NOVEMBER 2018 # 48

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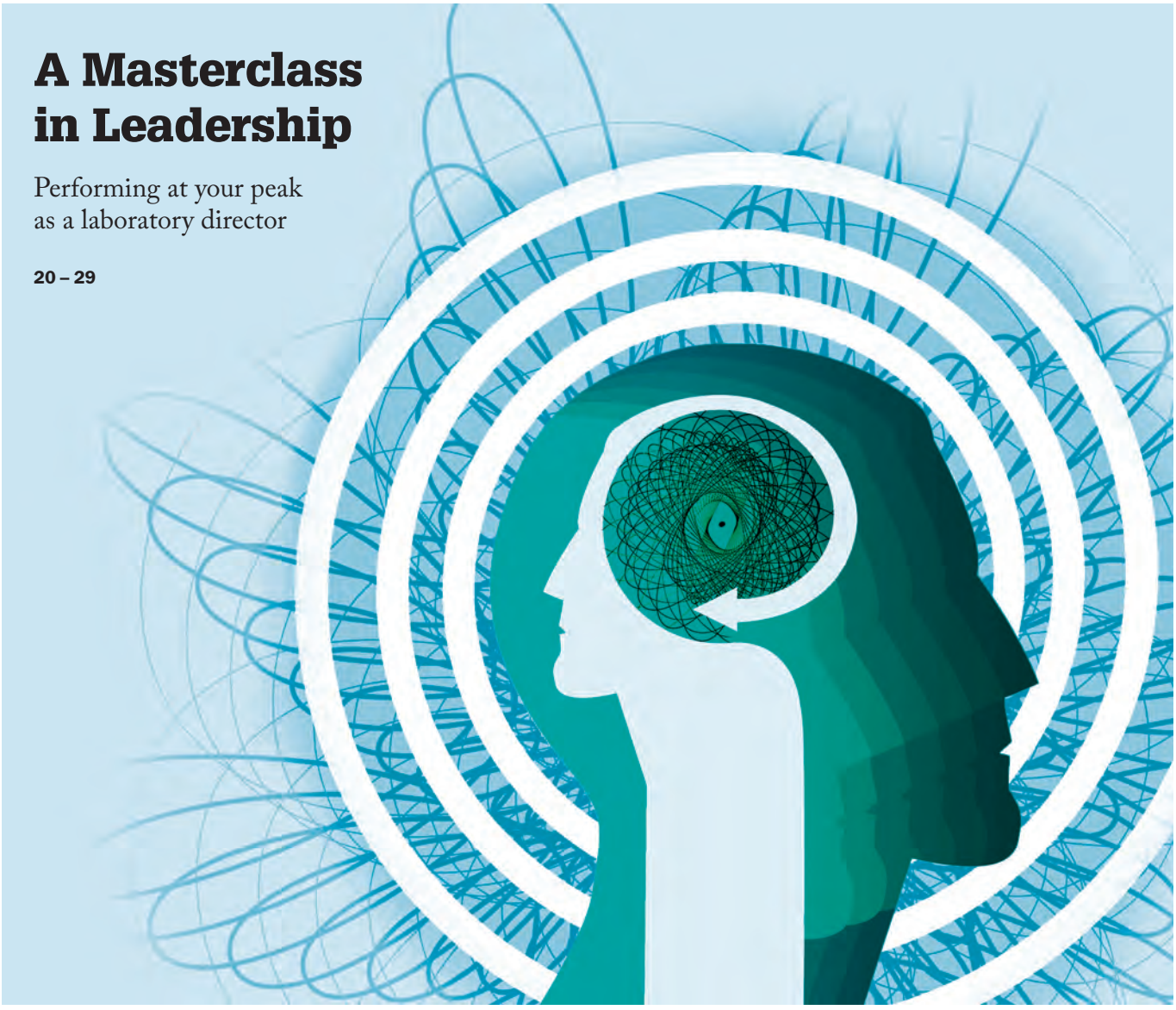


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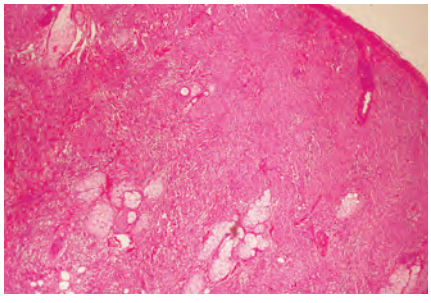
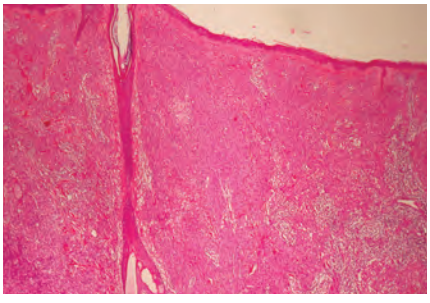
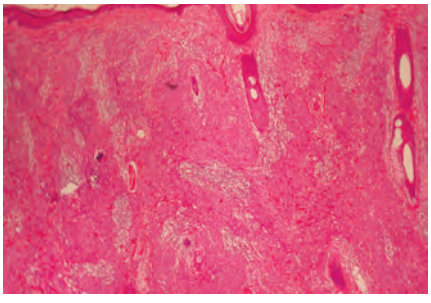
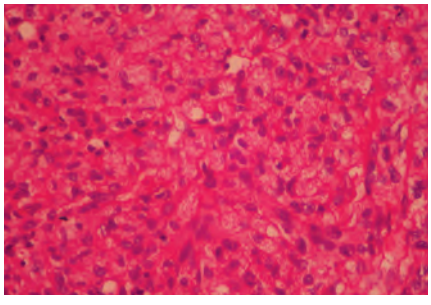
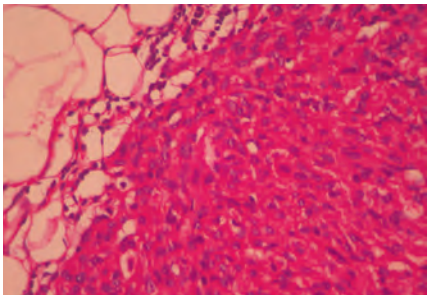
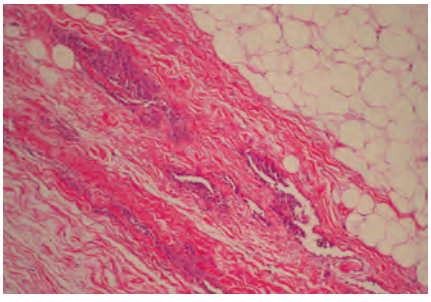
Case of the Month

A 73-year-old female presented with an oval lesion of the scalp measuring 16x12x0.7 cm. The surgeon was able to completely remove the tumor and provide the patient with a perfect skin graft.

What is your diagnosis?

A *Granular cell tumor*

B *Epithelioid angiosarcoma*

C *Granular cell schwannoma*

D *Granular cell angiosarcoma*

Answer to last issue's Case of the Month…

C. Glomangioma

Glomangioma, also known as glomovenous malformation, is a histologic variant of glomus tumor. It is composed of typical glomus cells arranged around cavernous hemangioma-like blood vessels. Most glomus tumors are solitary and benign, although in some cases they may be multiple and even malignant (1).

Reference

1. *AL Folpe et al., "Glomus tumours", World Health Organization Classification of Tumours of Soft Tissue and Bone, International Agency for Research on Cancer: 2013.*

Submitted by Ivan Damjanov, Professor of Pathology at the University of Kansas School of Medicine, Kansas City, USA.

To register your guess, please go to http://tp.txp.to/1118/case-of-the-month
We will reveal the answer in next month's issue!

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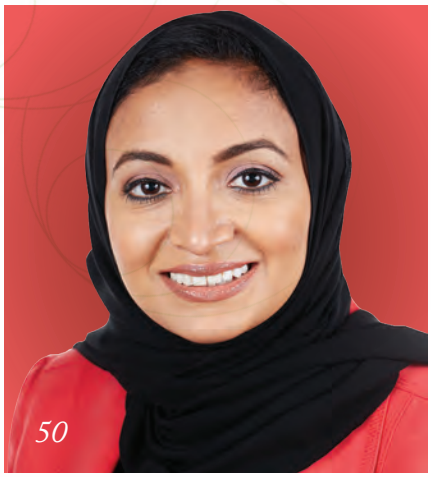
On The Cover

An artist's representation of the many different skills required to be the best possible lab director.



Report

Feature

In Practice

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Sitting Down With

the Pathologist

ISSUE 48 – NOVEMBER 2018

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Distribution:
The Pathologist (ISSN 2055-8228), is published monthly by Texere Publishing Limited, Booths Park 1, Chelford Road, Knutsford, Cheshire, WA16 8GS, UK
Single copy sales £15 (plus postage, cost available on request info@texerepublishing.com)
Non-qualified annual subscription cost is £110 plus postage

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Choosing Wisely®

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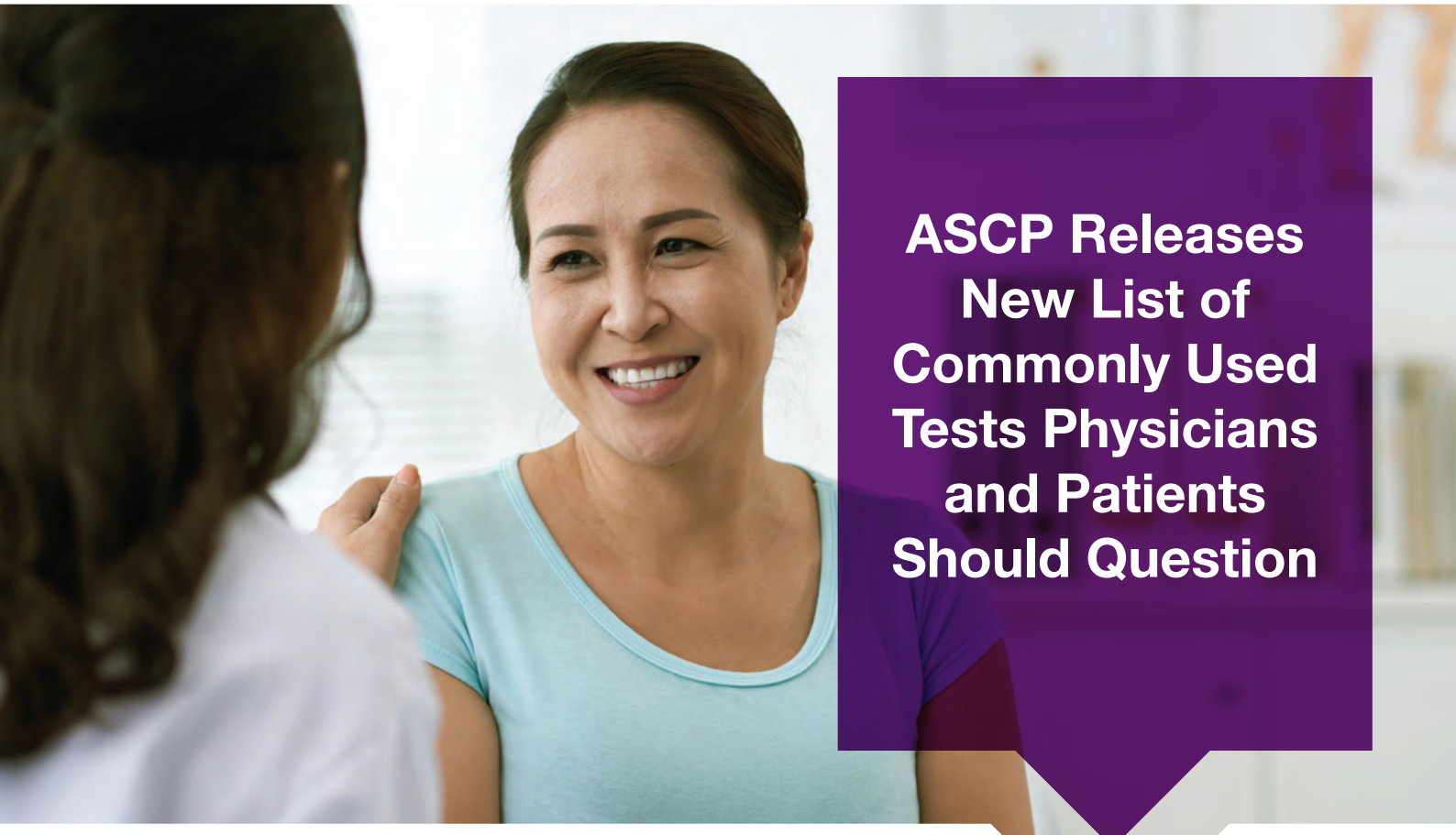


ASCP Releases New List of Commonly Used Tests Physicians and Patients Should Question

ASCP has released a new list of recommendations for laboratory tests that are commonly ordered but not always appropriate in pathology and laboratory medicine as part of the *Choosing Wisely* campaign, an initiative of the ABIM Foundation. The new list of five targeted, evidence-based recommendations expands ASCP's existing list to 25 recommendations and is designed to support conversations between patients and physicians about what care is really necessary.

Learn more at
www.ascp.org/choosingwisely

The Missing Act

We love to celebrate science with the public – so why don't more events include laboratory medicine?

As some of you know, The Pathologist is headquartered near Manchester, England – a city that hosted its 12th annual science festival in October. As always, I perused the program, selected far too many events, and then attended as many as I could. I heard (and saw) a synesthetic concert that used technology to render the music of a string quartet as colored light. I visited a pop-up museum of natural and medical curiosities from science past and present (some of which you may have seen on Twitter). I simulated an electric storm, mined blockchain currency, pedal-powered a blender to make myself a smoothie, and even pitted household appliances against one another in a battle royale.

But no matter how hard I scrutinized the schedule, I couldn't find anything showcasing the hard work that goes on in biomedical research and clinical laboratories. Where was the insight into today's disease research? The diagnosis and treatment of cancer, dementia, and other maladies that touch almost every life either directly or indirectly? Where was the awareness of the essential role of laboratory professionals?

Some might protest that the event was squarely aimed at children and families. But that's exactly my point – if we aren't telling current and future patients about pathology and laboratory medicine, how can we expect them to know who lies behind their diagnosis? If laboratorians don't have the opportunity to introduce themselves to their future colleagues early, how can we be surprised when they choose a different career path?

Luckily, the story doesn't end here. The annual science festival – as its name suggests – will be back again next year, and the year after that, and the year after that… Hopefully, those future festivals will make room for laboratory medicine – and its practitioners will take up the challenge and introduce their discipline to a new generation of potential pathologists and laboratory medicine professionals.

Are you involved in outreach and engagement activities? Do you work with the general public to further their understanding of pathology? Tell us about your work (edit@thepathologist.com) – we'd love to help spread the word about your efforts!

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

Characterizing Cancer

Can digital spatial profiling technology enhance therapeutic strategies for cancer patients?

What is the goal of our ongoing quest to discover new biomarkers for cancer therapy? Collectively, we want to improve personalized therapy for our patients. It may sound straightforward, but for oncologists trying to unravel the complexities of patients' tumors, heterogeneity presents a challenge. Tumor cells often behave differently depending on their location, which means that a single tissue sample may contain several cell types, making interpretation complicated. Worse yet, some cell types may not be present in the sample at all – meaning that a personalized treatment strategy might not tackle a patient's entire tumor.

Digital spatial profiling (DSP), a novel barcoding approach, aims to address some of these issues by extracting more data from a single tissue sample, potentially overcoming a consistent limiting factor in tumor analysis. "The high plex capabilities of DSP technology enabled us to interrogate many more potential biomarkers than would have been possible on these very small tissue biopsies with standard or multiplexed immunohistochemistry approaches," says Christian Blank of the Netherlands Cancer Institute. Blank used the technology to investigate how the pre-existing immune status of stage III melanoma predicts treatment response (1).

DSP can profile targets up to their thousands with a high level of precision. The technology has already successfully identified several protein markers that are thought to be involved in predicting response to treatment (1,2), and although it has only been used for one type of cancer so far, there are plans to apply the technique to other cancers to discover further biomarkers that could be crucial for treatment. Jennifer Wargo of MD Anderson Cancer Center, for instance, is using DSP to quantify protein expression in tumor-infiltrating immune cells before and during treatment (2). "With DSP technology, we were able to discover that both presence of particular immune cell populations and their activation status may be predictive of clinical benefit to this therapy," she says.

Although DSP is still a novel concept, its results in research are promising. The high sample throughput and multiplexing capacity is scaled to support large-scale clinical trials but, ultimately, it could help pathologists and oncologists characterize individual tumors more fully to identify the best possible treatment for each patient.

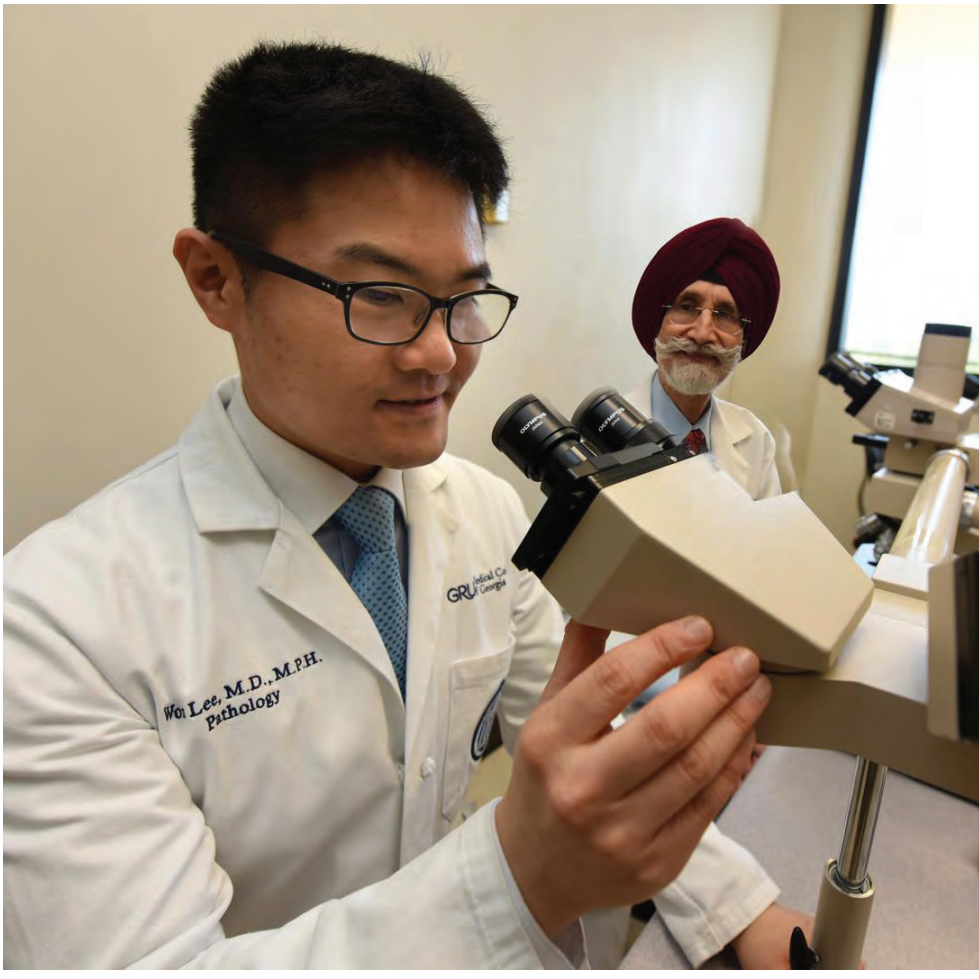
Reference

1. *CU Blank et al., "Neoadjuvant versus adjuvant ipilimumab plus nivolumab in macroscopic stage III melanoma", Nat Med, [Epub ahead of print] (2018). PMID: 30297911.*
2. *RN Amaria et al., "Neoadjuvant immune checkpoint blockade in high-risk resectable melanoma", Nat Med, [Epub ahead of print] (2018). PMID: 30297909.*

Credit: Phil Jones, Senior Photographer, Augusta University

An Untrustworthy Myeloma Assay?

Gurmukh Singh warns of inaccuracies in the serum free light chain assay



Even for blood cancers, the answer to diagnostic puzzles can be hidden elsewhere. Myeloma, a cancer of the plasma cells, is one such example. The serum free light chain assay (SFLCA) has a one-in-four chance of missing the signs of disease; other assays – such as serum protein electrophoresis (SPEP) and serum immunofixation electrophoresis (SIFE) – are more reliable, but equally invasive. Plus, they are less likely to be ordered if clinicians have faith in the newer SFLCA test. The solution? A simple, noninvasive legacy test that examines the urine for signs of disease.

Gurmukh Singh, Vice Chair of Clinical Affairs for the Department of Pathology at the Medical College of Georgia at Augusta University, explains: "During regular examinations of the data generally used in diagnosis and monitoring of multiple myeloma (and other monoclonal gammopathies) from patients being treated at Medical College of Georgia, I noticed disparities in the findings from protein electrophoresis results and SFLCA." The International Myeloma Working Group recognizes SPEP and SIFE as the gold standards for diagnosing myeloma, so the discrepancies between those tests and the SFLCA results prompted Singh and his colleagues to perform a retrospective analysis of the data (1).

Singh warns that SFLCA assay results are unreliable for diagnosis of myeloma and other monoclonal gammopathies. "In patients without monoclonal gammopathies, about 36 percent have an abnormal SFLCA result – and about 30 percent of patients with myeloma have a normal SFLCA." This false negative rate is even higher in lambda chain-associated myelomas and monoclonal gammopathies. "The need for a normal kappa/lambda ratio to qualify for stringent complete response introduces errors due to the frequent occurrence of oligoclonal patterns in patients treated with stem cell transplantation," Singh says. "The oligoclonal pattern often produces a false-positive, kappa-dominant abnormal kappa/lambda ratio."

He and his colleagues believe that the marked disparities in the SFLCA results in intact immunoglobulin myelomas warrant a re-examination of the criteria for definitive diagnosis of myeloma. Fortunately, noninvasive diagnostic options remain; Singh – an enthusiastic advocate for clinically useful tests and the curtailing of less-than-useful ones – has proposed that all SPEP orders at his institution also receive urine protein electrophoresis and immunoelectrophoresis (UPEP/UIFE) testing.

Reference

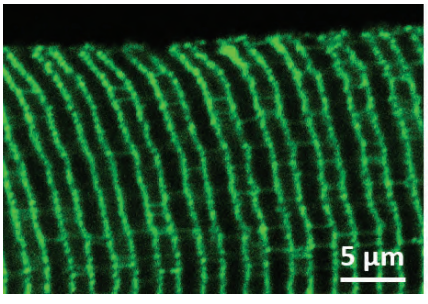
1. *WS Lee, G Singh, "Serum free light chains in neoplastic monoclonal gammopathies: relative under-detection of lambda dominant kappa/lambda ratio, and underproduction of free lambda light chains, as compared to kappa light chains, in patients with neoplastic monoclonal gammopathies", J Clin Med Res, 10, 562–569 (2018). PMID: 29904440.*

Muscling in on Malignant Hyperthermia

Bradley Launikonis describes a needle biopsy approach to diagnosing the dangerous condition

Major surgery is a nerve-racking experience under the best of conditions – but it's even more so for patients at risk of malignant hyperthermia (MH), a genetic disorder in which anesthetics can cause the muscles to go rigid and produce excessive heat – sometimes even leading to the patient's death. Although rare, MH is challenging to diagnose because genetic tests are reliable in only about half of cases; in the other half, painful and invasive muscle biopsies are the only way to be sure. The need for a more informative, less invasive test is clear.

My lab is interested in calcium regulation and excitation-contraction coupling in skeletal muscle, which is why studying how the ryanodine receptor (RyR) regulates this process is of high interest to us. To study these aspects of skeletal muscle physiology, we use single muscle fibers, which we mechanically "skin" by peeling away the outer plasma membrane with fine forceps to access the cytoplasmic components. In the last few years, we have moved our approaches – developed in rodent muscle – to human muscle obtained from needle biopsies. After we refined our approaches, we realized we could detect the activity of the RyR in resting muscle. These calcium movements are tiny compared with those in contracting muscle. Armed with this knowledge, we began to seek subjects with MH susceptibility. We expected to be able to observe differences in calcium handling compared with control subjects (1).



The plasma membrane of skeletal muscle has regular invaginations into the fiber to support the spread of action potentials that excite the fiber for contraction-regulating calcium release. This invagination – known as the tubular system, or t-system – ensures that the electrical signal spreads quickly throughout the cell despite the fiber's large diameter. The t-system allows us to create a unique experiment: we bathe an intact fiber in a calcium-sensitive dye, allowing it to diffuse into the t-system, then skin the fiber. This causes each of the tubules to seal off where they were connected to the surface. Because the t-system is adjacent to the RyRs, we can detect the activity of the RyRs with the high-affinity calcium pumps on the t-system membrane. How? The calcium flowing through the RyRs is pumped in to the t-system, where the pumps pick up tiny changes in the local calcium environment. The system has a small volume, giving it high sensitivity to concentration changes with only a small movement of calcium across its membrane, and it is sensitive enough to detect differences in the RyR activity of resting muscle in control and MH-susceptible RyR mutants.

This approach also allowed us to describe the movements of calcium across the t-system membrane and show how this membrane adapts to the leakier RyRs of MH-susceptible muscle.

At the moment, we are trying to develop diagnostic methods for MH using skinned fibers from needle biopsies. These techniques are likely to involve the use of a calcium indicator placed in the cytoplasmic solution that bathes the skinned fiber – a simpler approach than the dye-trapping technique. We know there is a lot of work ahead to validate any new technique, but we will continue to work on the diagnostic potential of skinned fibers from needle biopsies. Additionally, we are interested in the fundamentals of how resting muscle handles calcium – which changes significantly with mutations of the calcium-handling proteins, and with lifestyle (inactivity or heavy athletic training). There is a lot to learn, with many potential applications in medicine.

Reference

1. *TR Cully et al., "Junctional membrane Ca2+ dynamics in human muscle fibers are altered by malignant hyperthermia causative RyR mutation", Proc Natl Acad Sci USA, 115, 8215–8220 (2018). PMID: 30038012.*

Gone Fishing

A magnetic wire inserted into a vein captures circulating tumor cells and cell-free tumor DNA

Credit: Sam Gambhir

Blood biomarkers for cancer are often present only in low concentrations. But how can you interrogate the entire contents of an adult's circulatory system to ensure you've captured what you need? Sanjiv "Sam" Gambhir and his colleagues at the Canary Center at Stanford for Cancer Early Detection have developed a unique approach: an injection of magnetic nanoparticles designed to bind circulating tumor cells, combined with a thin, magnetic wire that captures them directly from the vein.

What prompted you to investigate in vivo tumor cell retrieval?

We were trying to develop a strategy that goes after rare biomarkers (such as circulating tumor cells or cell-free tumor DNA) in blood. When shed by small tumors, these markers are rare – and that poses a diagnostic and monitoring problem. To capture them, we needed a strategy to sample the entire blood volume. If you remove a few vials at about 7 mL of blood each, you may get lucky and spot rare biomarkers – but you won't see much of them. We needed a way to sample the entire five-liter blood volume of an adult. That's why we came up with inserting a magnetic wire into the patient and leaving it in for about 20 minutes to collect rare biomarkers.

What inspired this magnetic "cancer cell catcher?"

I knew that we needed a totally new approach to find biomarkers that are present at very low concentrations (if at all). I originally thought we might need an external magnet to make the idea work, but we ended up being able to do it with tiny 1 mm magnets strung together to form a 60 mm magnetic wire.

How would the new technique fit into the clinic?

Initially, I expect it to be useful in patients at high risk of cancer, who are tested every six to 12 months for rare biomarkers so that disease can be spotted early. It could also be used to remove circulating tumor cells from blood to reduce the likelihood of metastasis, or in non-cancer applications such as capturing bacteria in the blood.

The technique won't be much more expensive than a standard blood draw, but the injection of magnetic nanoparticles will increase the cost. It will also require the wire to be left in for 20 minutes and then withdrawn, which may be stressful for the patient – although hopefully less so than the risk of cancer.

What's next for your lab?

We continue to work on novel strategies for the early detection of cancer. Right now, we are working on a "smart toilet" to routinely sample biomarkers in stool and urine. We are also working on the molecular imaging of cancer so that, after a biomarker test reveals that a patient may have early disease, we can detect its location in the body.

Reference

1. O Vermesh et al., "An intravascular magnetic wire for the high-throughput retrieval of circulating tumour cells in vivo", Nat Biomed Eng, 2, 696–705 (2018).

OK Google: Scan This Slide

An algorithm trained to detect breast cancer tumors could be used as a "spell check" for pathologists

Google is the most frequently used search engine around the world – but what if its power of investigation could be used to search for tumors? The artificial intelligence (AI) team at Google have taken a step toward realizing this ambition by developing an algorithm that could act as a "spell check" for pathologists. Known as LYmph Node Assistant (LYNA), the tool can scan digital images of breast cancer patients' lymph nodes to detect how much of the cancer has spread beyond the breasts. Yun Liu of the Google AI team hopes that the method will allow pathologists to work more efficiently and accurately.

"We trained the algorithm to identify metastatic breast cancer in lymph node specimens. As it saw more and more examples, the algorithm gradually learned to distinguish tumor from non-tumor, to the point where it is more than 99 percent accurate on image patches," Liu says. This figure should be interpreted with a degree of caution, because – although it refers to the ability to identify whether or not an image contains cancer – most of the lymph node images shown to the algorithm did not contain cancer. Despite this, the algorithm was able to detect the exact location of 91 percent of tumors from the CAMELYON dataset (when allowed one false negative per slide). Considering that a pathologist detected 72 percent of tumor foci in the same 130 slides over a 30-hour period, the algorithm's accuracy is striking.

When LYNA was tested with pathologists to digitally review lymph node slides, the team found that those given the tool performed better than either the algorithm or the pathologists alone. Liu underlines these encouraging results. "The algorithm halved the time taken to review micrometastasis from about two minutes to one minute per slide, and also improved the micrometastasis detection sensitivity from 83 to 91 percent." In addition, pathologists reported that cases became easier to review with LYNA's help, offering hope that the algorithm could be used to assist overworked pathologists.

"Our ambition is to reduce the amount of time it takes to complete tedious tasks and improve accuracy when detecting lesions that are easy to miss," Liu continues. "We hope that technologies such as this will free up pathologists to focus on the more complex, challenging, or rare cases." The AI team at Google hope to see future work focusing on human-model interaction and are currently investigating the benefits and pitfalls associated with their algorithm's use in clinical workflows.

References

1. *Y Liu et al., "Artificial intelligence-based breast cancer nodal metastasis detection", Arch Pathol Lab Med, [Epub ahead of print] (2018). PMID: 30295070.*
2. *DF Steiner et al., "Impact of deep learning assistance on the histopathologic review of lymph nodes for setastatic breast cancer", Am J Surg Pathol, [Epub ahead of print] (2018). PMID: 30312179.*

Pre-Empting Relapse

Detecting treatment-resistant mutations associated with leukemia relapse is key to pre-emptive intervention

Acute myeloid leukemia (AML) is the most common type of blood cancer in adults. Starting suddenly and progressing rapidly, even those who achieve remission can't breathe easy; as many as one-third of patients who receive chemotherapy and a bone marrow transplant will relapse within three to six months. Unfortunately, transplantation is the only curative treatment for AML, so patients who relapse are left with few options.

Zhaolei Zhang, Principal Investigator in the University of Toronto's Donnelly Centre for Cellular and Biomolecular Research, believes a new DNA-based technique will improve the long-term survival of AML patients by predicting relapse after treatment. Using next generation sequencing (NGS), the test can detect mutations in the bone marrow that indicate the presence of treatment-resistant cancer cells. Although chemotherapy eliminates most of these leukemia cells, some persist after the patient has received a bone marrow transplant. The test can detect these mutations in the bone marrow three weeks after transplant, indicating that the cancer will likely return. "The early detection of actionable mutations after transplantation will increase the number of targeted therapeutic interventions available before relapse occurs, improving survival chances," Zhang says.

"After 21 days post-transplantation, we observed that close to 60 percent of patients with these treatment-resistant mutations relapsed, whereas only around 15 percent of those without the mutations relapsed," continues Zhang. Until now, the high cost of NGS assays made the analysis of such large amounts of generated data a challenge. However, technological advances and the development of sophisticated computational methods have made NGS assay analysis feasible. Zhang's team hope to replicate the observations of their study in multiple hospital sites and with larger cohorts before eventually getting regulatory approval for the test's use in clinics.

Reference

1. *T Kim et al., "Next-generation sequencing based post-transplant monitoring of acute myeloid leukemia", Blood, [Epub ahead of print] (2018). PMID: 30108064.*

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

Leading the Pack

The case for pathologist-driven diagnostic management teams

By Marisa Saint Martin, Assistant Professor of Pathology at Loyola University Medical School, Maywood, and Laboratory Medical Director at Gottlieb Memorial Hospital, Melrose Park, USA

Pathologists are at the forefront of diagnostic developments, helping clinicians and surgeons make the best out of the cornucopia of laboratory information. Pathologists are to clinicians and surgeons what diagnoses are to healing.

Clinical pathology consultations have happened informally for as long as laboratorians and anatomic pathologists have been in the business of diagnosing disease. However, Michael Laposata of the University of Texas Medical Branch has shone a different light on these consultations – and on pathology as a whole. He coined the term "diagnostic management team" (DMT) and, with it, sparked conversations across the nation about the clinical consultations we provide. DMTs consist of multidisciplinary/multi-specialty diagnostic experts who consult together to drive the diagnostic and treatment decision-making process. The DMT operation takes place in real time; the information the team extracts is uploaded to the medical record as a consultative report, resulting in clinically valuable information.

According to the literature (1), when clinical doctors order or receive results from complicated and multidimensional laboratory tests and don't know how to interpret or use the information, they may i) go back and review the patient's history, ii) research online, iii) order more tests, or iv) order the same test again. Very few clinicians take advantage of the expertise of those providing the test results: the laboratorians and the pathologists. More than 50 percent of all patients receive inappropriate, poor-quality, or cost-ineffective care due to under- or over-utilization of laboratory testing (2,3).

By issuing a comprehensive, integrated laboratory medicine consultation, DMTs can be a highly effective tool that improves patient care in real time. The overall goals of the DMT are to:

- decrease time to diagnosis,
- increase accuracy,
- optimize laboratory test utilization,
- increase communication among pathologists and clinical colleagues,
- increase colleague satisfaction,
- improve patient satisfaction and care, and
- decrease burnout.

"Pathologists are to clinicians and surgeons what diagnoses are to healing."

"By issuing a comprehensive, integrated laboratory medicine consultation, DMTs can be a highly effective tool."

When a complex test elicits myriad questions that may lead to confusion or additional testing before a therapeutic decision can be made, a DMT consult may be ordered. When that happens, the team meet (virtually or in person) to provide a written consultation note in the patient's chart that will be of diagnostic value to the clinical team and other consultants. Even though the pathologist will likely lead the DMT and write the consultation in the patient's chart, other members of the team may include expert diagnosticians, PhDs, clinicians, coders, IT experts, pharmacists, laboratory technologists and scientists, and residents and trainees. Depending on the case, even patients may be involved in the decision-making process that shapes their care.

At Loyola and Gottlieb, we are working to launch our first DMT in transfusion medicine, with the help of the Epic/IT team responsible for changes and improvements to our systems and the support of CMOs, CEOs, and our clinical colleagues. Once we have the transfusion DMT running smoothly and can assess the collaborative process and the possible obstacles and communication gaps we may face, we plan to expand to other areas where having a team of expert diagnosticians would aid and expedite diagnosis, therapy, and healing. Molecular testing, coagulation, renal pathology, and transplant pathology are examples of future DMTs we may develop.

To quote Michael Laposata on how DMTs work (4): "The front end of the process is assistance in selecting the correct tests." Here, pathologists may share their expertise by creating algorithms that assist with utilization management and reflex testing, ensuring that patients receive all of – and only – the appropriate tests. "The back end of the process is the generation of the expert-driven, patient-specific interpretation of the test results in a specific clinical context. This requires the knowledge of a true expert – not someone who may have a general idea about the meaning of a particular laboratory test result – and the participation of someone to help that expert search the medical record for relevant data to be included in the interpretation." And that's exactly what we hope to achieve by implementing DMTs at Loyola University Medical Center and Gottlieb Memorial Hospital: the expert input of a pathologist at every stage of the testing process, along with the support of other health care professionals who contribute to the best outcome for every patient.

References

1. *J Hickner et al., "Primary care physicians' challenges in ordering clinical laboratory tests and interpreting results", J Am Board Fam Med, 27, 268–274 (2014). PMID: 24610189.*
2. *JR Taylor, "A disconnect between physicians and laboratory professionals" (2016). Available at: https://bit.ly/2DuGJ6U. Accessed September 25, 2018.*
3. *M Laposata, "The definition and scope of diagnostic error in the US and how diagnostic error is enabled", J Appl Lab Med, 3, 128 (2018).*
4. *M Laposata, "The what and why of diagnostic management teams" (2017). Available at: https://bit.ly/2xOsLqr. Accessed September 25, 2018.*

Pathologists Versus AI

When it comes to new technology, shouldn't we be thinking in terms of collaboration rather than competition?

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

An automated artificial intelligence (AI) system for pathology that achieves a performance of 90 percent may appear to outperform human pathologists. But the conditions aren't quite the same, so "pathologist versus AI" may not really be the right comparison. Instead, we

"Pathologist versus AI' may not really be the right comparison. Instead, we may want humans and computers to work together."

may want humans and computers to work together, each performing to their own strengths.

Manual microscopy is the standard of care and current practice in pathology. Notably, microscopes are not FDA-cleared medical devices (because they pre-date the FDA); different microscopes have different optics and even light sources; and the microscopes in use are often not properly calibrated – so the human pathologist is starting off on the back foot. Now, we are asking those pathologists to assess 500,000–1,000,000 cells that can have considerable heterogeneity across a slide – and then to reduce that information to a single diagnosis or summary score. For example, in the case of a very simple immunohistochemical scoring, we ask the pathologist to determine the percentage of cells (to be evaluated against a threshold, for example, >10 percent) of a certain cell type (for example, tumor cells) that have staining (for example, DAB that can be collocated with hematoxylin) in a certain cell compartment (for example, the nucleus) that is above an absolute threshold – a very challenging computational task. And it seems obvious that it will lead to high inter- and intra-pathologist variation.

Furthermore, immuno-oncology, one of the major advances in drug development in recent years, now requires the pathologist to deal with even more stains, look at tissue context, and apply more complex scoring schemes. The level of analysis required is becoming impossible for a pathologist using just a microscope. A computer, on the other hand, would complete many of these tasks with little difficulty. With the increasing adoption of digital pathology, which enables computers to analyze images of histology slides, it's time to replace the microscope with more fitting tools.

And the most fitting tool for pathologists is a pathology AI system that uses machine learning for cell classification, where pathologists provide the tissue expertise (identifying different cell types and verifying proper classification), and computers tackle the computational tasks of counting cells, calculating objective measurements, and complex scoring.

Rather than going "all in" with an automated AI system intended to replace humans altogether, the use of AI as an aid allows pathologists to provide high-performance, high-complexity tissue analysis. Automated AI systems will have a hard time increasing their performance to 95 or even 99 percent – the minimum achievement necessary to be considered a "replacement" for a pathology AI system where both humans and computers work together.

The key problem for automated AI systems in pathology is the variation between samples. No two examples of a disease look the same – even in similar patients under similar conditions. Human pathologists know that the same cell type can have different characteristics in different patients, to the point where one patient's healthy cells can appear similar to another's tumor cells. An AI system would have tremendous difficulty with this concept and require exponentially more training data to become familiar with all of the potential disease presentations, especially in exceptional cases that a human might pick out by applying "common sense" rather than hard-and-fast rules.

The best way, and in our opinion the only viable way, to create enough training data for such systems (at a reasonable price point) is to have the training data automatically generated as part of the standard clinical workflow. The perfect intermediate step between manual microscopy and automated AI is to provide pathologists with the right tools – that is, a pathology AI system that, as part of its normal workflow, generates an abundance of free training data (pathologist-verified cell classification for the whole slide for all slides) that can be used to train a fully automated system. As that system's performance improves, it becomes obvious when it's "ready" – for deployment and, eventually, for commercialization.

Let's provide pathologists with the right tools – by replacing the microscope, not the pathologists.

"The use of AI as an aid allows pathologists to provide high-performance, high-complexity tissue analysis."

Leadership Is an Opportunity and Our Obligation

It's up to us to drive positive, innovative change for laboratory medicine

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

Pathology has always been at the forefront of medicine. The scientific methods we use to discern the causes of diseases have a history that stretches as far back as the Middle East during the Islam Golden Age and Europe during the Italian Renaissance. From the earliest autopsies to microscopic pathology in the mid-1800s to the first infectious disease investigators in the early 1900s, the men and women who study disease have dictated the direction of medicine.

Although the study of diseases had existed for hundreds of years, until the early 20th century, it was essentially an autopsy-based, theoretical academic subject taught in medical schools. The flu epidemic of 1918, was, in practical terms, the birth of modern pathology in the United States. While the epidemic ravaged the world, pathologists and laboratory professionals worked to find the cause of the disease. It took these medical detectives a few years to settle on a viral cause for the epidemic – but along the way, they discovered a battery of novel diagnostic techniques, such as the creation of chocolate agar to aid the recovery of fastidious bacterial organisms.

The leadership that pathologists displayed during the flu epidemic is evident in the early history of the American Society of Clinical Pathology (ASCP). Fueled by a desire to legitimize the burgeoning field of hospital-based clinical pathology as well as to improve its practice, Philip Hillkowitz and Ward Burdick founded ASCP in Denver, Colorado, in 1922. ASCP, in turn, established the Board of Registry (BOR) – the first certification agency – in 1928. The organization then followed up by publishing the first reference book for laboratory medicine practitioners (Approved Methods in Laboratory Techniques) and the first medical journal for pathologists and laboratory professionals (The American Journal of Clinical Pathology) in 1933. In 1953, the BOR was the first medical organization to use machines to grade their certification exams and, in 1955, it elected Emma S. Moss as its President. Moss was not only the first female President of ASCP; she was the first female President of any national medical association.

Although medical societies such as ASCP are essential for the future of the medical laboratory profession, thanks to education and policy initiatives, how else can we push for change? It's imperative that practicing pathologists and clinical laboratory scientists drive that change within their own institutions as well. It can be as simple as sending supplies to laboratories in need or establishing standards of practice in laboratories where none exist today.

"It's imperative that practicing pathologists and clinical laboratory scientists drive change within their own institutions."

It's implementing new technologies to streamline processes. It's discovering molecular diagnostics that will pave the way to personalized medicine. It's working with industry to force new paradigms in healthcare, such as pricing transparency or standardized laboratory reports.

We have always been leaders, and it's up to those of us in the field today to continue that leadership. Leading our staff, institutions, and the profession toward innovative changes is an opportunity as well as our obligation.

From Dream to Deployment

How Leeds Teaching Hospital are partnering with Leica Biosystems to achieve fully digital pathology for improved patient care

How many slides go through your lab per day? If your institution is anything like Leeds Teaching Hospitals NHS Trust in the UK, you may go through over a thousand per day – about five kilograms of glass in a meter-high stack. Imagine the resources involved in transporting, examining, labeling, storing, retrieving, and quality-controlling that volume – and imagine the personnel needed to keep such an extensive system working smoothly and accurately to ensure patients' health and safety.

The glass slide, despite its pedigree over the last century or more of pathology practice, has its flaws. They take up space (and must often be stored for years or even decades), require time to be physically transported from one location to another (especially if consultations from faraway experts are needed), and run the risk of loss, breakage, or degradation. They can even affect pathologists' health – because microscopes, though precision tools, are not the most ergonomic method for repetitive slide review. All of these reasons led the pathology department at Leeds to make a critical choice: to transition to a fully digitized service.

Uncontained excitement

"We have a lot of excitement around the lab and in the diagnostic department," says Bethany Williams, Digital Pathology Fellow at Leeds. Williams, who completed the world's first leadership and management fellowship in digital pathology and has spearheaded the project with a focus on patient safety and pathologist engagement. She explains, "In a conventional histopathology reporting workflow, a trained subspecialist views a piece of tissue taken from a patient using a standard light microscope to provide a definitive diagnosis. In digital pathology, we add an important step to this process." Williams continues, "We still have that precious specimen of human tissue, but once we've made the glass slides, we scan them using a specialized scanner in our laboratory." The scanner, a benchtop device, captures a high-resolution digital image of the slide, which can then be viewed by the pathologist on a suitable display screen for diagnosis and further assessment."

Azzam Ismail, Consultant Neuropathologist at Leeds, is an enthusiastic adopter of digital technology. "I have been practicing pathology for 25 years," he says. "I used to have to select a case, find the slides, match the slides with the case number and patient name, position them under the microscope, and then manipulate it to make sure I see everything important for diagnosis. If there is more than one slide, I have to switch between them." He explains that, after a three-hour session on the microscope, he suffered serious back and shoulder pain. "Now, I just scan the barcode and click to open the case on my computer. I can move and zoom easily without having to adjust focus. I dictate my findings at the same time – and, in two minutes, I've diagnosed the case." And it's not just the ease of diagnosis that has Ismail excited. "I can take a second look at cases when I'm not in the department. I can do this with trainees. I never have to worry about missing slides – and look how neat my office is now!"

In the laboratory

"Digital slides are fantastic for capturing whole-slide views," says Williams. "A lot of pathological diagnosis is based on architecture, so you can reach a diagnosis much more quickly – especially when the case involves a lot of slides."

The laboratory at Leeds Teaching Hospitals is a busy one. "We produce about 290,000 slides in our histopathology lab per annum in total," says Sian Gibson,

Pathology Services Manager in the Department of Cellular Pathology. All tissue samples that enter the lab are sectioned, stained, quality-controlled, and then placed in racks according to priority. At this point, every single slide is scanned. The lab operates six high-throughput Aperio scanners from Leica Biosystems, each of which can tackle 400 slides per cycle. It takes 2–4 minutes per slide (depending on the amount of tissue) to produce a scan at 200,000 dpi – a resolution that, if printed, would result in an image the size of a tennis court.

The best part? As soon as the slides have been scanned, pathologists trained in digital diagnosis can begin their work. Gibson explains, "Otherwise, they'd have to wait for us to rack up the slides in here, send them to the pigeonholes, and then, of course, it's up to them when and how often they check for new deliveries. This reaches their offices instantaneously – even those who work in a different wing." For Gibson, the major benefit is the ability to share images. "If pathologists want second opinions from anywhere in the country, that can happen. There's also a shortage of consultants at the moment; in the next five years, up to one-third may retire, and there aren't enough new pathologists to replace them. This helps us disseminate the workload across the UK, and standardize the process as well." She also highlights the fact that a digital archive saves on staff resources because there's no need to search stacks of glass slides – or worse yet, prepare new ones – each time a pathologist needs a particular case.

Solving shortages

Williams agrees with the need for creative solutions to staffing shortages. "We are in the midst of a pathology recruitment and retention crisis," she says. "Pathologists are also having to cope with increasing volume and complexity of workloads. We've got a year on year increase just in the crude number of specimens we're asked to report; our cancer screening programs are so successful that we're now being asked to look at smaller specimens taken from earlier stages; and, with the explosion of targeted therapies we're performing more tests on each individual case." On top of all of these demands, the pressure to reduce turnaround times is constant – especially in the NHS, where all patients have a maximum wait time from test to treatment. "So we've got more work to do, we've got to do it faster, and we've got to do it with fewer people."

"Digital pathology improves the efficiency of diagnosis and laboratory workflows. It also opens up opportunities for collaboration."

With a drive toward centralization and networking pathology resources, digital slides may help. "We've got more freedom as to who reports what, and from where," says Williams. "Digital pathology improves the efficiency of diagnosis and laboratory workflows. It also opens up opportunities for collaboration, both between different NHS institutions in the region and between the clinic and academia. It's really going to help recruit and retain new pathologists, too, by opening up more flexible ways of working that make the discipline more attractive."

And not forgotten are the benefits to patient safety. A paperless NHS means both patients and physicians have easier access to medical records, with fewer opportunities for errors or mislaid information. The images, unlike slides, cannot break or degrade, and continuity of care can be maintained wherever the patient may go.

An evidence-based approach

Leeds Teaching Hospitals' move to 100 percent digitization has gained international attention not only because of its ambition, but also because of the project's systematic deployment. "I think digital pathology has suffered in the past because it has been seen as something that a few enthusiasts have grabbed hold of and pushed to the front of the agenda," says Williams. "I think it's right that pathologists should be a little skeptical when they're being asked to use a completely new method of diagnosis in their everyday practice." As a result, the laboratory took a research-based approach to implementation. "At every step, we've examined the evidence, and created it where necessary. We've decided what equipment and workflow to use; we've created new protocols for efficient slide scanning and for training and validating individual pathologists in digital diagnosis; and we've shared and published everything we've learned."

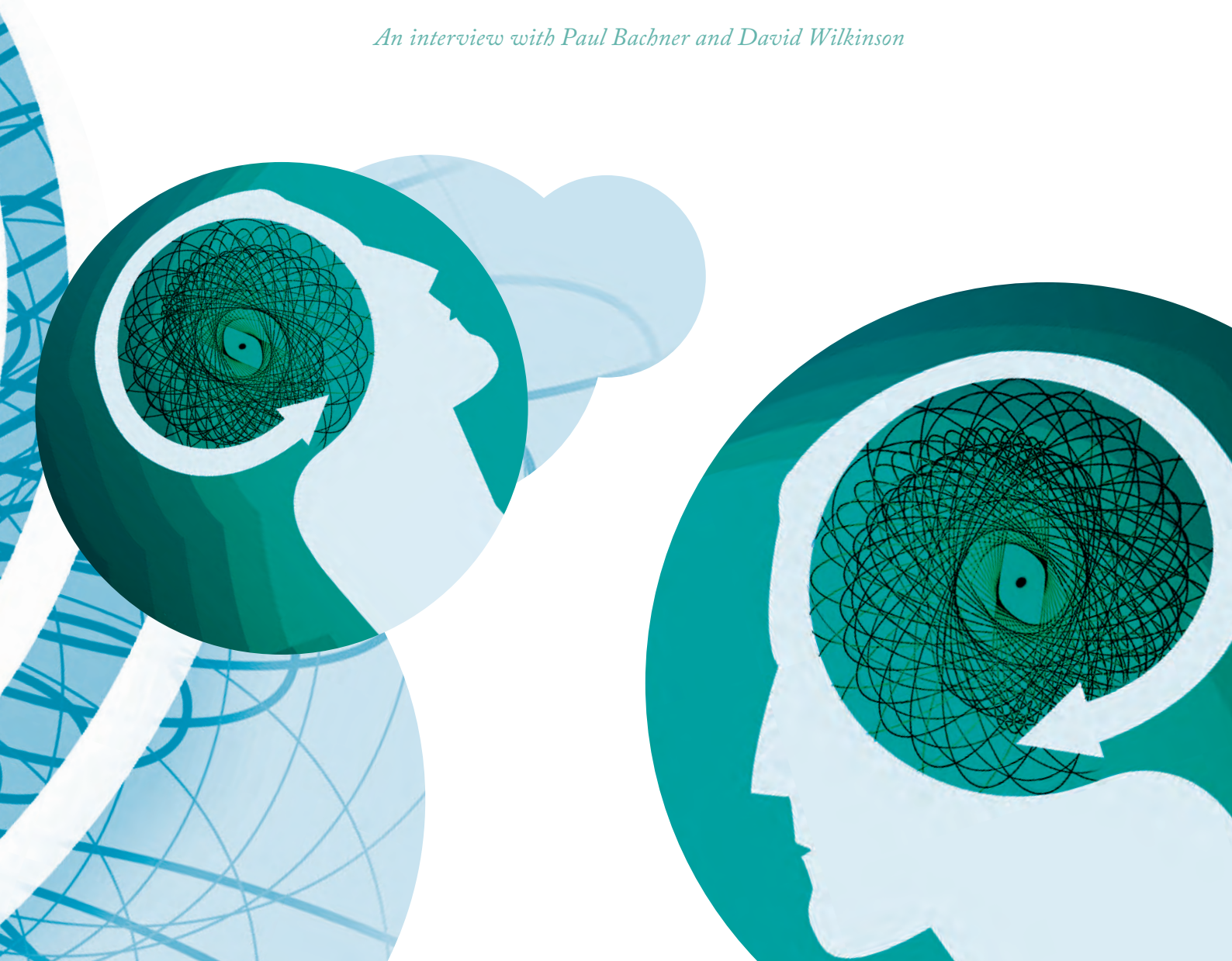
Darren Treanor, Consultant Pathologist and leader of the Digital Pathology Group at Leeds, concludes, "This technology is exploding. Making a diagnosis on the computer instead of on the microscope may sound like a small step, but it's an enormous change that we hope will allow us to use pathology for our patients' benefit as best we can."

The clinical use claims described in the information supplied have not been cleared or approved by the U.S. FDA or are not available in the United States.

A Masterclass in Leadership

How can newly minted – or veteran – laboratory directors rise to their full potential?

An interview with Paul Bachner and David Wilkinson



When you're just starting out in your career as a pathologist, it can seem like advice is everywhere – whether you want it or not. From common-sense proposals like exploring your options before making final decisions to more esoteric or specialized suggestions, there's no shortage of people interested in commenting on your potential career trajectory. But the higher you rise in the ranks, the less help you're often expected to need with managing your responsibilities. And yet, it's often at the highest levels that you encounter a need for new skills or expertise. With so many demands on your time and so little guidance available, how can you learn to shine as a laboratory director and a leader?

Here, former laboratory directors and educators Paul Bachner and David Wilkinson share the lessons they've learned over nearly a century of combined experience.

"THE **HIGHER** YOU RISE IN THE RANKS, THE **LESS HELP** YOU'RE OFTEN EXPECTED TO NEED WITH **MANAGING** YOUR RESPONSIBILITIES."

What exactly is the role of a lab director?

PB: Based on my personal experience as a lab director in many different environments over four decades, the main duties of a lab director are:

1. To ensure that pertinent local and federal regulations are met;
2. To ensure that accreditation requirements are fulfilled;
3. To confirm that all laboratory processes are of the highest possible quality;
4. To maintain constant, open-ended communication with caregivers (physicians), nursing, and administration;
5. To obtain adequate resources (such as equipment and staff) for the laboratory;
6. To monitor and provide support and guidance to laboratory staff.

DW: The responsibilities of a CLIA lab director are specified in detail in federal law and regulation in the United States – but, in addition to the six items identified above, I would add:

7. To keep up to date on the latest developments in science, regulation, and reimbursement as applicable to the practice of pathology;
8. To be active in professional organizations – something I have found to be very helpful with keeping up to date!

PB: As David said, there are certain things every laboratory director must do. You must ensure that federal regulations and accreditation requirements pertaining to labs are met. And that includes operational considerations; for example, ensuring that procedures are up to date and being followed, making sure that quality control is being implemented, and checking that proficiency tests or surveys are being done. These "must-dos" are what lab directors are held accountable for when laboratories are inspected for accreditation purposes.

There are also responsibilities that are somewhat harder to define; the most important of these, I think, is physical presence. Just being there makes a difference, in my opinion – and the benefits are twofold. First, you see and hear things that you would miss if you were not present. Second, being on the scene gives your staff a sense of your engagement, which is important from a morale standpoint. Ticking those boxes takes care of the internal requirements, but harder still are the relationships outside the laboratory. As important as it is to be available to your own staff, it's equally so to build relationships with medical staff, hospital administration, nursing, and the patients themselves. After all, you can be on top of everything internally, but if you don't have a means of sampling what the external world thinks of your lab – where they see efficiencies, where they want changes, where they want improvement – then you may not have all of the information you need.

Whether or not that's easy depends on what kind of institution your practice is in. I've been involved in all sorts of organizations, from small labs and small hospitals to very large tertiary care centers. Keeping your finger on the pulse of the medical staff is very different in these two extremes. In a larger institution, you're somewhat restricted to more formal environments, such as prearranged meetings, although you can

try to supplement them with day-to-day contact as best you can. In a smaller institution, I have always found that one of the most important ways to keep in touch with the medical staff is to go to lunch or take time out in the operating room coffee lounge to chit-chat with the surgeons and anesthesiologists. Either way, it's a combination of formal contact and informal contact, which I think is a key aspect of being a lab director.

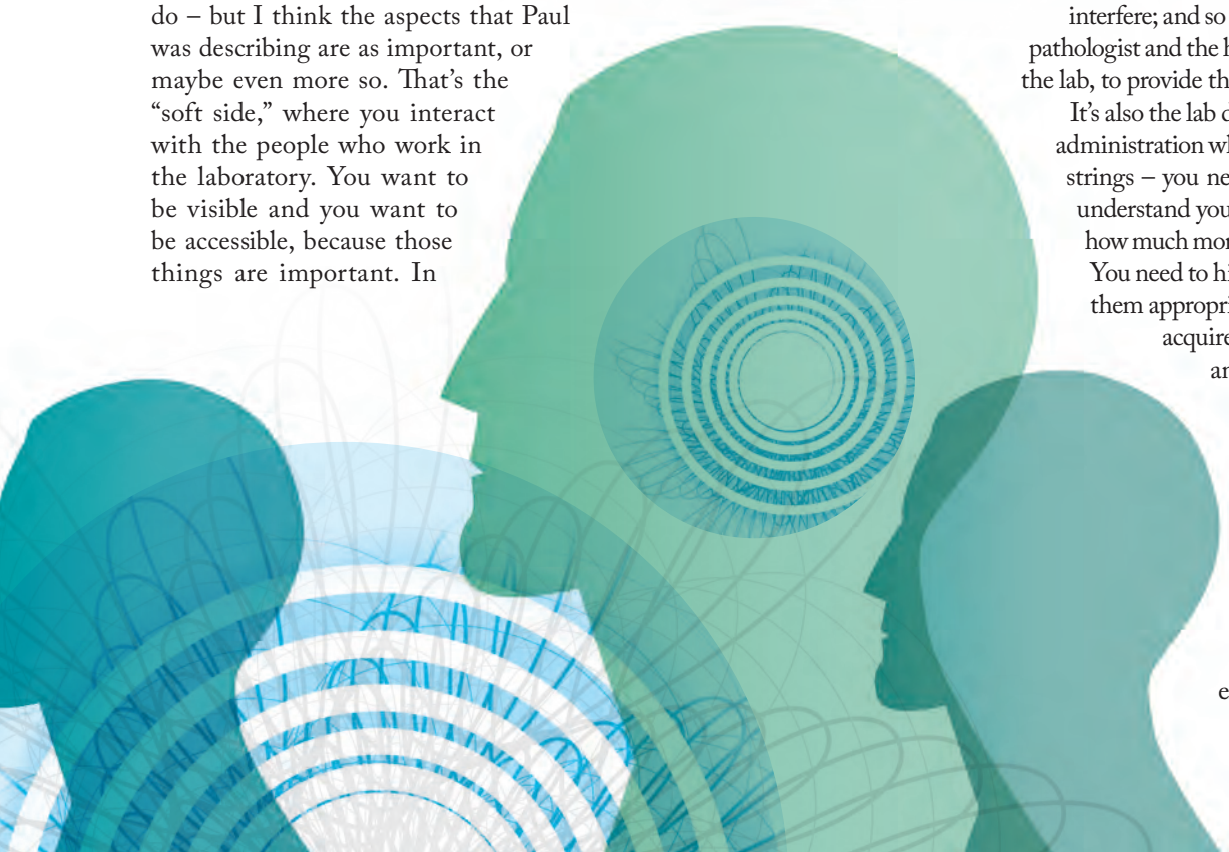
DW: In the United States, we have a law called the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88), which is written into the Code of Federal Regulations. It lists about 20 or 30 specific responsibilities of the laboratory director (1) – quite unusual in medical practice in the US. The laboratory is probably the most highly regulated area of medical practice and, although the title of "medical director" is quite varied, I don't think there's a single other one that has a federal law that spells out its responsibilities. CLIA '88 serves as a nice blueprint and a great reference for what a lab director does.

Those regulations spell out what we call the "hard side" of what we do – but I think the aspects that Paul was describing are as important, or maybe even more so. That's the "soft side," where you interact with the people who work in the laboratory. You want to be visible and you want to be accessible, because those things are important. In our institution, we have over 400 people working in the Department of Pathology, and I know that it can be hard for them to feel they have access to directorial staff unless we make an effort to see them on their territory. The lab is probably close to 100,000 square feet and our 400 employees operate across three shifts, seven days a week. So, to be most effective, a lab director in that kind of situation has to visit those people from time to time so they know who you are. And that way, if they have any issues they can tell you face-to-face, rather than leaving both of you to rely on a potentially flawed chain of communication.

"YOU WANT TO BE **VISIBLE** AND YOU WANT TO BE **ACCESSIBLE**, BECAUSE THOSE THINGS ARE **IMPORTANT**."

Paul also emphasized the importance of dealing with medical staff. Because most non-pathology medical professionals don't know much about the lab, they have this concept that you draw blood from a patient, send it to the lab, and then there's a black box; the lab just spits out a result. They have no idea what's involved – what is required to validate a test to ensure that reference ranges are appropriate for your patient population; how to troubleshoot results; what kinds of things can interfere; and so on. They look to you, as the pathologist and the highest-ranking member of the lab, to provide that information.

It's also the lab director's job to relate to the administration who (usually) hold the purse-strings – you need to make sure that they understand your requirements. "You need how much money?! Where does it all go?!" You need to hire adequate personnel, pay them appropriately, have adequate space, acquire adequate instrumentation, and more – and, much like money, those things don't grow on trees! Somebody has to advocate for them. So you're making the rounds yet again – this time with your institution's top management: the chief operating officer, the chief executive officer, the chief



information officer, the chief medical officer, the chief operating officer… All those folks have the power to make or break your lab, so you want to make sure you're on good terms with them.

Finally, you have to get to know the vendors who sell instrumentation and reagents. Those are the people who can tell you what's out there and what might be available in the near future, and the people who can help you implement major changes like new laboratory information systems or large chemistry systems. You need to be a part of such implementations yourself, and you need to make sure you know who's in charge on the vendor side. When we made major changes in my lab, it wasn't unusual for me to call the chief executive officer of a billion-dollar company with whom we were spending three or four million to say, "Hey, your systems aren't working," or, "Your people aren't doing what they're supposed to be doing." It's your job as laboratory director to stay on top of these aspects, too, making sure that they run as smoothly as possible – and one way of doing that is to forge connections with people who can help you and your lab.

How can lab directors and their colleagues work well together?

PB: I rely heavily on personal contact with physicians, nurses, and administrators to identify my laboratory's needs and shortcomings, and I supplement that with periodic surveys of laboratory users and laboratory staff. Should we need resources, I try to plan in advance whenever possible. I make our anticipated needs known to hospital administration and finance and, at the same time, I build support from clinical staff. It puts me in a good position to advocate for my lab. To maintain credibility, all communications and documentation submitted to administration should be well-researched and factual. A reputation for exaggeration will hurt you in the long term.

Common issues that arise when I liaise with non-laboratory medical staff are scope of testing (for instance, if a clinician wants a new test to be available routinely) and turnaround

time. I approach both topics with an open discussion with the clinician(s). Why do they need the tests? What are the negative consequences of not offering the tests in-house? How many tests do they think they will be ordering? What turnaround time do they expect? Answers to these questions can help me make "buy versus make" decisions. Turnaround time requests and complaints are usually linked to a request for point-of-care testing, which is a much more complex issue involving many resources and capabilities. It has a significant effect on laboratory staff and resources, of course, but unlike other forms of testing, it goes beyond the four walls of the lab.

And sometimes, pathologists should, too. Cytopathologists and blood bankers, for instance, often have patient contact – and it's a part of the job description that may become increasingly prevalent with the growth of molecular and genetic testing. Such tests, particularly the latter, are often complex and may be beyond the knowledge base of clinicians. But because the impact on patients – in terms of not only diagnosis, but also treatment and prognosis – may be great, direct contact with the pathologist may be indicated. When facilitating these types of interactions, the skills I find most useful are a solid knowledge base, basic interpersonal skills, and the ability to transmit highly technical material to the layperson. And that latter skill also comes in handy when making a case for additional resources to people who are not well-versed in pathology.

DW: Teaching these lab director courses for over 20 years at national meetings, I am surprised every year that people don't know the regulations or what they're actually responsible for as lab directors. I don't know why that is, but it's true. So, I think making sure that lab directors understand that they do have very firm, specific guidelines in federal law is an eye-opener for many people.

Every laboratory should also have a strategic plan that is updated on a regular basis to include projected needs for space, personnel, and equipment. I have found it useful to have regular (monthly or even more frequent) face-to-face meetings with the hospital administrator who has immediate oversight of the lab, so that I can make sure the administration is constantly aware of lab requirements. When I do have an unmet need, I find that financial arguments are usually the most persuasive to administration – either an increase in revenue or cost savings. It's not the only potentially persuasive argument, though; safety and new developments in patient care needs are also valid. After all, administrators are people, too – and, in many cases, they or others close to them are patients as well.

"THE **SKILLS** I FIND MOST USEFUL ARE A **SOLID** KNOWLEDGE BASE, BASIC **INTERPERSONAL** SKILLS, AND THE ABILITY TO TRANSMIT **HIGHLY** TECHNICAL MATERIAL TO THE **LAYPERSON**."

How can lab directors pave the way for major changes in the laboratory?

DW: When making such changes, it is very important to include key staff early in the decision-making process and, eventually, to educate the entire staff on the benefits of bringing in a new process or technology. In my experience, resistance to change is usually related to fear of the unknown, so anything you can do to remove the mystery of the change will decrease resistance. You need to understand who the informal leaders are in the lab and make sure they are on board with the proposed changes. You also need to have a strong implementation plan in place to ensure a smooth transition from the old processes to the new; for example, temporary increases in overtime or even supplemental workers for big projects. Finally, you need to ensure that personnel on all shifts have been fully trained in the new processes. And then – once everything is complete – celebrate your victories!

Can you tell us more about the soft skills?

DW: Much of what Paul and I teach together at our laboratory directors' workshop focuses on the soft side. It's similar to running any other company, though; the skills are not specific to pathology, or to being a lab director. They're the kinds of skills that anyone in a leadership position needs to cultivate if they're going to be successful.

PB: It's the hardest part of the job in my experience. I've been a lab director for close to 40 years. And the "hard" stuff – the regulations, the quality control, what instruments you're going to buy – that's easy, because there are plenty of ways we can learn

about those things. You can read about it. You can ask others who have had to deal with the same problems. It's teachable.

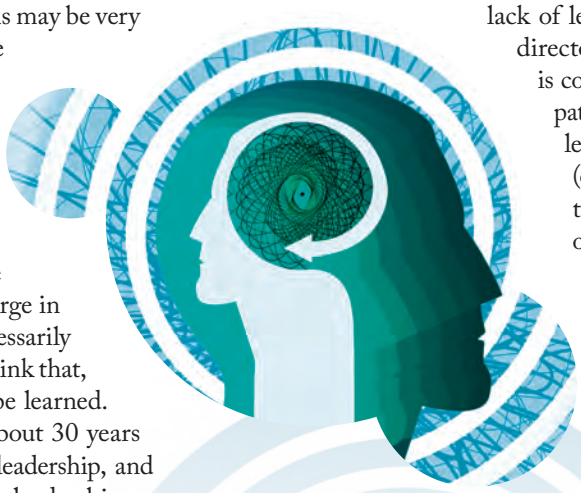
For me, dealing with people is the hard part. If you've met one administrator, you've met one administrator; each one is a different person with their own approaches and traits, and working with them all appropriately must be learned through experience. Some of them like to be given as much documentation and numbers as you can throw at them; others, you're better taking them to lunch. I always tell my residents that, when they're out there in the real world and they become lab directors, they are not going to be lying awake at four o'clock in the morning thinking about a puzzling slide or how to get approval for an instrument. They're going to be lying awake thinking about the chemistry supervisor who's been with them for 20 years but has started heavily drinking because of a failed relationship. Those are the types of problems that turn your hair grey.

Relationships with clinicians and nurses are critical. Hostile behavior on the part of clinicians may be very difficult for your staff to deal with. The director must engage with clinicians to make them understand the negative impacts of aggressive behavior, and with staff to help them develop coping mechanisms and strategies.

DW: I think certain people, just by virtue of their personalities, have innate leadership skills and are able to take charge in any particular group. Not everyone is necessarily born with these skills – but I definitely think that, for those who aren't, some things can be learned. There are excellent books out there. About 30 years ago, I focused on studying leaders and leadership, and I read a lot. I think I had some innate leadership skills, but I definitely enhanced them by reading about great people like [former US Secretary of Defense] George Marshall and [most decorated Marine in US history] Chesty Puller. These kinds of leaders were exemplary, and I learned a great deal just by looking at how they conducted themselves. Warren Bennis, at the University of Southern California, spent his whole academic career studying leaders and leadership. I read a number of his books and I think he really has some good insights to offer – I'd recommend them to anyone wanting to learn more about being a leader.

PB: I agree with David that leadership is both nature and nurture. Some people are just innately better at it than others; I think if you look back at the lives of really successful lab directors, they were probably president of their kindergarten class or something. But the reality is that a lot of people wind up in leadership roles without having had any past experience in leadership. The typical laboratory director or academic department chairman was named to their position because of their clinical or research acumen, not because they had any demonstrable interest or experience as a leader.

David is also absolutely correct about the vast amount of literature out there. You can spend your entire life just reading the literature on laboratory leadership – and that's without touching the books on people who are leaders in other spheres. But there comes a point where you have to stop reading about it and actually do it. If you want to learn to play the violin, you have to play the violin. For many years, I have been involved with a College of American Pathologists committee that deals with labs that have problems. I would say that, for a vast majority of these laboratories, the problem is a lack of leadership – situations where the director is a director in name only, or is concerned primarily with anatomic pathology activities, leaving the actual leadership to a laboratory manager (or even to no one in particular!) in the hope that everything will work out… somehow. You can't do that. Leadership is a job – something you need to think about and do every day.



"NOT **EVERYONE** IS NECESSARILY BORN WITH [LEADERSHIP] **SKILLS** – BUT I DEFINITELY THINK THAT, FOR THOSE **WHO AREN'T**, SOME THINGS CAN BE **LEARNED**."

To me, being a lab director or a leader of any kind involves a combination of learning (reading, taking courses, seeking help and advice from more experienced people) and actually doing it – making mistakes and learning from the mistakes you personally make. I could probably write a book, or at least a book chapter, on the mistakes I've made and what I've learned from them.

DW: You definitely learn more from your mistakes than you do from your successes…

What do you find most rewarding about the role?

DW: I had the good (or maybe bad!) fortune of ending up as a lab director within a few months of leaving my residency. I've spent most of my working life as a leader, without much time as a subordinate. But I find the scientific content of what we do very interesting – and, as a lab director, you're not focused on just one area. Academic laboratories tend to be highly specialized, so most pathologists and laboratory medicine professionals work in one area, like hematology or chemistry. If you want to be a good (and a successful) lab director, you need to be familiar with all the labs: surgical pathology, autopsy pathology, chemistry, hematology, cytogenetics – the list goes on and on. For me, the mental stimulation of trying to

keep up with all of that is exciting. Every day – even now, at age 73 – I learn something new, and it's wonderfully satisfying.

The other thing that really brings me pleasure is the "people" side of things. It makes you feel good when people in the lab say, "We really appreciate what you do. Thank you for going to bat for us on this, that, or the other thing." Or when the clinicians come and say, "I've had a really tough case, we used a lot of blood, and your lab did a great job at keeping up." Such feedback is very positive, and it has a great effect. Patient care is another aspect of my role and, just like any other medical professional, I love to hear positive things from my patients. There are so many rewarding things about what I do that I can't even list them all. It's a great job.

PB: I agree with everything David has said. I've been in practice for about 50 years now, and I've just retired. The change and the growth and the increase in complexity of pathology and laboratory medicine over those years is absolutely mind-boggling. I often spend a little time with my residents giving them a canned history. To give an example, when I finished training, there were three lymphomas; the last time I checked, there were 26! Imagine how the complexity will change over the next half-century. Trying to keep up with that has been a challenge, but it has also been a lot of fun. I think I've survived by virtue of being willing to be taught by others, and that, too, is certainly part of the pleasure.

I think, when I look back, the greatest pleasure – and the greatest long-term satisfaction – I've had is seeing the growth of people I've mentored. When I stepped down as the director of laboratories six months ago, I was replaced by a pathologist who was one of my earliest recruits as a young assistant professor. She went elsewhere to continue her career, but came back. Seeing her evolution over the years has been wonderful and, of course, being in academic pathology, seeing the careers of my residents evolve is always a great pleasure for me.

"I THINK I'VE **SURVIVED** BY VIRTUE OF BEING **WILLING TO** BE TAUGHT BY OTHERS, AND THAT, TOO, IS **CERTAINLY** PART OF THE **PLEASURE**."

DW: Like you, I stepped down from being a chair a few years ago, but I still work full-time. My two immediate supervisors are former residents of mine! Last Tuesday, I had to go and have my annual performance evaluation – which was done by a woman who was my resident at George Washington University twenty-something years ago.

PB: Did you do well?

DW: I did terrific!

If you could go back to the start of your career and give yourself advice, what would you say?

DW: Work hard. Be nice.

PB: I'd probably spend more time in the lab with my staff, because when I became a chairman, I became preoccupied with those duties. I also got very involved with the College of American Pathologists. As a result, the time I had available to wander around the laboratory became somewhat limited. So if I could do anything differently, I think I would change that.

DW: You can never spend too much time in the laboratory but, on the other hand, getting involved with the professional organizations carries its own benefits. Yes, it takes you out of the lab, but it gives you insight by letting you work shoulder-to-shoulder with people from other labs, learn from them, and make connections. It even helps your residents, because if you have a resident who

wants to do a fellowship in a particular area, you can say, "Well, you need to talk to so-and-so," because you've got the connections. I think that's one of the responsibilities of a lab director – and certainly of an academic department chairman. If you just stay within your own little castle, you will limit your ultimate success.

It can be hard to balance, though. While I was at George Washington University, I was chief of clinical pathology with 150 employees – I was able to say, "Hi," to each one of them every single day, because I would get in early enough to meet the night shift before they went home, work during the day shift, and then stay late enough to meet the evening shift before I went home. Now that I'm at Virginia Commonwealth University, I've got a department that includes both anatomical and clinical pathology with over 400 employees. I can't do here what I could do in my previous department. I wish I could, but there's just not enough time in the day to do it.

My best advice to other lab directors? Be a good listener. Communicate, communicate, communicate. Stay positive. Stay involved, but do not micro-manage. Build a strong team, delegate, hold people responsible for completing their tasks, trust your staff, and celebrate good performance.

Paul Bachner is Professor and immediate past chairman of the Department of Pathology and Laboratory Medicine at the University of Kentucky, Lexington, USA, where he was Director of Laboratories for 25 years.

David Wilkinson is Professor of Pathology, Associate Medical Director of Transfusion Medicine, Director of the Pathology Training Program, and former Chair of Pathology (1993–2013) at Virginia Commonwealth University, Richmond, USA.

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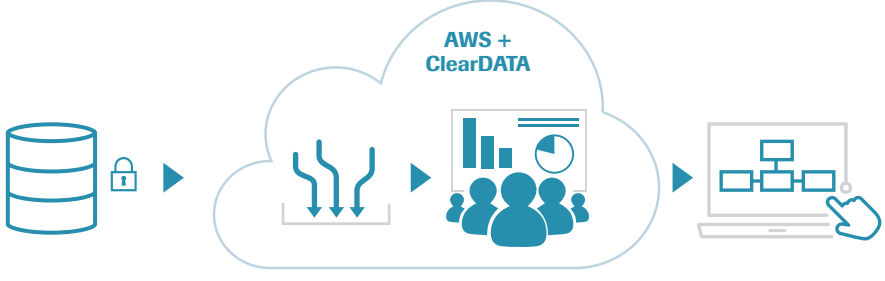

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In Practice

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The "We" in Team

The evolving role of pathologists in multidisciplinary teams

By Judith Hugh

Most pathologists in hospitals or clinics are familiar with the multidisciplinary team (MDT) concept. A group composed of specialized health care professionals representing every aspect of patient care, concentrating on optimal patient management, has become the norm in many jurisdictions. But what advantages do they really convey, and what is our role on the team?

Understanding MDTs

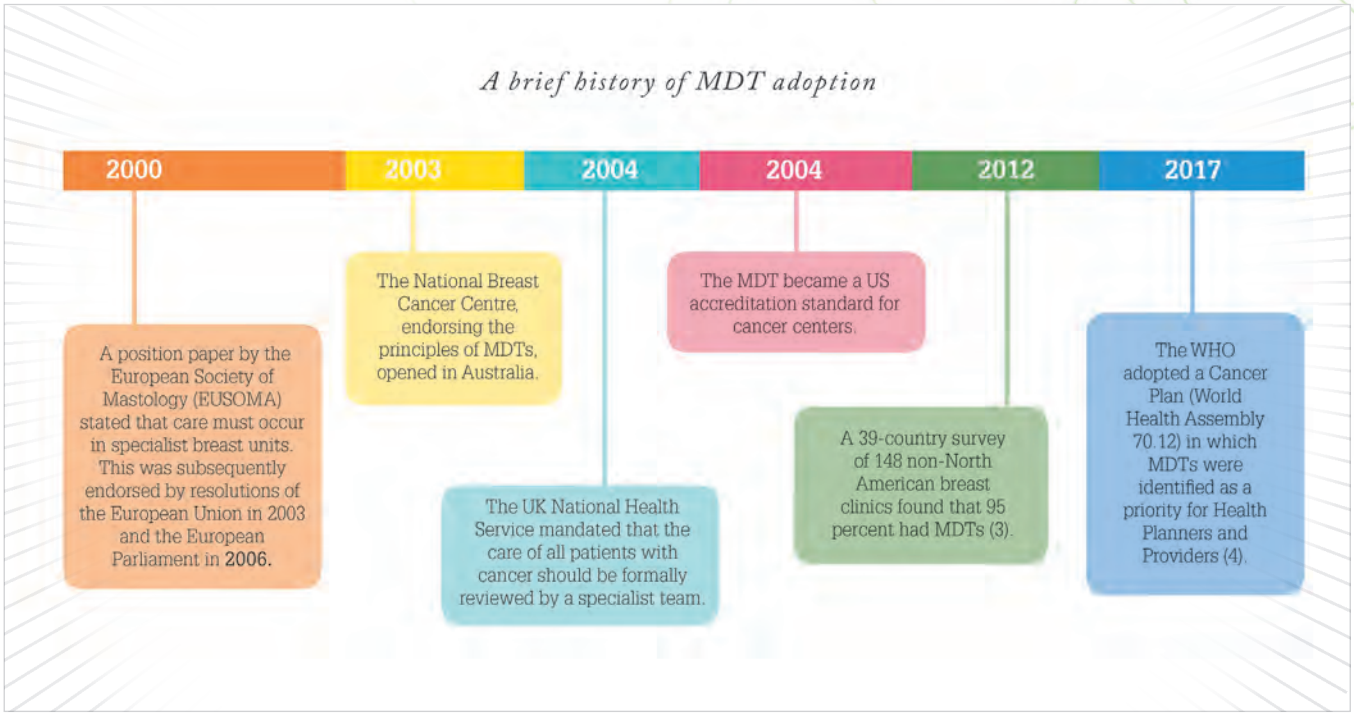
What exactly is an MDT? It can be defined as "collaborative patient care by a team of clinical and allied specialists whose collective diagnostic and therapeutic intent is individualized patient management (1)." For example, a breast cancer MDT is typically composed of pathologists, breast surgeons, medical oncologists, radiation oncologists, imaging specialists, breast cancer nurse specialists, and an MDT coordinator or secretary (2).

Despite their popularity, the question of whether or not MDTs actually improve patient outcomes has yet to be fully answered. Studies have shown that they increase adherence to guidelines, foster better teaching environments, and improve overall clinician and team satisfaction (5–7). Nevertheless, their survival benefit remains difficult to prove. Why? Partly because of the lack of appropriate controls – it can be difficult to compare patients whose treatment has involved an MDT against those whose hasn't. And even when the two groups can be compared, confounding variables abound.

One standout study was a retrospective, comparative, non-randomized interventional cohort study (8) that examined the effect of MDTs on nearly 14,000 patients diagnosed with invasive breast cancer in Scotland between 1990 and 2000. Prior to 1995, no MDTs were involved in the care of any of these patients; in the period from 1995 to 2000, Greater Glasgow (n=7,672) alone implemented a breast MDT, whereas services outside the intervention area (n=6050) did not. The trial featured no patient selection bias, had a contemporaneous control group, and used a strict definition of an MDT that included evidence-based guidelines, weekly meetings, and audits. The result? A noticeable difference. Before 1995, Greater Glasgow had a significantly worse five-year Breast Cancer Specific Survival (BCSS) at 71.3 percent, compared with 73.6 in the surrounding district (HR 1.11, 95% CI [1.00–1.20], p=0.04). After the introduction of MDTs to Greater Glasgow, that area's breast cancer-specific mortality was 18 percent lower, and its all-cause mortality was 11 percent lower, with a five-year BCSS of 79.2 versus 75.9 percent (HR 0.82, 95% CI [0.74–0.91], p<0.001). In 2000, MDTs were introduced to the remainder of West Scotland.

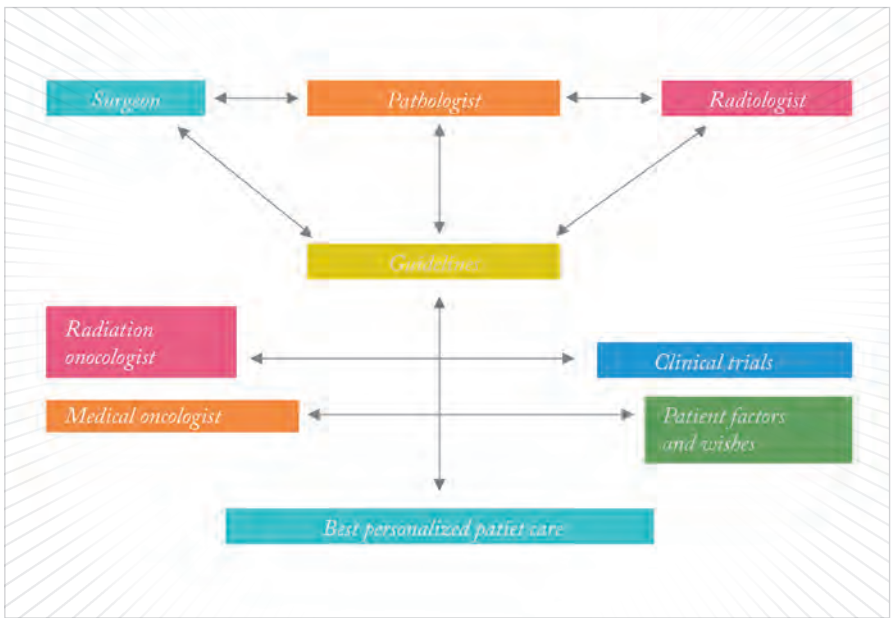
At a Glance

- *Multidisciplinary teams (MDTs) work toward optimal patient management by a group of specialized health care professionals*
- *The concept is popular and has existed for some time, but reliable data on the benefits of MDTs is harder to come by*
- *Pathologists should sit at the center of the MDT as leaders, not just as participants*
- *MDTs will probably be the way of the future and this is our opportunity to advance the profession and the practice of medicine as a whole*



The pathologist's role

The pathologist is – or should be – at the epicenter of a comprehensive management approach. Why? Because we integrate information from the radiologists and surgeons and provide the actionable data for patient care. However, it's not enough just to attend meetings and read our reports; we must be true participants in the team. An MDT performance assessment tool developed in 2011 (9) contains a rubric for pathological information that goes from 1 ("no provision of pathological information") to 5 ("review of pathological images"), with provision of pathological information from a report or account as the midpoint. The rubric also provides assessment guidelines for histopathologists, again ranging from 1 ("nil/impedes contribution of others") to 3 ("contribution inarticulate or vague") to 5 ("articulate and precise specialty-related contribution"). For Canadian pathologists who use the CanMEDS framework, the assessment covers the roles of collaborator, scholar, and health advocate.



A schematic diagram of an MDT, showing the pathologist's role.

- Collaborator: provision of inclusive reports (including the translation of pathology reports and the enabling of integration and clinical-pathology-radiology correlation)
- Scholar: promotion of evidence-based practice
- Health advocate: stewardship and resource utilization (including the need for specific

ICS2: Interdepartmental and health-care clinical team interactions: displays attitudes, knowledge, and practices that promote safe patient care through interdisciplinary team and leadership skills within the laboratory (AP/CP).

	Level 1	*Level 2*	*Level 3*	*Level 4*	*Level 5*
	Knows that MDT conferences aid appropriate patient care	Attends MDT conferences	Prepares and presents cases at MDT conferences	Can lead MDT conferences	Organizes and is responsible for MDT conferences
Has not achieved Level 1	Recognizes the importance of clinical input in diagnosis	Participates through observation and interaction with clinicians	Assesses, analyzes, and interprets pathology reports	Knows how subtleties may impact or alter patient care	Serves as a consultant to the health care team
	Understands the utility of communication with the clinical team	Appropriately triages information requests from the clinical team	Effectively communicates clinically significant or unexpected values	Participates in or leads communication with the clinical team	Fully participates as a member of the health care team; is recognized as proficient

Table 1. A summary of the milestones involved in MDT participation and leadership. Adapted from (11).

sample types or tests, such as biopsy or biomarker analysis)

How well are pathologists carrying out these roles? The 2011 study results, which came from the observation of five MDT meetings (three different MDTs addressing 112 total patients), were not favorable. When rated for information presentation, pathologists scored an average of 2.85 based on a surgeon's observations and 3.20 based on those of a psychologist. The contribution scores were even worse at 2.03 and 2.15, respectively – below a performance contribution of "inarticulate or vague."

When asked what we do, many of us may reply, "Diagnose disease." But that must not be our only function; many experts predict that artificial intelligence may one day replace diagnostic histopathology. An even more sobering study found that pigeons could be easily trained to accurately identify images of breast cancer (10). Interestingly, there was an affinity between the pigeons and histopathology; they weren't able to interpret radiologic images with the same accuracy. Our current and future value lies in our professional role. Locally, we are links in a larger collaboration, providing feedback on preanalytic factors, working on quality assurance, and developing testing algorithms. On a larger scale, we participate in working groups to share information, create guidelines, and select biomarker tests, among other things. We also have a part to play outside the lab – and outside medicine as a whole – acting as educators, advocates, advisors, and leaders.

The training ethos

This greater view of the role of pathologists was captured in the Pathology Milestone Project, which highlighted knowledge, skills, attitudes, and other attributes necessary for pathology residents to achieve Accreditation Council for Graduate Medical Education competencies. The milestones are grouped into five levels: 1) starting residency, 2) advancing through residency, 3) continuing advancement with a majority of milestones consistently demonstrated, 4) residency graduation, and 5) "aspirational" goals for continuing development – a level only a small percentage of residents are expected to achieve.

The milestones cover actions related to basic laboratory tasks, diagnosis, reporting, teaching, laboratory management, patient safety, pathologist wellbeing, and much more. Not least among them are the interaction-based goals, which specifically include effective participation in – and leadership of – MDTs (see Table 1).

However, as a profession, we suffer from a number of deeply ingrained negative stereotypes (12). This is largely because the

profession generally appeals to introverts. However, as noted in recent reviews and publications, introverts possess many characteristics that are increasingly recognized as key leadership qualities. These include good attention to detail, dependability, analytical thinking, integrity, and work ethic. To advance pathology and the practice of medicine as a whole, we have to start honing those skills for leadership and individual achievement. Our attention to detail becomes an ability to focus on the matter at hand and to be held accountable by others. Our dependability yields a commitment to service and an ability to form strong partnerships with our non-pathologist medical colleagues. Analytical thinking allows us to assess and evaluate the information we encounter during MDT meetings, and to strategically align our current efforts with the future of our institutions and our profession. Our integrity demonstrates our character and professionalism to other members of the team. And, finally, our work ethic makes us achievement-oriented and ensures that we not only set goals for ourselves and our MDTs, but also reach them. To be good team members, we must develop all of these skills – and we must remain self-aware and ensure that we always listen to our colleagues and make decisions as a single unit, rather than a dozen disparate doctors. A good introvert skill!

It's worthwhile to keep in mind that William Henry Welch (1850–1934), often referred to as the Dean of American Medicine and the champion of evidence-based medicine, was a pathologist.

What's next?

You're convinced of the value of MDTs. You're convinced of your own profession's vital role in them. But what do you do next? If you're interested in subspecialty practice, the answer is simple: join an MDT. If subspecialization is not for you, consider joining a special interest group to further the practice of pathology by contributing to workload distribution schemes, transparent workload accounting, or clinical research. If you're a director or otherwise have authority over the way your laboratory or institution is run, then ensure that there is protected time for MDTs, and encourage leadership opportunities for those of us who show an aptitude.

Of course, all of this is easier said than done. How we approach and solve the dilemmas around subspecialty practice, research, and professionalism will determine our future. But this is the way forward for the profession, for medicine and – most importantly – for our patients and our society.

Judith Hugh is Laboratory Site Chief and Divisional Director of Anatomic Pathology at the University of Alberta Hospital and Professor and Lilian McCullough Endowed Chair in Breast Cancer Research at the University of Alberta, Edmonton, Canada.

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One Drop at a Time

What insight can droplet digital PCR add to minimal residual disease detection from liquid biopsies – and how can pathologists use it?

An interview with Alexander Dobrovic and Cloud Paweletz

Liquid biopsy is a hot topic in pathology at the moment – but, like many hot topics, we must delve deeper to discover the true pros and cons, and to uncover the most effective methods of accessing the benefits while avoiding pitfalls. In the case of liquid biopsy, it's a minimally invasive technique that can provide rapid results. Droplet digital PCR (ddPCR) introduces speed and sensitivity, as well as absolute quantification to the liquid biopsy analysis. Alexander Dobrovic and Cloud Paweletz discuss their laboratories' experiences with ddPCR and how other pathologists can achieve the same results.

At a Glance

- *Both liquid and tissue biopsy have strengths and weaknesses – but when a rapid, minimally invasive test is key, then liquid biopsy has the edge*
- *Droplet digital PCR (ddPCR) is fast, sensitive, and accurate in cases where minimal tumor DNA must be detected*
- *Unlike other digital PCR technologies, ddPCR offers a simple workflow and rapid analysis using droplets for absolute quantification*
- *As biomarker technology advances, many ddPCR tests are moving into routine use – for instance, to detect activating BRAF and EGFR mutations*

Where do current methods of cancer characterization fall short?

Alexander Dobrovic: Current methods of cancer characterization based on tissue biopsies are often compromised by long turnaround times. In contrast, liquid biopsy samples can be taken as soon as the treating physician orders a test and sent directly to the laboratory.

Of course, every approach has its strengths and limitations. Tissue biopsy remains the method of choice in many situations, especially in initial diagnosis, where anatomical pathology is a key part of the tumor evaluation. The ability to use circulating tumor DNA as a biopsy tool clearly depends on the presence of a detectable amount of tumor DNA in a relatively small (10–20 mL) blood draw, which is often not the case, particularly in early-stage tumors.

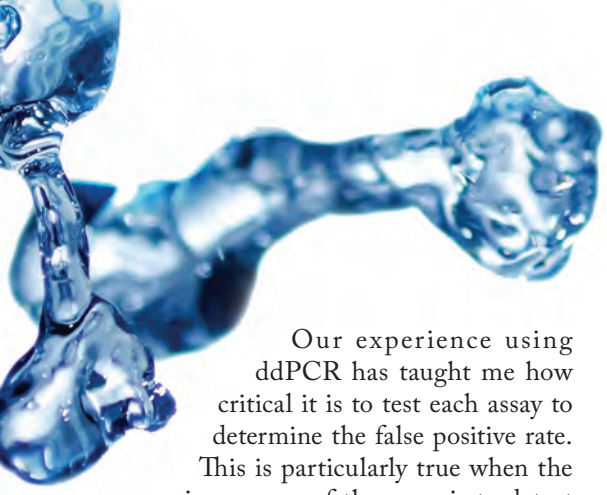
ddPCR is arguably the best approach to liquid biopsy for several reasons. Based on enumerating single molecules, it's a technique that enables absolute quantification, making it very efficient at detecting even miniscule amounts of tumor DNA. ddPCR is highly sensitive and specific. Unlike massively parallel sequencing, there's no need to batch samples for analysis, and results can be obtained in as little as six hours from the drawing of a blood sample in cases where an urgent result is needed.

Cloud Paweletz: I think it is worth mentioning that tissue biopsies are a fundamental part of cancer care and will not be eliminated. One has to remember that invasive biopsies are still the gold standard for making diagnoses, to clarify a diagnosis, to stage and re-stage, and to perform molecular testing. A good liquid biopsy can replace some inconvenient biopsies and open new opportunities that tumor biopsies may not offer. Philosophically, I see invasive and liquid biopsies as complementary.

So how can pathologists fit the technique into existing workflows?

AD: ddPCR precisely atomizes a single PCR reaction into approximately 20,000 micro-droplets as a stable emulsion in oil. These droplets act as micro-PCR reaction chambers. Only some will contain the DNA target of interest – so PCR amplification will only proceed in those droplets. Once the reaction is complete, amplification is detected by increased fluorescence using either intercalating dyes or probes; positive droplets are counted by flow cytometry.

"A good liquid biopsy can replace some inconvenient biopsies and open new opportunities."



Our experience using ddPCR has taught me how critical it is to test each assay to determine the false positive rate. This is particularly true when the main purpose of the assay is to detect minimal residual disease (MRD), because it determines the threshold above which one can make a confident positive call. It is reasonable to consider that the better we become at detecting emerging residual cancer early and accurately, the better our patients' outcomes will be – so a thoroughly tested ddPCR assay whose evaluation of MRD can be trusted is an invaluable resource.

CP: We have to separate liquid biopsy from ddPCR; they are not synonymous. Liquid biopsy is the sampling and analysis of non-tissue samples. ddPCR is a technique to analyze samples, which can be based on tumors or plasma cell-free DNA), and next generation sequencing (NGS) is another such technique.

ddPCR takes advantage of recent developments in microfluidics and surfactant chemistries. Conventional digital PCR involves diluting input DNA into individual wells for analysis; ddPCR emulsifies the input DNA into thousands of droplets that are PCR amplified and fluorescently labeled, then read in an automated droplet flow cytometer. Each droplet is individually assigned a positive or negative value based on its fluorescent intensity. A flow cytometer reads the number of positive and negative droplets, which is used to calculate the concentration of either wild-type or mutant allele (see Figure 1).

Any good (molecular) pathology laboratory that practices good PCR techniques and follows CLIA GLP/GDP guidelines will have no problem fitting ddPCR into their workflow. In essence, it adds two extra steps – droplet generation and automated droplet reading.

What obstacles remain for ddPCR's widespread implementation?

AD: ddPCR needs a cancer-specific marker to function. However, this is also the downfall of the technique. In many cases, individual patients may need a bespoke marker – something that may not be financially or practically viable. And that's why, at the moment, such assays remain boutique tests for the most part.

In my laboratory, we have always been aware of potential problems with PCR contamination – an issue with which every lab should be more than familiar. We now take even more precautions, using physical separation of laboratory areas to eliminate potential contamination, because even a miniscule amount of template can sabotage MRD detection.

The most useful ddPCR assays are based on driver mutations that can be used for both diagnosis and monitoring of response to treatment – and the more common the mutation, the more likely that test is to enter routine use in the clinic. Examples of tests that have made the leap are *BCR-ABL* for chronic myelogenous leukemia, *JAK2* V617F for myelodysplasia, and *BRAF* V600E for melanoma.

CP: The main advantage and the pitfall of a liquid biopsy is that it promises to offer compelling insights at our fingertips without the hassles of obtaining a tumor biopsy – the complex scheduling, the risk for the patient, and the fact that they are not always successful. It's important to understand how to interpret liquid biopsy results (whether NGS or ddPCR) so that the community doesn't let a bad liquid biopsy supplant an inconvenient tumor biopsy.

I am agnostic to the method of analyzing cell-free DNA. In some cases, ddPCR may be the approach of choice – for instance, if one needs a rapid test to study a single variant of a single gene. In other cases, more comprehensive analysis using NGS may be more appropriate.

"Liquid biopsy is an exciting space to be working in at the moment."

How did you make a business case for ddPCR?

AD: My colleagues and I made a business case to our hospital for a trial to diagnose and monitor disease in melanoma and lung cancer patients. Although our arguments were sound and our evidence base solid, it was critical to have the hospital's medical oncologists support our case. We had already been providing this service to them from our research funds, a solution that was unsustainable in the long term. During this trial period, the value of ctDNA monitoring became apparent.

Liquid biopsy is an exciting space to be working in at the moment. As thrilling as it is to be at the cutting edge of new technologies, the most gratifying aspect is the positive contributions it makes to patient management.

Alexander Dobrovic is Head of the Translational Genomics and Epigenomics Laboratory at the Olivia Newton-John Cancer Research Institute, Heidelberg, Australia.

Cloud Paweletz is head of the Translational Research Laboratory at the Belfer Center for Applied Cancer Science, Dana-Farber Cancer Institute, Boston, USA.

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Biochip Breakthrough

Can a rapid and portable test for drug-resistant pathogens offer new hope in the fight against antimicrobial resistance?

By Luke Turner

Antimicrobial resistance represents an increasingly serious threat to public health around the globe. Molecular diagnostics systems enable rapid identification of pathogens through nucleic acid amplification tests (NAATs) and occasionally facilitate the detection of resistance-causing mutations. But despite the promise of enabling appropriate antibiotic selection, existing systems are restricted by their limited multiplexing (the maximum number of strains and sequences that can be detected) and low accuracy for identifying point mutations, such as single nucleotide polymorphisms (SNPs). Now, a team of researchers has developed a new approach: a miniaturized semiconductor biochip and multiplexed NAAT that is capable of swiftly amplifying, detecting, and quantifying DNA or RNA sequences in their hundreds.

At a Glance

- *A new portable biochip boasts the ability to detect microbes simultaneously and rapidly in clinical samples*
- *The technology should allow doctors to identify drug-resistant strains and select the most effective treatments*
- *Its creators hope that the technique will help with the fight against antimicrobial resistance by avoiding inappropriate antibiotic use*
- *With the development of an open-source version of the platform, clinicians will be able to create custom chips that "scan" for new microbes as they are discovered*

A novel platform

Arjang Hassibi, CEO of InSilixa, the company responsible for the new technique, started his career in a different discipline before turning to biotechnology. "I was trained in Stamford as an electrical engineer, but toward the end of my PhD, I switched from just doing electronics to building analytical instruments and platforms." It wasn't until 2012 that Hassibi founded InSilixa and joined the fight against antimicrobial resistance. "The push toward antimicrobial resistance was just starting, and as we moved on, we found that there was a need for an analytical platform that could not only identify the organisms, but also look at the drug susceptibility profile and drug resistance."

The new platform comes in the shape of a disposable biochip composed of 1,024 independent DNA biosensors that use inverse fluorescence techniques. Although the multiplex capacity of conventional, solution-based qPCR assays is constrained by the availability of dyes with different spectral properties, the new platform can detect hundreds of different sequences. The researchers demonstrated their method's genotyping accuracy by simultaneously identifying

"We found a need for an analytical platform that could not only identify organisms, but also look at [...] drug resistance."

multiple respiratory viruses within a single clinical sample – but, even more impressively, the platform was able to detect mutations that distinguished drug-resistant from drug-sensitive *Mycobacterium tuberculosis*. Hassibi highlights the potential significance of the technique: "You know exactly what drug to use, and which drugs aren't going to be effective, so the expectation is that the treatments are going to be much more efficient. I think it would save lives in certain cases; for example, with hospital-acquired infections and times when you're dealing with patients who are fragile or have supressed immune systems. It would also slow the increase of drug-resistant strains to some degree, because you're not using antibiotics and antimicrobial agents willy-nilly."

The biochip can perform microbial scans in under two hours, without the need to culture the microbes in the lab, which often delays the whole process by days or even weeks. Hassibi believes such time-savings could have direct benefits for patients. "After developing a urinary tract infection in the aftermath of surgery, a patient was given antibiotics that didn't work. Only after a second and third course of antibiotics was a drug susceptibility test carried out, after which the right antibiotic was prescribed to cure the infection. It took two and a half months and the patient was suffering for this long period," he says. "Now, we have the technology to do it in hours. There are generally three or four different drugs that can be prescribed for urinary tract infections, each conferring resistance to different antibiotics. Why

"Why should you go through months of pain and suffering when the technology is there to check for resistance?"

should you go through three months of pain and suffering when the technology is there to check for resistance? The patient has to demand that."

Pursuing perfection

A limitation of the new platform is its inability to discover new microbes and mutations; it can only detect previously characterized target sequences or mutations that are known to represent a medically important phenotype. And so, Hassibi and colleagues hope to develop a molecular diagnostics system with an open platform, allowing pathologists to create new biochips when new strains of microbes are discovered. "Every year, there might be a new strain that needs to be added. A lot of labs are very competent in doing the critical work and they're set up to do various diagnostics. If they have access to technology that can produce a new diagnostic test within six months while also putting it through clinical approval and everything else they need, that would be a game-changer. We are opening it up so that our partners and customers, who have their own specific applications, can use the technology to create a product that they can take to market."

A big challenge during the development of the laptop-sized biochip reader was the lack of funding available for the creation of new diagnostic technologies – which is accompanied or driven by a poor attitude towards the value of diagnostics.

"The US is a treatment-driven society, and I think diagnostics are not a big part of it. Specifically, for areas in which the urgency is not out there and where the cost of treatment is not considered high, people think they can afford not to do the proper diagnostic testing and go bouncing off different antibiotics or treatments," Hassibi says. "Diagnostics in healthcare is the ugly duckling. It's a stark point of view, but there is some truth in it. The clinicians do care, but they will talk about the large investment required to make these technologies happen, and the industry incentives are lower. The problem is that, alongside an increase in antibiotic resistance, why should our treatment-driven society worry? If you look at it from an investment-motivated point of view, if you're selling the drugs and they're buying without testing, why should you worry?"

Hassibi believes that more investment is required in diagnostics, while also directing efforts toward developing complete or so-called actionable diagnostics. "My personal opinion is that you will win if you pay a little bit more for precision diagnostics than you pay for the treatment. There will be an incentive for more effective drugs, so they will not lose out financially – but, rather than having mundane antibiotics, they might have new ones. Doctors would be happy; patients would be happy. I don't think there would be any losers. The overall cost of healthcare might not go down drastically, but the outcomes would be better."

What's next?

After proving the viability of the biochip, Hassibi's ambition for the next few years is to take the product to market. "We're getting to the product development and manufacturing stage, which is a very capital-intensive process; we have to be very careful because once you start it, you cannot slow it down." However, the fact that Hassibi's company plans to develop a platform technology rather than a clinical assay will dramatically reduce the cost required to take the product to market – the clinical work and applications will come from users of the platform. "Our model is not very common in biotechnology, because most companies adopt a vertical model and use integrated systems that do everything; they have the software, the instruments, the chemistry, and they do the clinical work." Though Hassibi doesn't think there is anything inherently wrong with the "old and proven" model, he believes that biotechnology should draw inspiration from other areas, such as the technology industry, where it is common to use parts from different sources in a more horizontal model.

"You will win if you pay a little bit more for precision diagnostics than you pay for the treatment."

Despite the challenges ahead, Hassibi is relatively optimistic about microbe profiling platforms. "Low-cost platforms near the point of care for patients will definitely exist in our lifetime. But whether it will take five years or 25 years, I don't know." The ultimate aim is to enable the simultaneous profiling of 100 microbes or strains, which would facilitate the detection and identification of multi-drug resistant pathogens. If successfully translated into the clinic, such rapid molecular diagnostics platforms would give healthcare professionals actionable data on the most effective drugs – a big step forward in the ongoing fight against antibiotic resistance.

Arjang Hassibi is the President, Chief Executive Officer, and a board member of InSilixa, which he founded in 2012 to commercialize the proprietary CMOS biosensor technologies that he had been developing in academia for almost a decade.

Reference

1. *A Hassibi et al., "Multiplexed identification, quantification and genotyping of infectious agents using a semiconductor biochip", Nat Biotechnol, 36, 738–745 (2018). PMID: 30010676.*

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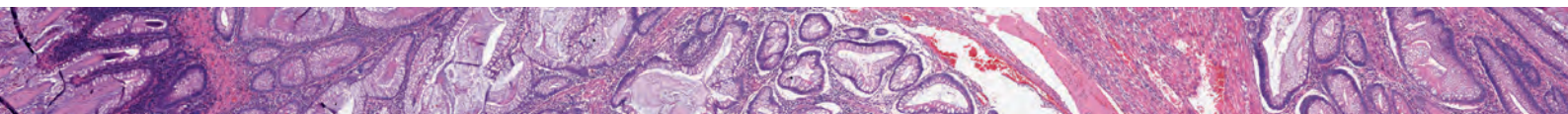

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Peer-to-Peer, Featuring Fátima Carneiro

A guiding light in pathology shares four decades of experience in the discipline and offers advice to those who follow in her footsteps

Ivan Damjanov interviews Fátima Carneiro

Fátima Carneiro is Professor of Pathology at the Medical Faculty of Porto University and a senior staff member at one of the University's scientific Institutes, Instituto de Patologia e Imunologia Molecular da Universidade do Porto – better known around the world as IPATIMUP. Internationally, she is renowned for her contributions to gastrointestinal pathology, including research on the molecular pathology of sporadic gastric cancer and hereditary gastric cancer syndromes. In Europe, she is also known for her many leadership roles in the European Society of Pathology (ESP), for which she gave numerous seminars, actively collaborated on the European School of Pathology, and served as its President. Most recently, she was co-editor of the latest edition of the World Health Organization (WHO)'s Blue Book on gastrointestinal pathology, helping diagnostic professionals around the world recognize and diagnose diseases of the digestive system. She was also voted #1 in our 2018 Power List, nominated by multiple colleagues and lauded for her work by our expert panel of judges.

Throughout her four-decade career in medicine, Fátima Carneiro has learned a lot about pathology, both within and outside her specialty. Now, she shares some of those lessons.

At a Glance

- *Pathology offers opportunities for research, clinical work, and teaching – so for those who want all three, there's no need to compromise*
- *Education is vital for spreading the word about pathology and encouraging promising students*
- *We need better recruitment and better pay to overcome the impending shortage of pathology practitioners*
- *Pathology is a profession and an integrative discipline – and now is an excellent time to join the field*

How did you decide to become a pathologist?

I made the decision after graduating from medicine. Until that point, my dream had been to become a pediatrician – quite a different discipline! So what happened to change my mind? It was 1978 and I had just finished the medical course at Porto University. At the end of my final academic year, my professor of cell biology invited me to become a monitor on his team! It was an unexpected invitation – but, after briefly hesitating, I told him that I thought cell biology was a bit too a quiet for me and did not meet my career expectations. It was his turn to be taken by surprise; such invitations are rare and I should have considered it a high compliment. He asked me about my expectations, which were very clear in my mind. I wanted to participate in clinical activities in the hospital; to participate in teaching, which I had loved ever since I had taken my first clinical medical course; and to do research. After I told my professor all of this, he told me I should go into pathology. I had never thought about the possibility before, but his proposal sounded good, so I went to the Department of Pathology to speak to the professors there – Daniel Serrão and Manuel Sobrinho-Simões. The latter, well-known for his affability, replied with a fair degree of curiosity that I could begin working with him the next day. That day turned out to be the first of a lifelong experience.

"I wanted to participate in clinical activities in the hospital; to participate in teaching; and to do research."

When I entered the discipline, pathology was quite popular – at least in the School of Medicine/Hospital São João, where I studied. Candidates were recruited from among the best students, who were attracted by the opportunity to combine professional medicine with a research career. Today, the scenario is different. The recruitment system is solely based on the ranking candidates obtain in a national examination; professors and department heads have no input into student selection. And unfortunately – but completely understandably – candidates nowadays make their choices according to their expectations for a future in well-paid employment, an area in which other specialties are much more competitive than pathology.

Why did you focus on gastrointestinal pathology?

I began by working in thyroid pathology with Manuel Sobrinho-Simões. Along the way, he decided to redirect some of his students to gastric cancer research, because the disease is so prevalent in Portugal (and because, as a result, it attracts much more funding). Luckily, I was one of those students, because I quickly got interested in gastric carcinogenesis. Later, as a second-year resident, I added liver pathology to my interests. Ultimately, I was able to complete an internship in digestive pathology in Leuven, Belgium, with Valeer Desmet and Karel Geboes, which played a conclusive role in my attraction to the field of GI and liver pathology.

I have been fortunate enough to have had the opportunity to make numerous contributions to that field over the years. In my opinion, the most important of these is my work on hereditary cancers affecting the stomach. I worked with the International Gastric Cancer Linkage Consortium (IGCLC) and, early on, I began studying the pathology of hereditary diffuse gastric cancer (HDGC). More recently, I had a similar experience in the characterizing the histological profile of GAPPS (gastric adenocarcinoma and proximal polyposis of the stomach) syndrome with Xiaogang Wen. Together, we spent countless hours studying the full length of the gastric mucosa in stomachs removed from carriers of germline mutations of the *CDH1* gene, as well as hundreds of digital images of GAPPS. But the work was worth it to improve the lives of patients with these diseases.

It was also a privilege to work on the WHO book, "Tumors of the Digestive System" (4th Edition, 2010). Fred Bosman (to whom I express my gratitude for this experience) invited me to act as a co-editor for the sections concerning the upper GI tract. The hardest parts, in my opinion, were complying with the deadlines and dealing with the differing opinions of the contributors who attended our consensus meetings. Each of them was chosen for their contributions to the field and thus deservedly considered an authority in their subject. How do you challenge the opinion of a world expert? How do you come to a consensus on controversial topics? It was not easy, but the four editors – Fred Bosman, Neil Theise, Ralph Hruban, and I – worked well as a team. We got the work done!

Tell us about your work with the European Society of Pathology…

The ESP presidency was probably the most demanding period of my professional career. The motto of my presidency was "Education in Pathology," so I focused on the following three areas:

1. Reinforcing the role of the ESP in the field of pathology education, which included: a) developing e-learning initiatives and maintaining and expanding courses in the framework of the European School of Pathology (EScoP) and tutorials at ESP headquarters in Brussels, b) supporting residents and trainees with bursaries for participation in ESP congresses, and c) supporting the maintenance of progress tests at the European level as a tool to harmonize graduate education in pathology.
2. Reinforcing internationalization and linking pathology with other international organizations in laboratory medicine, and in medicine in general. Under my presidency, the ESP also revised its rules and statutes and joined the Alliance for Biomedical Research in Europe.
3. Reinforcing links with national pathology societies in Europe. ESP provides scientific and financial support to numerous national societies for educational activities and academic development.

Filling the position of President gave me a "go-for-it" approach to problems and challenges while maintaining my professionalism. It helped me to improve the society's management approach so that we could better deliver advances in science, achievements in basic and advanced education, and good quality diagnostic services for the benefit of patients.

According to a recent survey of national pathology societies in Europe, the burning issues affecting us today are:

- insufficient recruitment of young doctors, resulting in a critical shortage of pathologists and excessive workloads,
- low salaries in many countries

without higher pay for higher performance, and
- loss of motivation and "brain drain."

This scenario is not good at all, but I think we should view these challenges as opportunities. The ESP may be able to help bridge the gap between academic (research-driven) and clinical (service-oriented) pathology. With such a wide remit, though, there is no "one-size-fits-all" solution because our specialty has developed so heterogeneously across Europe. Many countries have adequate pathology services. Unfortunately, some more realistically qualify as precarious – they need major, immediate action to improve the health of their pathology services. The ESP does what it can, but sadly lacks the power to make all of the necessary changes in each country.

The society's mission is "to promote high quality diagnostic practice, applied and translational research, and under- and post-graduate education in the field of human pathology." The current leadership, President Dina Tiniakos and Director-General Raed Al Dieri, is discussing the ESP strategy for the near future. Two recently launched initiatives deserve to be highlighted: the ESP Alfonso Giordano Fellowships, which promote advanced training for young pathologists in selected centers of excellence throughout Europe, and the newly launched ESP Junior Academy, whose goal is to stimulate the development of future pathologist-scientists.

What do you consider your greatest achievement to date?

I am proud of my involvement in pre- and post-graduate teaching in histopathology and molecular diagnostics. But beyond that, I am proud of two things. One is my seniority in my main field of interest – gastric cancer – reflected in collaborations with several scientific societies, about 200 papers on gastric cancer (and over 350 peer-reviewed publications in total), and authorship of chapters of multiple well-known and well-loved gastrointestinal pathology textbooks. The other is my international networking through teaching, research, and professional initiatives. I have collaborations on four continents – North and South America, Africa, Asia, and Australia – as well as my work in Europe.

What advice do you have for our younger colleagues?

The pathologist of the future must be able to understand the mechanisms of disease and to translate new knowledge to patient care. That is a question of education and learning; you must envision pathology as both a profession and an integrative discipline. Pathology is an amazing discipline, and one that plays a pivotal role in clinical medicine and in all of our efforts to better understand disease.

Fátima Carneiro is Professor of Anatomic Pathology at the Medical Faculty of Porto, Head of Anatomic Pathology at Centro Hospitalar São João, and Senior Investigator at IPATIMUP, Porto, Portugal.

Ivan Damjanov is Professor of Pathology at the University of Kansas School of Medicine, Kansas City, USA.

A Global Citizen

Sitting Down With… Malak Abedalthagafi, Assistant Research Professor of Genomics and Neuropathology at King Abdulaziz City for Science and Technology, Medical Director of Molecular Diagnostics at King Faisal Specialist Hospital, Saudi Arabia, and part-time faculty member at Harvard Medical School, Boston, USA

What inspired your journey into pathology?

When I was very young, I was diagnosed with a rare genetic disease that required frequent trips for treatment. I lived in London for a year, then went back and forth between Makkah and Riyadh for follow-up treatment. Those visits to a specialist in Saudi Arabia, as a young girl in the late 1980s, gave me my first glimpse of the possibility of becoming a physician-scientist. That specialist, Nadia Sakati, became my first role model. I later learned that she had established one of the first genetics departments in Saudi Arabia.

Initially, I intended to concentrate on studying genetic diseases in children – but as I studied, I moved toward molecular pathology and then became more focused on surgical oncology, molecular genetics, and neuropathology. Now, my goal is to improve personalized medicine in the clinical management of cancer patients.

I am extremely pleased that I made the decision to become one of only a few board-certified molecular neuropathologists in the world. To reach that goal, I was fortunate to have a mentor who spoke candidly about – and helped me to overcome – the obstacles women still face in science and medical careers. I also obtained an MBA degree, which serves me well in directing research and clinical labs. My background is somewhat unique, but it has helped me to carve out an equally unique niche. I find it very rewarding to not only diagnose cases in the classical way, but also guide oncologists toward new targeted therapy approaches that save lives.

You've been educated around the world – was it hard to settle back in Saudi Arabia?

It's true that my career path was quite a journey, but by that time in my life, I was used to it. I attended medical school at King Abdulaziz University in Jeddah and then, thanks to the King Abdullah Scholarship Program, had the privilege of studying at world-renowned American universities. Although I was driven to seek out the best education I could find, eventually, the cultural differences – notably the misconceptions I kept hearing about the Middle East – had me eager to return home. I was thrilled to become part of the Saudi Human Genome Program in 2014. Now, I wear many hats – as a genomics researcher, clinician, and educator.

"My goal is to improve personalized medicine in the clinical management of cancer patients."

What are the most important issues in pathology today?

The quick transition to molecular diagnostics is a key issue right now. To stay relevant, pathologists must continue to specialize and take a personalized approach to their work. I hope the next generation of pathologists will standardize integrated reports and play an active part in molecular tumor boards.

As I've hinted, discrimination is also a big problem in the medical community, from both patients and other health care providers. At its worst, people refuse to believe I could have received an adequate education at home. As a Saudi woman, it's common for people to assume I can't speak English or understand basic concepts. Working in world-class institutions, I was shocked to hear some of the misconceptions people had and the questions they asked. There is a prejudice that non-western doctors don't have the same quality of education and experience – in fact, even when I trained alongside western colleagues, they questioned my abilities!

Pathologists and medical professionals worldwide can benefit from a larger worldview and a more inclusive mindset. I was fortunate enough to be surrounded by collaborative mentors who taught me to overcome discrimination. If we are all more conscious of our attitudes and preconceptions, we will come together more effectively.

How are new technologies changing the face of modern pathology?

My research involves the genomes of tumors – particularly brain. My clinical genetic specialization involves diagnosing disease using the latest genetic technologies, especially in the field of cancer. Today, novel technologies are having a major effect on our field. Artificial intelligence (AI) and next generation sequencing are popular examples, but I urge my colleagues not to get too excited without considering the potential downsides. For instance, doctors who create AI platforms may run into conflicts of interest, as advanced AI could threaten laboratory jobs. In general, my position on new technologies is positive, but cautious.

What's your advice for younger pathologists?

Mentorship has benefited me immensely, and I encourage all younger pathologists to find role models in their specialty. I recommend mentoring networks, so people can surround themselves with others who are driven to succeed. Multiple mentors are ideal; each will keep you on track in a different way. I also recommend sitting back from time to time to assess how you want to learn and grow in your career.

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