor their progress through treatment, track their minimal residual disease, and conduct follow-up testing for potential relapse. We also monitor chimeric antigen receptor T cell (CAR-T) therapy patients for treatment response and potential relapse of disease. CAR-T cells target a specific epitope, typically CD19 or CD22 in B cell leukemias or alternative epitopes in solid tumors. But following a period of successful response to therapy, there is always the potential for relapse – and the relapsed disease can then evolve to stop expressing its target epitope. This loss of expression affects the way we have to analyze the resulting disease; gating strategies have to change, which involves using different, potentially non-lineage-specific markers. We can do this down to two cells in a million where phenotypic aberrances are pronounced. Detecting returning disease at such low levels allows for changes in disease management and therapy with greater effect than waiting for relapse to become clinically frank.



In addition, we run biomarker tests for diseases such as neuroblastoma. It's a cancer, prevalent in pediatrics but nonexistent in adults – and it has a very poor prognosis. We want to work out how to detect it at low level, or when it has infiltrated into the bone marrow (as this alters the disease staging and treatment). We also monitor the efficacy of CAR-T therapies that might improve outcomes for neuroblastoma patients.

RAPID RESPONSE

Simon Heales

Our “rapid response” laboratory operates at a high throughput 24 hours a day, seven days a week. We refuse to call it a routine laboratory, as I said, because there's nothing routine about it. One key difference between this and an adult lab is the much smaller

sample volume. We have to be highly proficient at conducting tests on very small amounts of sample, because children simply have less blood to give.

The other significant difference is that children are not just small adults – at least in terms of their biochemistry – and so it's vital that we understand those differences and remain child-focused. For one thing, changes happen faster and have a greater effect, so even more than in adults, speed is always of the essence. In some of the disorders we work with, rapid diagnosis can prevent irreversible brain or organ damage – or even death. Adults are often at the other end of the spectrum; diseases like Alzheimer's or Parkinson's move slowly and may not have effective interventions.

The speed required in our work is just one more way in which pediatric pathology is completely unique. We're working on puzzles that no one has previously attempted to solve, and we're trying to do it as rapidly, comprehensively, and collaboratively as possible.

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Tackling the Testing Challenge
in Lung Cancer

New information on the genetics
of lung cancer has led to an update
to molecular testing guidelines.
Neal Lindeman tells us what
we need to know.

Tackling the Testing Challenge in Lung Cancer

Revised recommendations for molecular testing can help us ensure that every patient is appropriately treated

By Neal Lindeman

Lung cancer remains one of the world's most significant causes of death, with the disease accounting for approximately one-fifth of all cancer mortality worldwide. As with most cancers, it's possible that we could reduce those numbers with the help of appropriate testing to detect lung cancer early, stratify patients by risk, and identify appropriate treatments for each patient's unique disease. Molecular testing can help – but to take full advantage of its scope and power, we need up-to-date testing recommendations to help guide its use.

At a Glance

- *New discoveries in lung cancer genetics and biomarkers have led to the need for revised molecular testing recommendations*
- *Three organizations have teamed up to issue updated guidelines that include new genetic tests*
- *Genes such as ROS1, ERBB2, MET, BRAF, RET, and KRAS can provide new insight into the disease and offer a pathway to investigational therapies*
- *Lung cancer is a rapidly evolving field and laboratories are encouraged to review and adopt the new recommendations as soon as possible*

Whys and wherefores
We always knew that the existing guidelines for molecular testing in lung cancer would need revision – just like we know that these new guidelines will need another revision at some point. The field moves very rapidly, with new discoveries emerging and new technologies maturing at an astonishing rate. We felt in 2016 that – between the importance of *ROS1*, the emergence of next generation sequencing and liquid biopsies, and the advances in immunohistochemistry (IHC) – enough significant changes had “declared themselves” that the time was right to launch this revision.

One of the major changes is the introduction of new genetic tests to the lung cancer repertoire. For instance, we now have compelling published evidence of clinical response to *ROS1* inhibition that has translated into real-world clinical practice – in fact, the *ROS1* story was beginning to emerge even while we were finishing off the initial guideline. We also have extensive published evidence of clinical responses to *ALK* inhibition when IHC was used as biomarker, of the value of next generation sequencing as an efficient way to detect multiple alterations concurrently, and of the response of *EGFR*-resistant lung cancers with the acquired T790M mutation to third-generation *EGFR* inhibitors.

I think the more challenging thing to explain – and to implement – is the recommendation regarding the “intermediate” genes: *ERBB2*, *MET*, *BRAF*, *RET*, and *KRAS*. For these, we felt there was good clinical evidence from small, single-arm studies that indicated medical necessity... but it wasn't compelling evidence from large, controlled studies – and this was a fine line. In the end, we believe that it is necessary to offer

investigational therapies to lung cancer patients when the standard treatments are not appropriate, and this expanded testing is the portal to those therapies.

Continuous change

Collectively, we look forward to the continuing evolution of diagnostics and care for lung cancer patients as technology, scientific understanding, and clinical practice advance. Because these recommendations represent current best practice in a rapidly developing field, we anticipate an ongoing need for additional updates in the future. I think one of the big challenges is to provide these updates rapidly, as the field outpaces our ability to generate the recommendations! We are also seeing a transition in care, with lesser levels of evidence being used as a basis for treatment strategies.

One example, might be the approval of the *BRAF*/MEK1 targeted inhibitor combination for lung cancers with the *BRAF* V600E mutation. That came just a little too late for us to incorporate it into the new guidelines, but we knew it was unpublished even as we were finishing off our recommendations. We fully expect this alteration to be a standard part of lung cancer diagnostics by the time we develop

the next guideline – and we'll probably see other up-and-coming tests such as *MET* splicing variants, too.

Quis custodiet?

The international, multidisciplinary panel was established jointly by the College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology. It included pathologists, oncologists, pulmonologists, a methodologist, laboratory scientists, and patient representatives who collaborated to develop the guideline following the Institute of Medicine's evidence-based process. We really tried to adhere to the formal evidentiary basis of the recommendations, and to avoid falling back on opinion statements. The rigor of the process takes time, but in the end, we are confident that our recommendations are robust.

This update process began approximately 18 months after the publication of the 2013 guidelines, due to the rapid pace of discovery in the field. The panel reviewed the evidence published since the 2013 recommendations had been made and found that the literature either still supported or even strengthened some of those initial recommendations. We also reviewed all available evidence to address the new "key questions" that we had defined with regard to consideration of new genes, new technologies, and new subtypes of lung cancer. A public open comment period provided feedback on the draft guidance, which the authors considered in writing the final guideline recommendations. Finally, a rigorous, independent scientific peer review completed the publication process, with the final guideline appearing in all three organizations' journals (1).

New techniques; new technologies
Our recommendations are determined by the strength of the available evidence at the time of their writing. At the moment, the evidence does not support the use of

cell-free DNA for routine initial diagnosis, despite its growing popularity. In some clinical settings, however, tissue-based *EGFR* analysis cannot be performed – either because tissue biopsy material is unavailable or insufficient, or because tissue re-biopsy is not feasible. In these situations, a cell-free DNA assay to identify activating *EGFR* mutations is recommended as an alternative molecular diagnostic procedure. However, in progression, testing for *EGFR* T790M is required, and good evidence supports the use of either biopsy or cell-free circulating DNA methods in this context. As technologies and testing methodologies continue to advance and more evidence becomes available, we will continue to update the recommendations as needed.

"We encourage pathologists and laboratories to adopt [the guidelines] so that we can provide patients battling lung cancer with the greatest possible treatment benefit."

One particularly exciting area is the notion of quantitative monitoring of disease burden by analyzing mutations in cell-free DNA. I expect that this will emerge in the coming years, and, in the next guidelines, we may be looking into the standardization

of quantitative cell-free DNA assays for mutation load assessment, in a manner analogous to *BCR-ABL1* fusion testing in chronic myeloid leukemia.

Need to know

The guideline's purpose is to set the standards for the molecular analysis of lung cancers to guide targeted therapy treatment decisions, but it's a rapidly evolving field. We base our recommendations on the evidence that has been published at the time, and what that evidence indicates is necessary to provide adequate care for lung cancer patients today. New findings will emerge, practices will evolve, and we will issue new recommendations when the evidence to do so has accumulated satisfactorily – but, in the meantime, all providers who care for lung cancer patients are advised to keep abreast of advances in the field.

As with any evidence-based clinical practice guideline, following these recommendations is not mandatory – but we encourage pathologists and laboratories to review and adopt them so that we can provide patients battling lung cancer with the greatest possible treatment benefit. The guideline was a successful collaboration of international, multidisciplinary experts from CAP, IASLC, and AMP, all of whom spent countless hours working to assess the available evidence and determine the best path forward to ensure clinicians stay apace and provide optimal patient care.

Neal Lindeman is AMP Co-chair and Member, Director of Molecular Diagnostics at Brigham and Women's Hospital, and Associate Professor of Pathology at Harvard Medical School in Boston, USA.

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The Diagnostic Power of DNA Methylation
Sequence mutations aren't the only players on the field of genetic disease. Epigenetic analysis can be informative – especially when paired with machine learning.

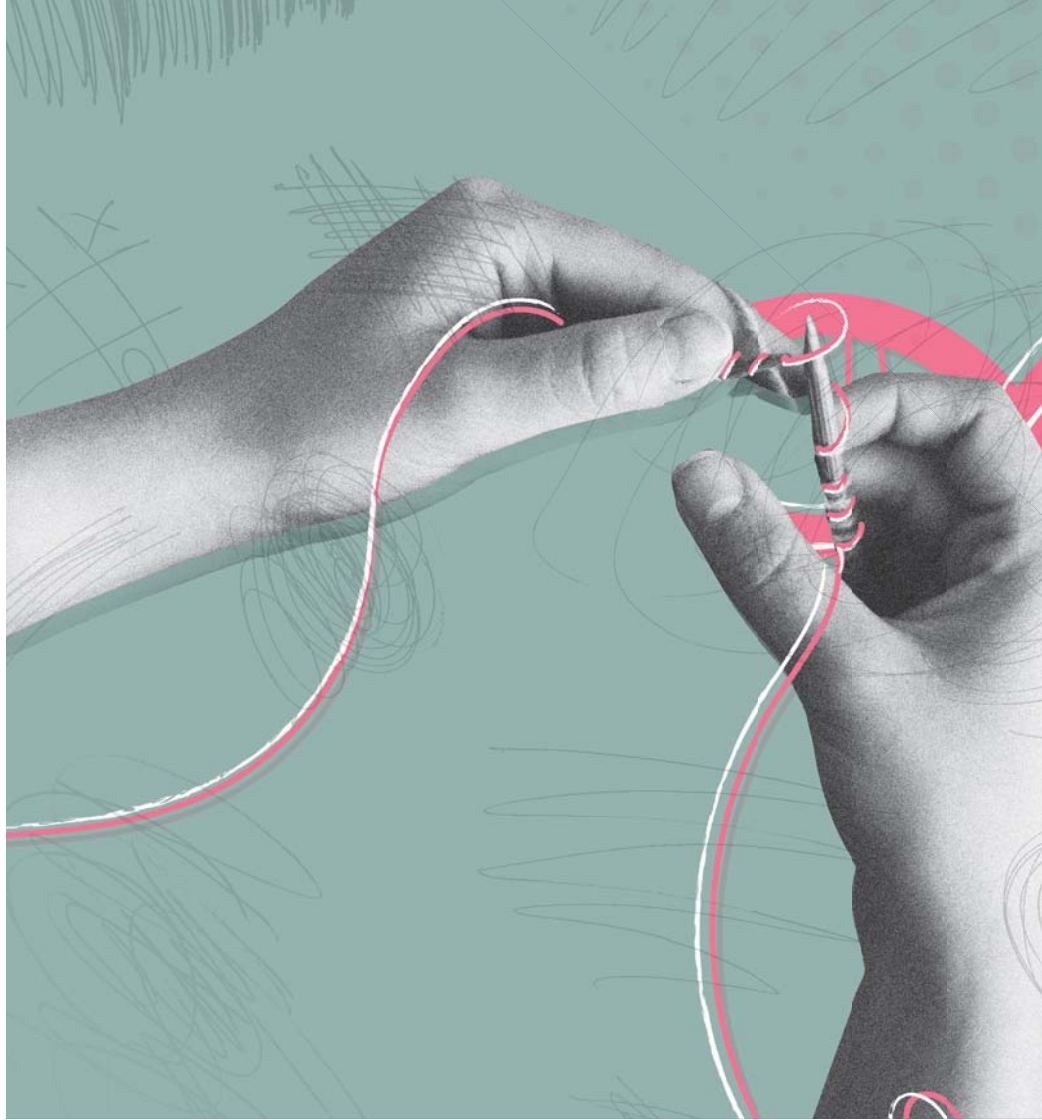
The Diagnostic Power of DNA Methylation

How epigenomic analysis of peripheral blood, coupled with machine learning, could give labs access to clinically relevant information

When my career started, constitutional genetics and epigenetics were limited to very specific purposes, such as imprinting disorders or specific methylation assays. About 10 to 15 years ago, this targeted approach began to give way to genome-wide methods using microarrays and similar technologies. Baylor College of Medicine, where I had my clinical fellowship, was one of the hubs at the forefront of introducing these technologies, and now they've carried out over 100,000 pediatric microarrays. In the process, they have discovered new clinical associations for dozens of new microdeletion and microduplication syndromes. The work set a precedent – and it got me to start thinking about

At a Glance

- *DNA methylation can be an important diagnostic indicator of genetic disease*
- *When combined with machine learning, methylation analysis becomes a powerful tool that grows more accurate and effective over time*
- *Methylation analysis can help determine whether variants of unknown significance are pathogenic*
- *Creating open databases will help facilitate the continued growth of epigenetics*



methylation technologies as something that I could exploit in a similar way.

My current lab at the London Health Sciences Centre, Canada, has been working with peripheral blood and detecting DNA methylation within it. We're now at the point where we've tested thousands of patients in large, internal databases, and we've adopted a machine learning approach to gain new patient cohorts and ask the question: do patients with intellectual disabilities have identifiable and specific changes in their epigenomes – and can we find the answer in peripheral blood?

We discovered that, although the changes were mainly caused by gene mutations, there were significant genome-wide DNA methylation alterations as well – and that we could, in fact, detect them in peripheral blood.

Carrying out these DNA methylation tests allowed us to determine, with absolute certainty, whether a variant of unknown significance (VUS) was pathogenic. A pathogenic VUS results in a consequent “epi-phenotype” DNA methylation signature, which we used as a secondary assessment in our investigations.

We looked into neurodevelopmental Mendelian disorders in children caused by epigenetic mutations involved in DNA methylation. Our goal was to demonstrate that we could combine machine learning with DNA methylation epi-signatures to yield a diagnostic indicator of the disorders. We recently published a number of papers describing clinical genetic variation in neurodevelopmental syndromes, including one that demonstrates



more samples the database includes, the more refined the methylation signatures and scores become – our study demonstrated over 99 percent sensitivity and very high specificity.

“Even with such useful information and high sensitivity, I think we’re only at the very early stages of taking epigenetics in this capacity to the clinical setting.”

the broad applicability of machine learning algorithms to the systematical identification of specific (epi)genetic disorders in peripheral blood samples (1).

Machine learning

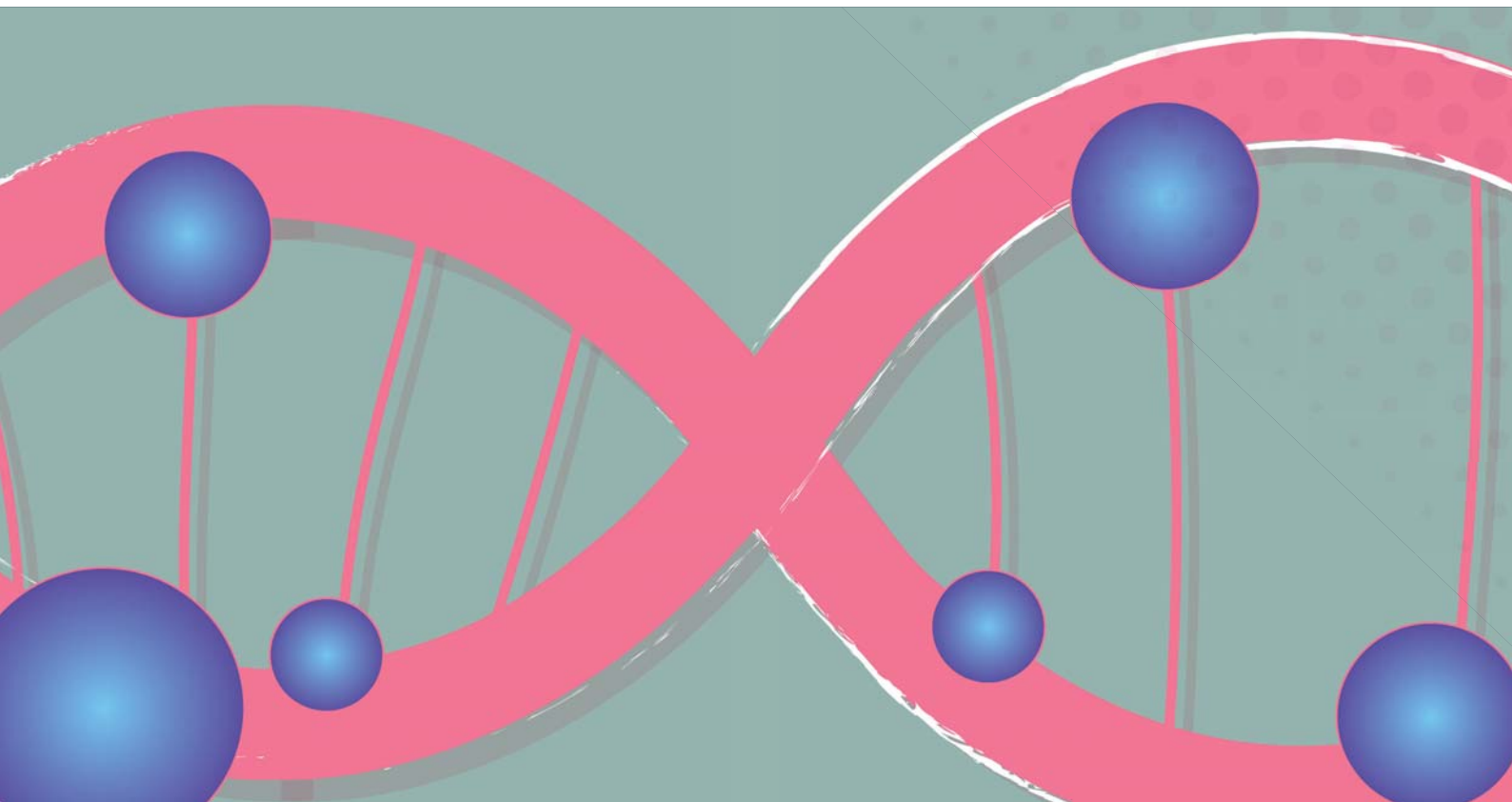
I’ve found machine learning approaches to be useful in epigenetic analysis. We have developed an application of machine learning that allows us to assess DNA methylation samples from patient cohorts and identify unique epigenetic signatures. Our recent publication refers to a methylation classification score that predicts the probability of a methylation profile relating to any of our tested conditions with an epi-signature. This is scored from zero to one (a higher score means a higher chance of carrying a methylation profile), and it is entirely generated through machine learning.

It allows users to concurrently generate scores for multiple conditions for various disease groups; in our study, for instance, we focused on Kabuki syndrome, ATRX syndrome, Sotos syndrome, CHARGE syndrome, Floating-Harbor syndrome, ADCA-DN, and intellectual disabilities caused by *KDM5C*.

The idea is that, once we’ve built these scores for any condition that has an epigenetic signature (and we have created a database of references), we could introduce those scores and the database into a clinical setting. Any lab in the world could generate DNA methylation profiles with a basic piece of equipment – and, when paired with microarray screening or exome sequencing, it could form an ad hoc diagnostic. Best of all, it’s a self-learning system, meaning that the

There’s so much more we can explore with methylation and machine learning, and until we have databases with tens or even hundreds of thousands of signatures and scores, I don’t think we’re realizing its full potential. In other words, even with such useful information and high sensitivity, I think we’re only at the very early stages of taking epigenomics in this capacity to the clinical setting.

I’d compare it to the introduction of microarray screening in the pediatric population 15 years ago. Back then, only a dozen or so microdeletions were known – but now that millions of children have undergone screening and been included in the databases, we’ve seen the publication of hundreds and hundreds of papers that refine and define new microdeletion/duplication syndromes.



“Pediatric or constitutional hereditary testing is low-hanging fruit from an analytical standpoint, and introducing it into routine clinical care seems achievable.”

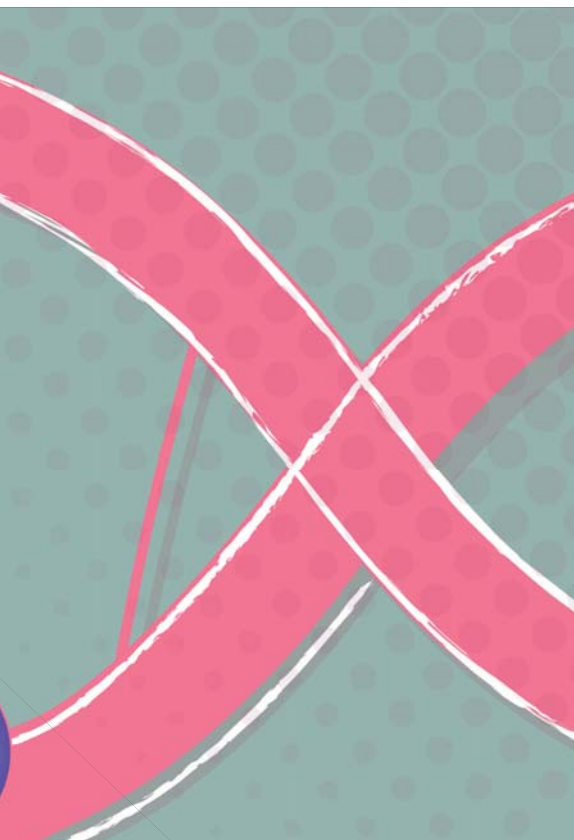
I think the machine learning approach is going to be high-throughput and computational without necessarily requiring a prior hypothesis – but I also think that hypothesis-driven analysis will allow us to derive more accurate data than we would otherwise. In some of our earlier publications, my lab used different kinds of statistical methods, but over the last year and a half, we’ve narrowed down our machine learning approaches. Now, they are more accurate and systemic, allowing us to derive signatures from conditions that would have eluded us before.

The pediatric perspective
Changes seen in pediatric patients are often associated with an underlying genotype. When we see a genome-wide methylation change, it is very highly specific and involves dozens or even hundreds of loci spread across the genome. Pediatric or

constitutional hereditary testing is low-hanging fruit from an analytical standpoint, and introducing it into routine clinical care seems achievable – so that’s what we’re gearing up to do next.

There is a plethora of labs that do genetic testing, and there are hundreds, if not thousands, of patients who have reports with VUS. We now have the ability to resolve these through a simple peripheral blood DNA methylation test. Once this is rolled out into clinical settings, I think it’s only a matter of time until we’re able to tackle imprinting disorders and conditions like Fragile X. All it takes is some time to grow the size of the database, which will let us capitalize on the additional statistics to discover new things.

For now, we’re focused on pediatric constitutional hereditary conditions, but we have ongoing projects to expand beyond that. I think the technology is



tissues, but the end goal is to perform it in peripheral blood – a liquid biopsy for DNA methylation.

“DNA methylation is one of the only changes that is ubiquitous across cancer types, which means it could yield valuable information.”

broadly applicable to areas outside those types of conditions. The issue is that, especially in oncology, DNA methylation changes are not often as specific as what we’re seeing in these constitutional “epi-syndromes.” DNA methylation is one of the only changes that is ubiquitous across cancer types, which means it could yield valuable information if we can develop a full understanding of its complexities.

We are also in the process of validating our technology for *BRCA1* and *BRCA2* gene deletion testing. The question here is: are these patients also affected by the “loss” of these genes through DNA methylation changes? The question is clinically significant because certain tumor subtypes that display a loss of *BRCA1* or *BRCA2* genes are responsive to PARP inhibitor therapy. We’ve performed DNA methylation testing on buccal swabs and many other tissue types, including tumor

Building databases

From my perspective, there are very few challenges standing in the way of making this testing method a clinical reality. The actual technology used for testing is widely available and not proprietary. The challenges mostly revolve around the licensing and reimbursement of testing. This is a completely new clinical diagnostic approach and, as such, clinical utility will need to be better defined. In the future, clinical guidelines will need to be written to address the most appropriate utilization of such testing along with existing clinical diagnostic technologies.

One significant limitation is the time and effort needed to create databases that can safely and efficiently store data. There are two main solutions: you can either try to build your own database over time, or you can partner with others to become an informatics/database resource for other labs that want to do the same. I think the latter

option is where the future of information in this field is heading. I believe we’ll arrive at a point where databases – and the large cohorts of data within them – are shared and mutually accessible. At the moment, there are private databases and patent-locked data – but when that information becomes open to all, it enables more approaches and interpretations than any private collection of information, no matter how large. Resources like ClinVar (2), funded by the NIH, benefit the scientific community by helping to facilitate such data sharing. I predict that these types of databases are going to become increasingly important over time. Currently, they are primarily focused on curating genetic information – but I think that, as epigenetic information becomes more clinically useful, databases will expand. We’re sitting atop the tip of an epigenomics iceberg; I think that it will be the next big field to expand in the clinical diagnostic community.

About a decade ago when I was a postdoc in Toronto, I regularly chatted with colleagues in the epigenetics journal club about the hypothetical idea of genome-wide epigenomics as a clinically useful tool. We always thought it might eventually happen, but we never even dreamt about the possibility of using global epigenetics to direct immediate patient care – and now, it seems like that may soon be a reality.

Bekim Sadikovic is Head of Molecular Genetics at London Health Sciences Centre (LHSC), and Associate Professor at Western University, London, Canada.

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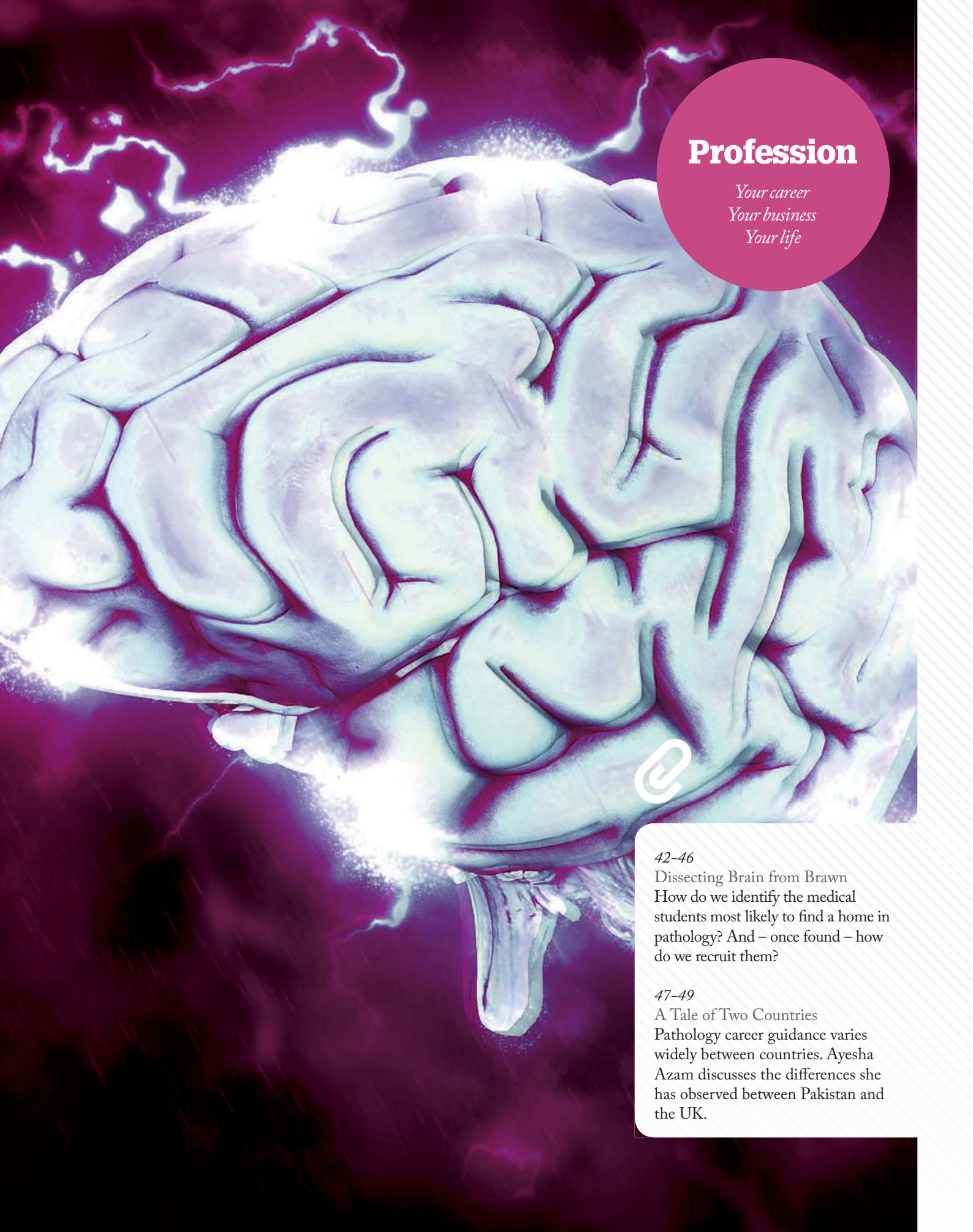


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Dissecting Brain from Brawn
How do we identify the medical students most likely to find a home in pathology? And – once found – how do we recruit them?

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A Tale of Two Countries
Pathology career guidance varies widely between countries. Ayesha Azam discusses the differences she has observed between Pakistan and the UK.

Dissecting Brain from Brawn

We need to do more to fully expose medical students to specialty of pathology – and we must more actively pursue those who show interest or aptitude

By Austin McHenry and Kamran Mirza

When it comes to choosing a medical specialty, there is a distinct conflict between personal interest and societal bias. The question of specialty selection touches every part of a medical student's life: feelings of personal accomplishment and fit; emotions like pride, guilt, and remorse; time frames for training and planning for a family; and the seldom-voiced – but palpably sensed – desire for a distinct earning potential, a specific working lifestyle, and the perception of power and influence. Medical students' biases toward popular specialties may remain deeply rooted because popular culture tends to define physicians by these latter influences. Many students enter training with an idealized version of their future selves as mighty surgeons or distinguished

At a Glance

- *When choosing a medical specialty, many students lean toward “flashier” or more popular fields of study*
- *Pathology is, in many cases, a lesser-known specialty; many students never truly learn what we do*
- *We must introduce all students to pathology as a specialty – and then actively seek out those who are interested*
- *Once given the opportunity to truly understand pathology, we can better entice students to pursue it further*

clinicians, respected and praised by their patients. (They don't realize that at that point that life as a doctor is less *Grey's Anatomy* and more *Scrubs*!) Few students, however, arrive at medical school with the distinct goal of becoming a pathologist, let alone with a full appreciation of what those within our specialty do. Even fewer come with views of pathologists as “powerful,” “influential,” or – dare we say – “sexy.”

A first-hand experience

When Austin McHenry entered medical school in the fall of 2015, he understood the uniqueness of pathology better than the rest of his class; he had already spent a gap year working for a shared research biobanking facility within a large university hospital. The facility used many

of the same resources as the university's pathology department, and the quality and number of specimens received for research depended entirely on what the pathologists could afford to part with after diagnostic requirements were met. Although pathologists performed most of the groundwork for the research, non-pathologist physicians and non-physician researchers were also heavily involved. All projects required a group discussion – in person – to decide exactly what services were being requested by the research teams. And these meetings afforded Austin the rare opportunity to gauge other professionals' understanding of pathology. It became increasingly clear to him that most researchers did not fully understand what they were actually requesting when





they asked to collect tissue in a designated orientation, isolate a specific cell type by one method and not another, or extract DNA from certain specimens and not others. Often, the meetings would consist of the pathologist explaining to the researcher a better way to obtain the data he or she sought. The combination of witnessing pathologists' diagnostic processes under the microscope and hearing firsthand the kinds of questions they were interested in investigating sparked his own interest in the field. And although he's still ashamed to admit it, Austin would likely never have forged this interest if not for his gap year experiences.

Pathology for the patient
The inescapable question arising from

Austin's experience is how other medical students with the same cerebral inclinations and desire for deeper understanding of disease and diagnostic approaches can possibly make an informed choice about pathology – one based not on societal biases, but on personal interests. How do we help students discover that they are interested in pathology before they commit themselves to a field less suited to their inclinations? Because ill-informed bias continues to drive talented medical students toward popular specialties, we believe we must make a greater effort to prevent individuals with a true personal interest in pathology from slipping through the preclinical years without proper exposure. Pathologists should be aggressive in their early outreach efforts. How? By combating the “no patient interaction” argument head-on instead of fleeing from it; by challenging students to think more deeply about the differing roles of surgeon and pathologist in the care of a patient; and by highlighting the uniquely cerebral and definitive aspects of pathology not found in other specialties – the diagnosis and understanding of disease.

Whether with medical school colleagues or at post-fellowship social events, when we mention our interest in pathology, we frequently hear others' qualms about giving up patient interaction – usually garnished with a sprinkling of other gross (no pun intended) misperceptions. Although the social aspects of the patient interaction argument seem justifiable, we believe it exaggerates the profundity of most physician-patient encounters. Unfortunately, we have arrived at a time in medicine where productivity is measured in the numbers of patients seen each day. When the average acute visit is 15 minutes long, a physician's day becomes much more about getting through each patient on time than about giving the right amount of face time to each individual. More often than not, the physician spends considerable effort steering the conversation toward

only those problems they are willing to address. Physicians are notorious for interrupting patients – in one well-known study (1), patients were allowed to complete their opening statement of concerns in its entirety in only 23 percent of physician interviews. What is more, the average time to interruption was 18 seconds! There is no longer space for the kind of reflective silence that is integral to any other normal conversation. Although it is admirable to say that one should value patient interaction, it is a goal less congruent with modern medicine than with many other lines of work. Similarly, the frequent, incisive counter that pathologists – especially those in academic settings – spend their days in lonesome silence is far removed from reality.

Like any other field of medicine, pathology is a discipline that requires a large staff to move patients in and out the door. In our case, although we see but parts of the whole, our patients are no less real and important to us. To say that the experience of examining a person's flesh under a microscope holds the same amount of meaning as examining any other inanimate object is not only wildly false, but also fails to grasp the seriousness of this responsibility. There exists a tangible sense of intimacy in holding a patient delicately between two panes of glass in your hand, knowing that your observations have consequence. Isn't this a form of patient interaction? The experience of discovering, on histology, a cancerous finding in an otherwise unsuspecting patient harbors the same gravity as physically palpating an unsuspected mass in an exam room.

Power and influence

In the same way that the outpatient argument hinges on patient interaction, so too does the inpatient defense focus on feelings of close proximity to disease itself. Many students of science are drawn to medicine because they want to be as intimately involved as possible in the

ailments they study. They thrive on taking care of those who are the most sick and, as a result, may have a tendency to perceive the fields of surgery and oncology to be of greatest authority. Students should not be faulted for wanting to succeed; however, these perceptions of greatness are not always an accurate reflection of “power” or “influence.” The offices of surgeons are often brimming with “thank-you” edibles and holiday appreciation gifts. That the same cannot be said of pathologists is largely a product of how society understands medicine – after all, surely it was the clinician, or perhaps the surgeon, who diagnosed your mother’s diffuse large B cell lymphoma.

The appreciation of the more “visible” doctors is understandable, but it would be unwise to delude oneself into believing this opinion should be shared by those within the field of medicine. Anecdotally, we find that a significant number of students who switch from general surgery to pathology (yes – it does happen on occasion!) were misled into thinking that the surgeon makes the diagnosis. The pathologist in the laboratory was never a consideration. Once they enter the field and find that what they truly wanted was the cerebral stimulation of the differential and the responsibility of the final diagnosis – that’s when they realize that they need to separate brain from brawn.

Think of the mighty surgeon requesting a second opinion on an initial ovarian mass biopsy reported as a fibroma.

Because this diagnosis is inconsistent with the patient’s elevated serum tumor marker (which suggests dysgerminoma, a true malignancy), the otherwise intimidating and powerful surgeon’s mind remains occupied all day by a question unanswerable in her chosen specialty.

Visualize one of the highest-paid surgeons in a medical center whose procedure is reduced to stillness as the team waits for the examination of frozen surveyed lymph nodes. It is in moments like these, when the surgeon stands motionless, hands resting on top of the patient, that notions of “power” and “influence” seem utterly reversed.

The savvy medical student will quickly learn the true value of the pathology report to the surgeon, the medical oncologist, the radiation oncologist, and – most importantly – the patients themselves. Information provided by the pathologist’s examination of a simple biopsy can mean the difference between additional surgeries and going home. It can mean the difference between years of close follow-up and no follow-up at all. Thus, one might argue to the student that it is, in fact, the pathologist who holds the “power” and “influence.” But because no sane pathologist would utter a statement so conceited, the student may never truly receive this perspective without some external suggestion early in training. Power and influence are outdated remnants that our popular culture has long projected onto medicine. They are

archaic, unneeded components that future generations of doctors and patients will not recognize.

“The savvy medical student will quickly learn the true value of the pathology report to the surgeon, the medical oncologist, the radiation oncologist, and – most importantly – the patients themselves.”

What is a pathologist?

When reviewing applications for entry into Loyola University Chicago Stritch School of Medicine’s combined anatomic pathology/clinical pathology (AP/CP) program, Kamran Mirza looks for pathology experiences. Although many medical students are beginning to recognize the positives of a pathology career (hours, lack of call, income potential, job security), far too often, they use a pathology application as a “backup” when their specialty of choice is highly competitive or their board scores are low. These applications become obvious immediately in their choice of



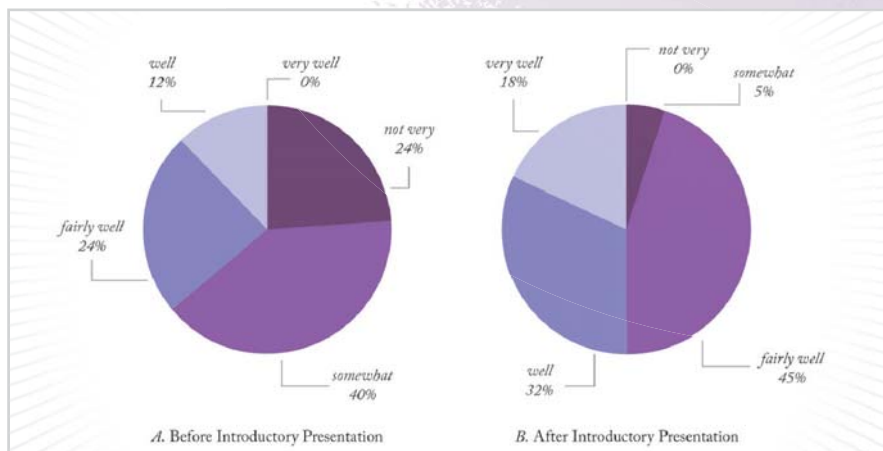


Figure 1: First- and second-year medical student survey responses to the question, “How well do you understand pathology as a medical specialty?” both A) before and B) after an introductory mini-symposium presentation titled, “Pathology: A Career in Medicine.”

recommendation letters, and even more so in their personal statements. In contrast, some students are true “pathophiles” with their fingers on the pulse of pathology as a life beyond Robbins, Pathoma and MS2. The pictures their words paint in their personal statements are amazing: “The pathologist is the trunk of a tree where research is the roots and clinical specialties the foliage.” How brilliant is that? “The pathologist is the conductor of an orchestra controlling and facing the musicians with their back to the audience...” And our personal favorite: “The pathologist is the director of a play; the audience sees the actors, but the director, behind the scenes, controls what they do.”

What is it that sets these medical students apart from the hundreds of others who never understood what the choice of pathology truly meant – and yet excluded it just the same? The answer: preclinical exposure to real-world pathology.

The crux of the argument for pathology must focus not on defense of its criticisms, but rather on excitement about its uncommon advantages. Pathology is a uniquely cerebral discipline within medicine. Austin had

the chance to scrub in on an ambulatory surgery case to perform a wide local excision of a high-grade squamous vulvar intraepithelial neoplasia (VIN) lesion. Before the procedure, he sat with the surgical PGY2 trainee, who was frustratedly flipping through a pocket gynecology/oncology handbook to find information about VIN. Austin suggested she try looking in the cervical intraepithelial neoplasia section. She retorted that it would be fruitless because they are “completely different diseases.” She may, of course, have meant that the two lesions are treated differently – but these pre-cancers have identical pathophysiology. To state that they are different is not to understand what and where the squamous epithelium is; it is to ignore the one neoplasm for which we can identify with certainty an etiological origin. Austin realized in that moment that a surgeon does not need to understand the pathophysiology of a symptomatic mass to surgically remove it...

Pathologists are lucky; we have the freedom to allow our minds to fully develop the questions other physicians cannot. Where other fields accept poor answers, we aim for the definitive. We occupy ourselves with the goal of the

truest understanding of why our bodies function the way they do, and how they can become dysregulated and disease-ridden. As a medical oncologist, one may not need to understand in intricate detail the histomorphologic, phenotypic, or molecular underpinnings of why a specific drug is approved to treat small-cell lung cancer and not adenocarcinomas to prescribe it. The oncologist’s mind may instead be appropriately occupied by clinical intricacies, such as whether or not an insurance provider will cover the cost of the drug, or whether it can be properly administered to the patient. Similarly, a clinician need not understand the function of alpha-fetoprotein (AFP) to know that its elevation is associated with yolk sac tumors. It is pathologists who allow themselves to be fascinated by the mechanism of AFP production; to wonder why it is that AFP is also associated with developmental birth defects, hepatocellular carcinomas, ataxia telangiectasia, and so on. In the same way, we afford ourselves the ability to appreciate that every cancer is different. We task ourselves with discovering what those differences are. We are at liberty to go beyond algorithms and guidelines. The individualized cellular morphology of each organ in the human body can, at times, seem to transcend our ability to comprehend it. Nonetheless, we do understand it, and we have the capacity to continue to learn more about it. To physically visualize disease at its most basic, yet simultaneously complex level, is to experience the true awe of human pathology.

Active engagement

To ensure that these arguments do not fall on deaf ears, pathologists must learn to engage with medical students. In places where such engagement already exists, it needs to improve – to start chipping away at the gross misperceptions of our careers and the personalities others assume we all have. For change to occur, we will truly

need to be “out there” in as many ways as possible. Academic pathologists must be more visible – which means actively cultivating their own online presences. We are at a point when social media outreach is not only acceptable in academia and the workforce, but expected. Like it or not, Twitter and Facebook are active forums where pathologists communicate with one another. Exciting cases are discussed, educational opportunities are announced, journal articles are shared, and extracurricular pathology events are advertised. Medical students must be made aware of this community! In the same way, pathology student interest groups need robust institutional involvement and departmental support.

At Loyola University Chicago Stritch School of Medicine, we have witnessed what is possible with just limited resources. Our pathology interest group, Students Curious in Outrageous Pathology Experiences (SCOPE), had slowly dwindled out of existence over a few years’ time, eventually losing status as a student organization formally recognized by the institution. With the enthusiastic oversight and guidance of only a few individuals, we have – in just two short years – become a powerful voice for pathology among our medical students. As well as having recruited a robust group of core supporters, we have organized several events to give preclinical students exposure to the field, including laboratory tours, histology reviews, histopathology workshops, mini-symposia, autopsy observations, transplantation lectures, and even community exhibitions of pathology art. Perhaps most importantly, we organize introductory meetings called, “What is Pathology?” intended for, and led by, medical students. Our data (see Figure 1) suggest these short introductions help students form more informed opinions about the specialty. Since instituting them, applications for

our pathology elective clerkship have increased over 500 percent, with month after month of at-capacity students and increasing rejections.

Because societal bias continues to drive talented students toward medicine’s most popular specialties, we must make heightened efforts to prevent individuals with a true, personal interest in pathology from slipping through the cracks. Pathologists should be aggressive in their early outreach efforts by countering the patient interaction argument, challenging students to think deeper about the differing roles of surgeons and pathologists in patient care, and highlighting the uniquely cerebral aspect of understanding and discovery not found in other specialties.

“The crux of the argument for pathology must focus not on defense of its criticisms, but rather on excitement about its uncommon advantages.”

The conflict between interest and bias requires the observer to challenge their understanding of choice itself. A student may become a surgeon, her choice of career resting on the assumption that she is the conscious source of her thoughts and actions, and that her experience of wanting to do surgery is what has caused her to select surgery as a specialty. But

external influence is ubiquitous in and outside of medicine. If one has never heard of the ruins of Angkor Wat, how could one possibly make a decision about traveling to Cambodia to see them? Similarly, if our student never really knew what pathologists do, how could she possibly have made the decision not to pursue pathology? In reality, we are not talking about dozens of students a year, but only a few. In each graduating medical school class, there can be no more than one or two students who pursue pathology, because – of course – residency spots are limited. More importantly, the aim should not be to increase this number; rather, we must make sure that, when ruling out pathology, all students are making an informed decision rather than acting on preconceived notions. Our wills are a combination of chance and determinism; they arrive from both coincidence and a long sequence of prior causes. It is our collective responsibility to prevent students passionate about discovery and understanding from making uninformed decisions just because they were unlucky enough not to be exposed to our amazing field. Understanding this truth matters, and it should change the way we view medical specialty choice.

Austin McHenry is a medical student and Past President of SCOPE at Loyola University Chicago Stritch School of Medicine. Follow him on Twitter @AustinMcHenry.

Kamran Mirza is Assistant Professor of Pathology and Laboratory Medicine and SCOPE faculty liaison at Loyola University Chicago Stritch School of Medicine, Maywood, USA. Follow him on Twitter @kmirza.

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A Tale of Two Countries

From Pakistan to the United Kingdom – a comparison of the guidance received by medical students along their career paths

By Ayesha Azam

The words “career guidance” hold different meaning for pathologists from dissimilar backgrounds. Those who are lucky think of mentors who introduced them to new opportunities, structured programs that helped them identify and explore their interests, and a system designed not only to welcome them into the world of pathology, but to help them grow and develop within it. Those less fortunate may have fewer associations with the phrase – or possibly none at all. Imagine the surprise when international medical graduates move to a country with a broad base of support for trainees and early-career pathologists. They begin to understand just how much help good

At a Glance

- *Areas with limited resources are often unable to provide extensive career support and guidance to medical students and trainees*
- *Without such support, early-career doctors may lack the information they need to choose and pursue appropriate specialties*
- *My own experiences in both developing and developed countries taught me the need for good career guidance*
- *To encourage aspiring doctors to explore pathology, we need to provide good information, structured support, and mentorship*



career guidance can provide. It’s an area in which I think many developing healthcare and medical education systems are lacking, and one in which I think we must start learning from one another, if we want to give our aspiring pathologists the tools they need to succeed.

A guiding hand

In Pakistan, medical students look for career guidance from their senior colleagues, friends, and fellow college students – in particular, “house officers” (equivalent to foundation doctors in UK) who have just graduated and started their first jobs. This person-to-person guidance is usually based on individual experience. Unfortunately, a significant proportion of medical students are not personally acquainted with any senior students or early-career doctors, so

they often lack the in-depth guidance so necessary to a successful medical career. For instance, those students might choose a specialty based solely on their personal likings – without any familiarity with, or any way of learning about, the details of a career in that specialty (such as working life, hours, exams, nature of the work, length of training, skill and knowledge required) until they are already committed.

Career support and guidance in the UK is very different. It is much more structured, and it begins at a very early stage – in secondary school, in fact. This guidance can take form of apprenticeship opportunities, local careers clubs at school, or nationwide science, technology, engineering and mathematics (STEM) activities offered by the government, charitable organizations, and private employers.

“A significant proportion of medical students are not acquainted with any senior students or early-career doctors, so they lack the in-depth guidance necessary to a successful medical career.”

UK medical schools have well-structured career departments, most of which offer guidance on 1:1 (mentee-mentor) basis, as group talks, and even via regular specialty career fairs. Each medical school also has specialty-specific societies known as forums, which help students obtain career-related information and support. These clubs have links with hospital-based trainees and consultants in their relevant specialties who can arrange “career tasters” or “job shadows” for students who want to learn more about a particular field. Students are encouraged to explore various specialties to gain insight into the practical aspects of each one and the differences between them.

Career support in Pakistan

The standard of medical education is very high in Pakistan – it provides a sound knowledge base to use as a jumping-off point. In terms of career support and guidance, though, it all depends on your

Recommended resources

<i>Who</i>	<i>What</i>	<i>Where</i>
Health Careers website	Extensive information about health careers	http://tp.txp.to/healthcareers/nhs
Careers tasters	Samples of careers in various specialties	Check with your local trust
National Careers Service	Web chat about career options and services	http://tp.txp.to/national/careers
Foundation tutors and career advisors	Personnel available in each hospital for guidance	Check with your local hospital
Deanery career support	Face-to-face 1:1 meetings and online assistance	Check with your deanery
Career planning tools and workshops	Many offered free by the NHS and Health Education England	Check with your local trust
Appraisals	Career planning considered a key element	Check with your local hospital

individual effort – or maybe your luck! My own interest in pathology began to develop very early in my medical schooling. I felt almost immediately that this was something I wanted to do... but, like many of my peers, I did not have access to any kind of career support network; there were no websites related to medical or pathology career options; there was no system in place to arrange a taster week to explore it further or to see the work-pattern of a pathologist. Soon after my graduation, I moved to the UK. It was only after going through a well-thought-out process of job tasters, aptitude tests and career guidance clubs in my new home that I finally joined pathology. Having such support during

my foundation training made a huge contribution to my career decisions, and I finally felt that I was truly making an informed career choice.

Using the UK system

If I could use one word to describe the career guidance system in the UK, it would be: outstanding.

I have found it extremely helpful to discuss my career planning with my supervisor for guidance. The National Health Service (NHS) offers career management workshops free to foundation doctors and medical students, which encourages you to consider the specialties that match your skills, personal abilities and strengths. Those weren't my

only resources, though; in fact, career planning was a mandatory element of my quarterly and annual appraisals. I was encouraged and given protected time to spend time in specialties of my choice to explore them further. I also went to local, regional, and national career fairs, which proved to be extremely useful. They were attended by representatives from each specialty who provided me with information on typical work, practical aspects, work pattern, competition ratios, exams, and essential prerequisites to apply. All extremely useful knowledge to have when selecting a career path to pursue for the rest of my life!

“If I could use one word to describe the career guidance system in the UK, it would be: outstanding.”

Giving back

After my experiences as a trainee in the UK, I decided that I wanted to help others the same way the system helped me. I took on an active mentoring role. For instance, I’ve developed informative resources like career posters and presentations to be used across the region; I’ve provided one-on-one career guidance to interested medical students; I’ve organized histopathology career stands at local, regional, and national career fairs – and the pathology section of the University of Birmingham’s Virtual Career Fair; I’ve presented exploratory workshops on

pathology as a STEM ambassador in local schools. I have also taken on some more formal roles to promote pathology as a career option – as regional lead trainee for careers in pathology and as Public Engagement Regional Coordinator with the Royal College of Pathologists.

Words to the wise

None of the platforms I’ve mentioned exist in Pakistan – and I think it’s likely that other developing countries lack those resources as well, despite huge demand and need. On a recent trip back to Pakistan, I conducted a workshop for careers in histopathology. Feedback and evaluations from the students revealed (unsurprisingly) that none of them had ever experienced a formal career guidance workshop before. Equally unsurprisingly, 100 percent of the participants were keen to have more career guidance in future.

I opted for the workshop format because that’s what I myself found particularly helpful. The workshops in which I participated in the UK gave me a stepwise approach to career decisions:

- self-assessment,
- explore your options,
- make your decision,
- apply and (hopefully) interview.

Our future doctors need a structured career guidance platform. We need to organize career fairs and provide formal career guidance and support (even if only from a distance) to medical students in developing countries so that they can make the same kinds of informed career choices as their peers in other places. This will result in increased job satisfaction, enhanced performance, and – ultimately – better patient care.

My advice to medical students in developing countries is to start their information-seeking journeys at the earliest possible stage of their careers. Without a structured system in place,

students may have to seek (or even create) their own guidance by using online resources for self-assessment and contacting specialists themselves to arrange job shadow or career taster sessions. And, once those students have become seasoned doctors with ample experience, I hope that they will turn around and provide future medical students with the opportunity to explore specialties in detail before making career choices.

“My advice to medical students in developing countries is to start their information-seeking journeys at the earliest possible stage of their careers.”

I have experienced the striking differences between the UK and Pakistani career support systems, and I understand how it feels to practice where resources are limited. Providing guidance and support to our newest colleagues is our responsibility to help future generations of doctors.

Ayesha Azam is a post-fellowship senior registrar in cellular pathology, based in the UK. Her areas of interest include dermatopathology, computational pathology, science communication, and medical education.

A close-up portrait of Sarah Coupland, a woman with short, light-colored hair, smiling warmly. She is wearing a light-colored top with a decorative, sequined neckline. The background is softly blurred, showing what appears to be a laboratory or office setting with shelves and equipment.

A Vision for Pathology

Sitting Down With... Sarah Coupland, Professor and George Holt Chair of Pathology at the University of Liverpool and Honorary Consultant Histopathologist at Royal Liverpool and Broadgreen University Hospitals NHS Trust, UK.

What inspired you to enter (ophthalmic) pathology?

My father was a medical oncologist and my mother was a nurse, so I grew up with “medical speak” over the dinner table – it became second nature to me. After graduating from medicine in Sydney, I moved to Berlin and began a PhD in ophthalmology. I examined the immune mechanisms involved in corneal rejection, which meant performing corneal transplants in rats followed by histological and immunohistological examination of their eyes. And that’s how I rediscovered my enthusiasm for the morphological understanding of disease mechanisms.

After completing my PhD, I did a three-month elective with William Lee in Glasgow – a period during which I finally made the decision to specialize in histopathology. I then spent seven years training in general pathology with Harald Stein at the Charité Benjamin Franklin – at that time a referral center for lymphomas, head and neck surgery and ophthalmic tumors – and emerged with a number of pathology subspecialties under my belt.

You make it sound straightforward, but there were a few “bumps in the road”... I’ve not encountered what I would consider true adversity, but I have experienced a number of challenges along the way. Learning German in my mid-twenties to a sufficient standard to work as a pathologist, write complicated medical reports, and teach students was particularly demanding. To complicate things further, human anatomy in the German medical system is still described in Latin, so I had to learn that as well!

The most dramatic (and literal) bump in the road was my pregnancy with triplets near the end of my pathology training. Unfortunately, my contract was due to end during my maternity leave, and there was a strong prevailing

opinion that I was unlikely to return to work – so there was considerable doubt that I would have a job to return to at all! Luckily, I was able to organize a phased return to work. I completed my training two years after the children’s birth (despite the complication of HELLP syndrome, which put us all in intensive care for a few weeks!) and then submitted my Associate Professor thesis, becoming the first female “Privat Dozent” from the Stein lab.

What is unique about ophthalmic pathology?

As an ophthalmic pathologist concentrating on ocular oncology, I interact closely with clinical teams. Ophthalmological diagnoses are very reliant on morphology and images. The beauty of the eye – and the surrounding structures – is the ability to see many pathologies in situ in the patient, which can allow for easier interpretation of the samples. That being said, many cases are difficult because the samples are tiny! For example, intraocular biopsies of the choroid or vitreous can be very demanding; one is expected to squeeze out as much information as possible: morphology, immunophenotype, and genotype.

My favorite aspect of the work is making a difficult diagnosis in a timely manner to improve a patient’s outcome. The typical scenario would be a vitreous biopsy for suspected vitreoretinal lymphoma. These are notorious for the fragility of the tumor cells and the relatively high rate of non-diagnostic samples. By working closely with the vitreoretinal surgeons, we have been able to make recommendations with respect to how the sample is taken, transported, and processed in the lab to improve the diagnostic yield. And that is essential because vitreoretinal lymphomas are high-grade tumors where diagnostic delays must be avoided.

How are advances in fields like molecular pathology influencing your work?

My training in hematopathology has meant that I have always incorporated molecular pathology into my diagnoses. I co-founded our Hemato-Oncology Diagnostics Service (HODS) here in Liverpool, and also established the Royal Liverpool University Hospital’s molecular pathology laboratory. I no longer lead HODS or the lab, but am actively involved in national molecular pathology initiatives.

Molecular pathology is a broad and rapidly developing field; it is not essential in all cases, but is often integral for diagnostic, predictive or prognostic purposes. The new generation of pathologists must be trained in the available tests, as well as the strengths and weaknesses of the differing molecular pathology platforms and how to integrate and interpret the results. Unfortunately, parts of the UK are really behind the curve in this area. Molecular pathology is not the future; it is already here and should be widely available.

If you could change one aspect of your field, what would it be?

I was taught that the pillars in the understanding of medicine are the “three Ps”: pathology, physiology and pharmacology. If we are to make progress in the understanding of the pathogenesis, prevention and treatment of disease, we have to invest in these cornerstones of scientific medicine. Academic pathology is one of the most fragile subspecialties in medicine at present, and we have to increase awareness of its importance and create initiatives to make it attractive and prevent its complete disappearance.

If you could go back in time to give yourself some advice, what would you say?

Pick your battles. Don’t waste time on things that take you away from science. And don’t spend too much time writing long emails!

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