MAY 2019 # 54

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Know Your Strength

An expert panel takes questions about women's career issues in the lab

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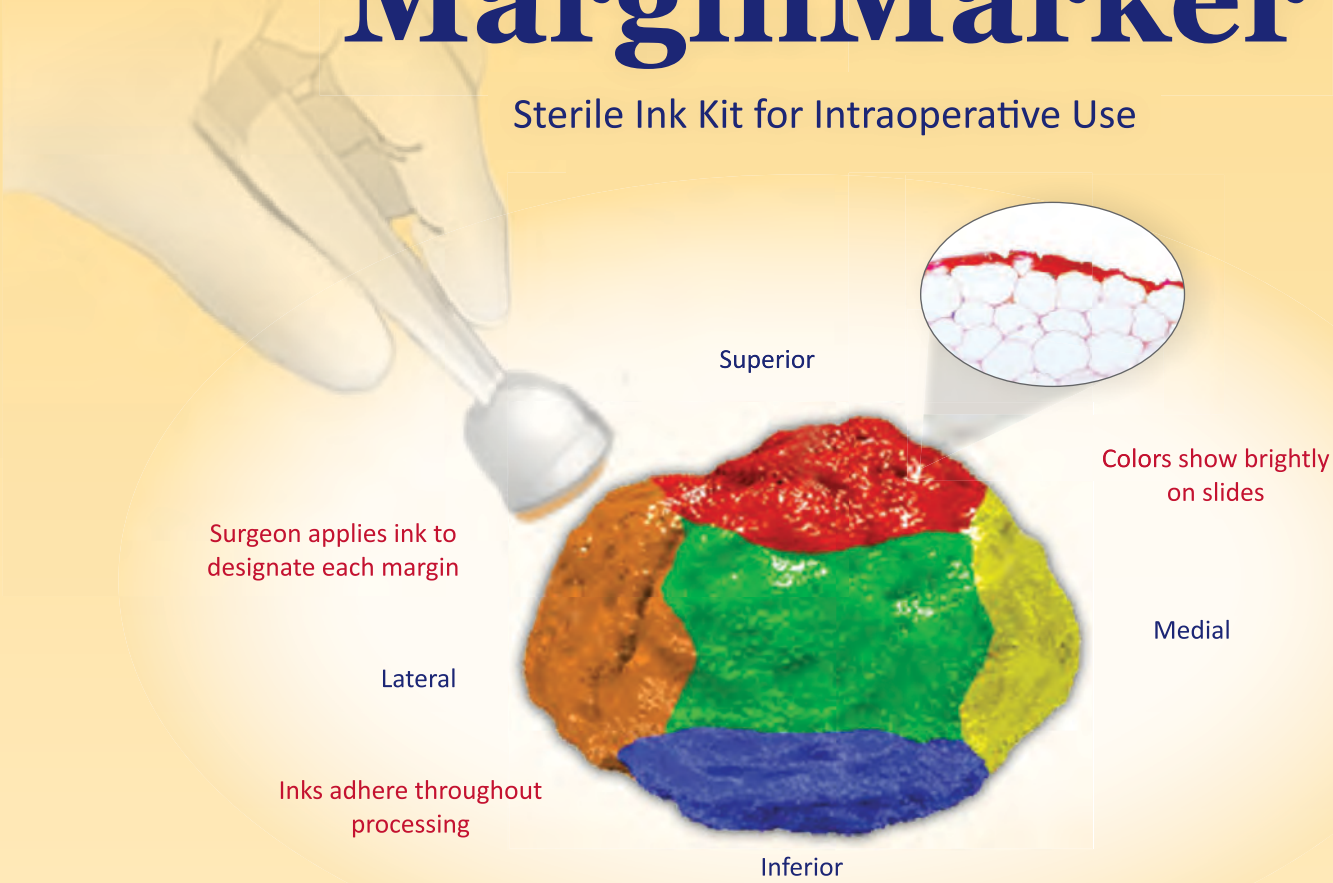

Pathology Receives Specimens With Margins Clearly Marked by the Surgeon

In cancer surgery, the single most important predictor of local recurrence is the tissue margins.[1] Research shows discordance rates as high as 52% in the identification of specimen margins.[2,3] Re-excision rates exceed 20% in breast surgery.[4] Use of Vector Surgical's MarginMarker can result in:

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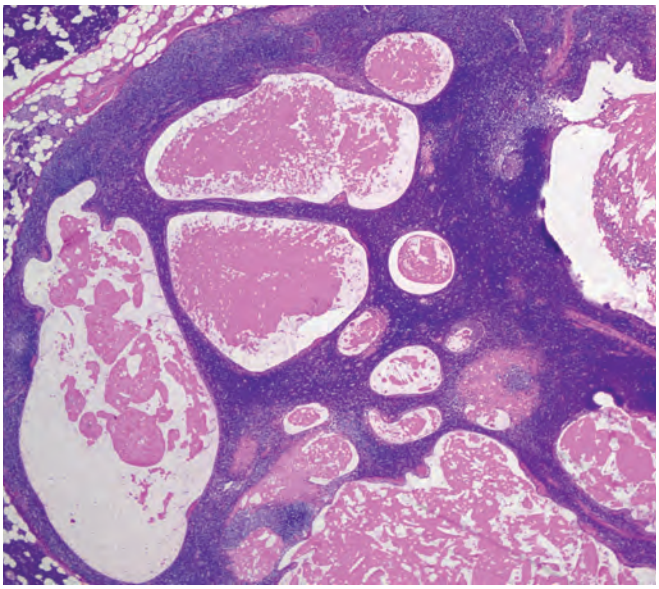
Case of the Month

A middle-aged patient presents with a superficial parotid mass. Fine needle aspiration is followed by superficial parotidectomy.

What is your diagnosis?



A. *Lymphoepithelial cyst*

B. *Sebaceous adenoma*

C. *Mucoepidermoid carcinoma*

D. *Warthin's tumor*

Answer to last issue's Case of the Month…

B. Respiratory bronchiolitis (RB)

Respiratory bronchiolitis (RB) occurs exclusively in smokers and is almost always detected as an incidental finding in lung carcinoma resection specimens. Clinical manifestations are either absent or very mild (1–3). Aggregates of smokers' macrophages occupy the lumens of respiratory and terminal bronchioles, and their walls may exhibit fibrosis, mild inflammation, or both. The accumulation of smokers' macrophages in alveolar ducts and airspaces immediately adjacent to bronchioles that exhibit RB is a common finding, but interstitial inflammation and fibrosis are not.

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Submitted by Yale Rosen, MD, SUNY Downstate Medical Center, Brooklyn, NY, USA

To register your guess, please go to http://tp.txp.to/0519/case-of-the-month
We will reveal the answer in next month's issue!

Contents

On The Cover

A photo collage featuring portraits of all six women on our pathology and laboratory medicine expert panel.

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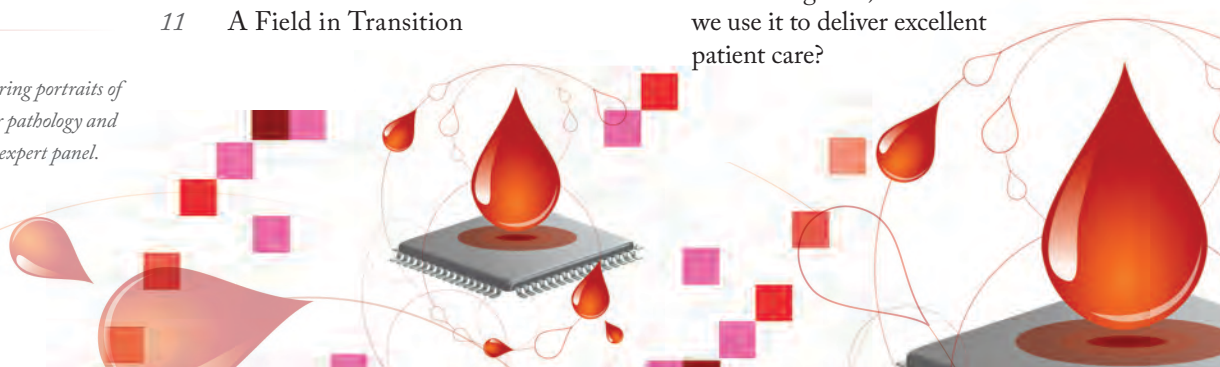
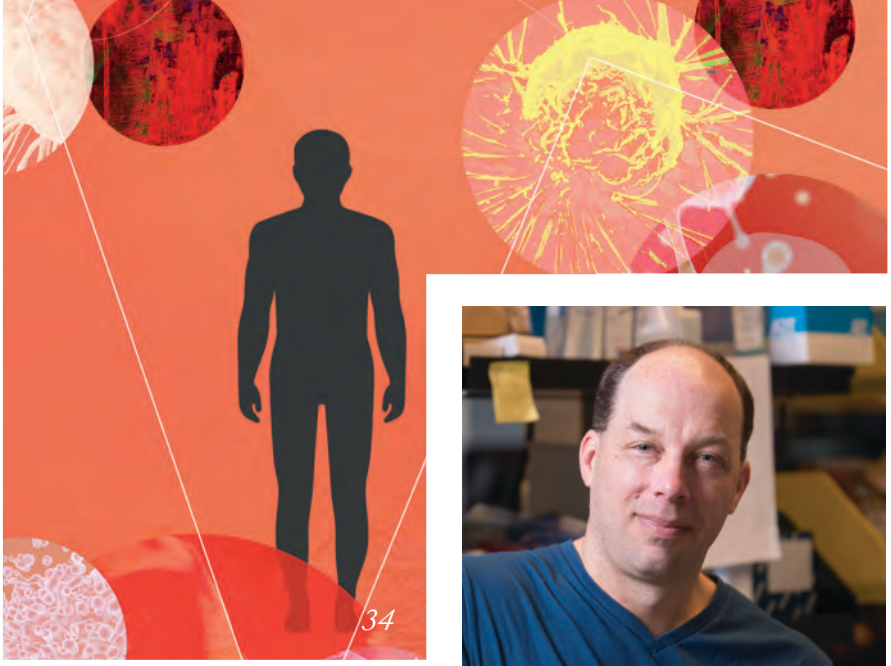
In My View

From The ASCP





Report

Feature

In Practice

NextGen

Profession

Sitting Down With

the **Pathologist**

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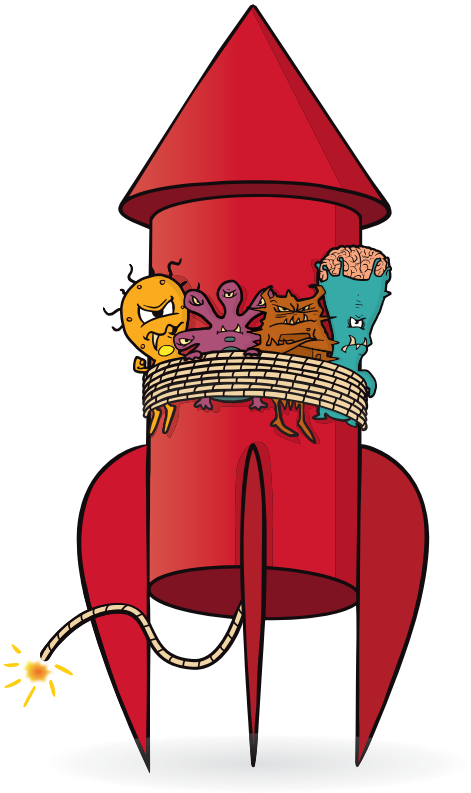

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Consider Yourself One of the Family

Laboratory medicine has a unique and precious attribute – its warm collegiality

As a science communicator, I love introducing new people to the things I do and the fields I study. That's true at any level – teaching schoolchildren about DNA, diagramming the components of the cell for aspiring artists, or showing doctoral students just how broad and how fascinating pathology and laboratory medicine can be. Recently, I attended a science fiction convention to talk about how the human body has evolved over time; I gave a talk on science and medical writing to a group of postgraduate communications students; and I hosted a workshop on scientific and medical realism for novelists.

And, best of all, I traveled to one of the year's largest pathology conferences with my colleague, Luke Turner, whose name you will have spotted on several of our recent articles. What particularly warmed my heart was seeing how pathologists and laboratory medicine scientists welcomed Luke and how eager they were to tell him about their research, their clinical work, their subspecialty interests. Indeed, many people in attendance had never met either one of us before, yet they welcomed us as part of the community.

And "community" is not a word I chose lightly. Over the course of the conference, I watched old friends greet one another and sit down for a shared meal. I saw junior pathologists consulting on cases with emeritus professors from institutions thousands of miles away. I saw students learning about careers in everything from molecular pathology to medical laboratory science – often from people who may, in a few years' time, become their colleagues or even their employers.

In my line of work, I have many questions for laboratory medicine professionals. In fact, I often use this page of the magazine to ask them. But today, I just want to say congratulations – and thank you. Congratulations on creating a warm and welcoming community, both online and in person. Congratulations on working so hard to bring new and aspiring colleagues into the fold. And thank you for numbering all of us at The Pathologist among you.

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

What Do You Know About CQI?

Cate Wight explains why continuous quality improvement is relevant to pathologists

I've heard it said that continuous quality improvement (CQI) is for laboratory staff – to improve their processes so that slides or results reach pathologists in a timely manner. From there, the pathologist can undertake the interpretation and write the report for clinicians. But I don't believe CQI is the exclusive domain of non-pathologist laboratory staff; I firmly believe that CQI is for pathologists, too.

Reporting is a process. For me, it involves continuously asking, "Is what we are doing the best way of doing it for the clinician and the patient?" For instance, how do we decide which case to report first? What steps are involved? Are any steps duplicated – and, if so, why? Could technology be used to speed up the reporting process? How could we minimize frustrating defects, such as histology slides needing deepers or blood tests needing to be repeated? Could the pathologist coordinate an improvement project with the lab staff involved to minimize the defects that carry the greatest time costs? Is my office tidy enough that staff who need to find slides for multidisciplinary meetings have a chance of locating them? Could we implement a system of colored trays to make their job easier and quicker – thus giving the pathologist more review time?

It's important to ask questions like these about every step of every process in the laboratory. So how can you and your colleagues get involved? The Royal College of Pathologists have launched the first annual CQI Awareness Month in May 2019 – and they've created several activities to help. These range from podcasts, in which pathologists who have experience of CQI tell you what they learned in the process, to a social media challenge in which participants apply the Lean 5S process to their own workspaces (#5SMyDesk). The organization is keen to help pathologists and laboratory medicine professionals move toward CQI, so it's also offering CQI mentoring, audit certification schemes, and a variety of online resources and workshops.

Game of Exosomes

A new lab-on-a-chip device aims to facilitate rapid, noninvasive early cancer detection from a single drop of blood or plasma

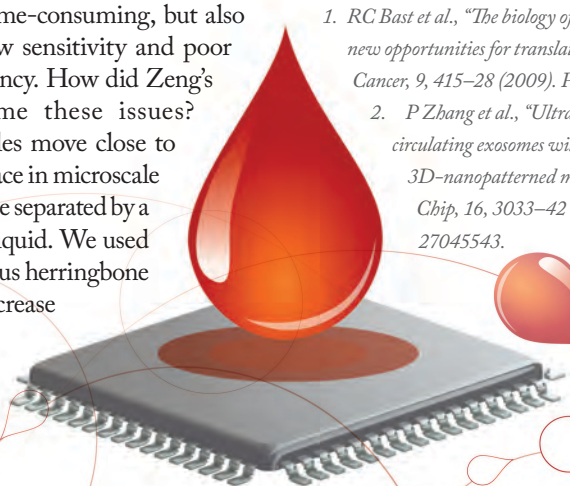
Early cancer detection is an elusive, but highly appealing goal – especially in cancers that often go undiagnosed until the advanced stages. One example is ovarian cancer, in which well over half of women are diagnosed at stage III or IV (1). Now, a new lab-on-a-chip device can detect cancer quickly and noninvasively in a droplet of blood or plasma by identifying tumor exosomes (2) – extracellular vesicles that play an important role in cell-to-cell communication.

Although exosomes were historically thought of as cellular "trash bags," recent discoveries have revealed their unanticipated significance. "In the past decade, we have realized that exosomes deliver molecular instructions in the form of nucleic acids and proteins that affect the function of other cells," says lead author Yong Zeng. When produced by tumor cells, exosomes stimulate tumor growth and induce metastasis, making them ideal targets for cancer detection. But their rarity during the early stages of cancer makes spotting them a challenge that requires an ultra-sensitive biosensor.

Existing methods for exosome detection are not only time-consuming, but also suffer from low sensitivity and poor isolation efficiency. How did Zeng's team overcome these issues? "When particles move close to the sensor surface in microscale channels, they're separated by a small layer of liquid. We used a 3D nanoporous herringbone structure to increase the surface area for exosome capture within the chip and physically push exosomes into contact with the chip's sensing surface, which contains antibodies specific to the proteins present on exosomes." Zeng likens this approach to draining a million tiny sinks to allow items floating on the surface to touch the bottom.

When the device was tested in ovarian cancer patients, it was able to detect tumor exosomes in miniscule amounts of plasma. Specifically, the team discovered that a protein called folate receptor alpha is present in ovarian cancer exosomes, but not in those from healthy controls. The fact that the device identified exosomal folate receptor alpha in the plasma of early-stage ovarian cancer patients underlines its potential suitability as a biomarker detector.

One of the most attractive aspects of the device is its accessibility; the lithography-free fabrication method permits low-cost, rapid, and large-scale production of 3D nanostructured patterns. Without the need for high-tech nanofabrication equipment, the device could easily translate into any clinical setting. So what's next? The team intends to pursue clinical applications by targeting multiple cancer types. "Although there is still a long way to go before we validate the device for clinical use, its potential adaptability to different diseases and biological targets – such as cells and viral particles – gives us great optimism for the future."



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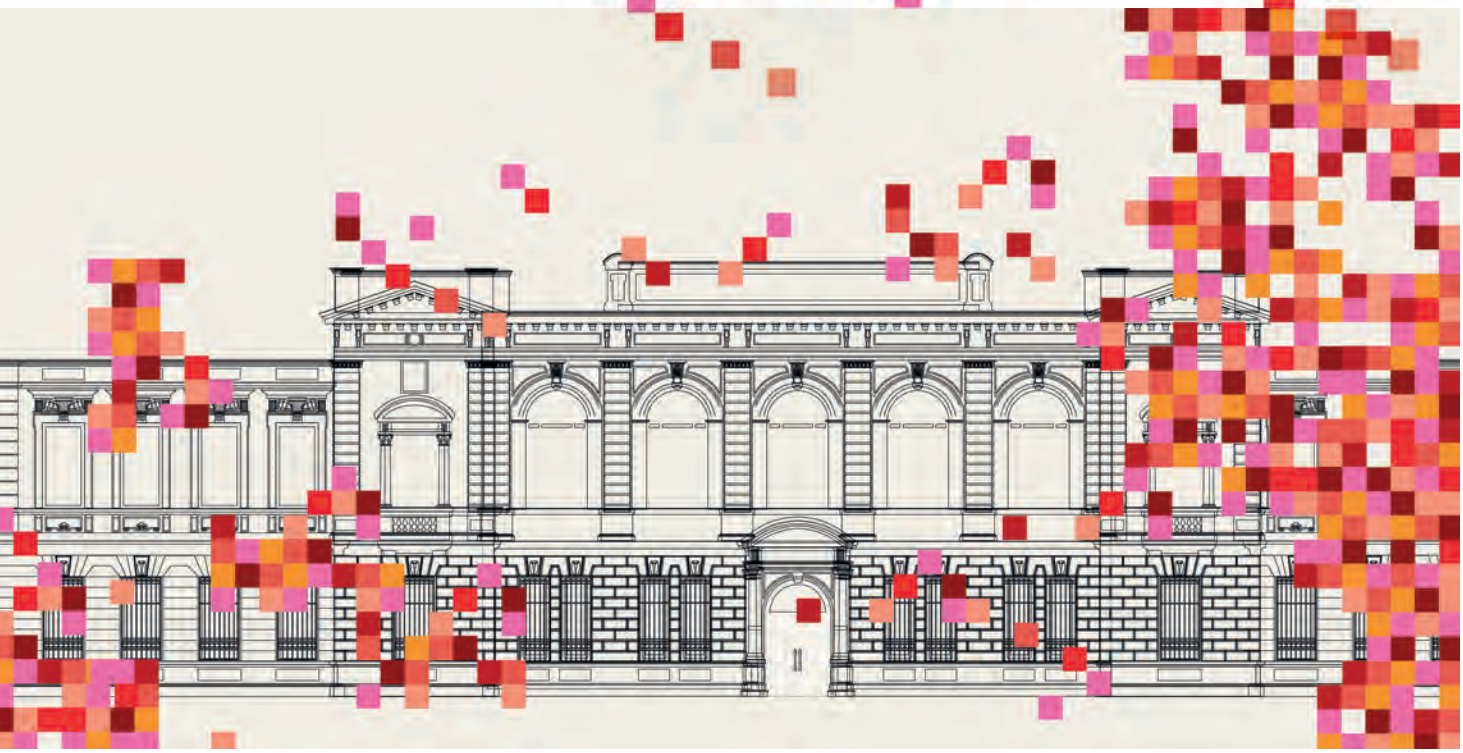


A Digital Museum

Digitizing an entire pathology museum to provide unlimited access to specimens

Established in 1959, the F.A. Hadley Pathology Museum at the University of Western Australia is home to over 3,500 pathology specimens. These cover a wide variety of pathological processes and include all of the human body systems. On the face of it, the collection is a vitally important resource for teaching and learning – but, unfortunately, its educational impact is limited due to access restrictions, heavy and fragile tissue specimens, and few experts to demonstrate specific disease processes. Thanks to a new project, those restrictions are about to be lifted…

What?

The Pathology Education and Learning Centre (PELC) aims to catalog the entire collection of specimens in an online database. High-resolution images and the original pathology findings are available on the PELC, which classifies specimens according to the Systematized Nomenclature of Pathology – the original system used in the museum. Each specimen provides information on the clinical history of the patient, microscopic and macroscopic findings, and the original diagnosis.

Why?

Rather than running traditional "bottle tutorials" – requiring access to the physical specimens and a large amount of space – the PELC allows students to explore the specimens at any time, in any place. The high-quality images showcase the specimens in more detail and with more clarity than would be possible from holding the glass bottles. With the ultimate goal of delivering insight and showcasing discoveries to improve the future health of society, the PELC shares valuable knowledge with the wider community to highlight the importance of pathology in healthcare delivery.

Who?

Although the primary target audience of the PELC is students from school year eight (ages 12–14), the specimens provide a valuable resource for students of all ages and practitioners in health-related disciplines. For this reason, the PELC is freely available worldwide; users just need to register before accessing the entire database. Its creators are working to secure partnerships and further funding to ensure long-term sustainability.

When?

Over 1,200 specimens are already available through the PELC, 30 percent of which contain images. The future ambition is to focus on high-quality content – including photography – as well as functionality to provide a seamless, enjoyable, and rewarding learning experience. Those behind the project hope to have the whole F.A. Hadley Pathology Museum collection of 3,500 specimens on the PELC by the end of 2020.

A Field in Transition

How close are we to the full-scale clinical deployment of AI? We round up some of the most exciting stories in computational pathology today

What's the Holdup?

Although the vast majority of labs use digital viewing systems for quality assurance and professional development, the use of digital pathology in routine workflows remains relatively uncommon, and whole-scale adoption is even rarer. A key challenge in driving this adoption is the business case – cash-strapped providers are often reluctant to back digital pathology. "Linking the business case to lack of staffing helps, but the efficiency savings in existing senior staff time, as well as multidisciplinary team time savings are the real levelers," says Jo Martin, President of the Royal College of Pathologists.

Predicting Prognosis

Digital pathology has opened a number of doors for the development of image analysis tools to detect disease. But what if we could use digital techniques to predict recurrence risk, disease aggressiveness, and long-term survival? Hoping to offer alternatives to molecular assays, Anant Madabhushi and his team have already made technological breakthroughs in several disease domains, including breast, prostate, and lung cancer. Their ultimate aim? Routine use of computer vision algorithms to identify and extract histological biomarkers visible in the tissue.

Putting the Algorithms in Pathology

Although numerous studies have demonstrated deep learning algorithms' potential to match – or even better – the accuracy of highly trained diagnostic experts, they haven't yet entered routine clinical use. "I get very envious when I see fields such as ophthalmology and radiology already using FDA-approved deep learning algorithms – we need to bring pathology to this level," says Johan Lundin, Research Director at the Institute for Molecular Medicine. To drive development and broaden the potential applications of AI, Lundin calls for more accurate annotation, wider sharing of annotated images, and the use of supervised learning to develop algorithms for less subjective endpoints.

Centers of Excellence

A number of UK centers backed by government funding are striving to advance the clinical deployment of AI for disease diagnosis. David Harrison, Lead of the iCAIRD Consortium in Scotland, believes that the key to success is to use digital pathology to transform workflows and inform decisions, rather than to make a diagnosis. The NPIC Consortium in Leeds has similar ambitions, aiming to digitize 760,000 slides per year with the ultimate goal of full digitization of National Health Service (NHS) laboratories. Meanwhile, the PathLAKE Consortium is building a data lake of "real-world" NHS data that will culminate in the world's largest repository of annotated pathology images.

Into the Deep for Histopathology

Jeroen van der Laak, Group Leader of the Computational Pathology Group at Radboud University Medical Center, has explored the potential of deep learning for pattern recognition in digitized breast cancer slides. "The most straightforward application is automated assessment of the lymph node status, which may support tumor staging," says van der Laak. The team has also developed algorithms that automatically recognize and count mitotic figures, aiding breast cancer grading. They hope that, with the discovery of novel prognostic biomarkers, these algorithms will drive the advancement of precision medicine.

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

Working As a "Neither"

Pathologists' assistants may not be well-known, but our contributions are invaluable

By Alice Levin, Pathologists' Assistant in the Department of Pathology and Laboratory Services, Denver Health and Hospital Authority, Denver, USA

For more than a decade, I have worked in more than a dozen hospitals and laboratories as a "neither." In healthcare writ large, but particularly the laboratory, there is a vastly misunderstood in-between into which highly trained, specialized practitioners fall: neither a doctor nor a laboratorian in the traditional understanding. We are in nearly every community hospital, university, academic facility, and reference laboratory in the United States, and we have an expanding international presence. If an organization recognizes our existence as a credentialed specialty not synonymous with any other laboratory role, we are nevertheless often lumped in with any number of other laboratorians for practical purposes – a situation that leaves us without clear definition in the institution's organizational structure.

We are, by education and training, experts in macroscopy. Depending on how far afield of our professional title an employer may stray, you may know us as many loosely applicable descriptors, but we are, in title and in certification from the American Society for Clinical Pathology, pathologists' assistants.

Professionally, my experience is one of belonging to neither the category of provider nor the category of laboratorian. We are most often managed by laboratory administration, but simultaneously beholden to the pathology group (whether a separate business entity or internal to the larger organization). We serve two masters, yet neither is entirely clear on our place in the healthcare hierarchy. Because our education, experience, and certification place us in a higher pay grade than some laboratory supervisors or managers who may be laboratorians by training, we not infrequently face the difficulty of earning somewhat more than our bosses. As such, our administration may be reluctant to negotiate a competitive rate of pay or provide us with benefits or perks that they may readily offer to a non-laboratory provider.

"It seems as if all pathologists' assistants must explain their existence on a daily basis."

Some organizations define us as non-exempt hourly employees, similar to a medical technologist or cytotechnologist in the lab, whereas others define us as exempt salaried employees (as they would a physicians' assistant or other advanced practitioner). Some hospitals group us with physician's assistants and provide employment perks commensurate with those afforded to other advanced practitioners. These institutions may also require us to be credentialed in the

same category as those who are free to dispense controlled substances or – my personal favorite – require us to know the Association of Operating Room Nurses guidelines for donning, doffing, and scrubbing in for sterile procedures… for no practical reason.

We are more than grossing techs (said with all the respect due to the histotechnologists and others who gross large volumes of non-complex specimens at some facilities). Our education, practical training, and experience allow us to be expert teachers in the gross room for resident physicians, medical students, medical laboratory science students, and any number of other learners. We provide educational lectures and tours to students, other laboratorians, and visitors. Our expertise and attention to detail compel us to contact providers, surgeons, nurses, or administrators when we suspect a specimen is suboptimal or compromised or an unexpected finding may necessitate additional specimens or testing. Frequently, we serve in official or unofficial administrative roles – writing procedures, collecting data, creating maintenance logs, inventorying, preparing for inspections by CAP or the Joint Commission, and so on. Some of us are technophiles and work with IT to troubleshoot the LIS/HIS, optimize voice transcription software utilization, or bang on hardware in the gross room. We are the backbone of a well-run gross room and morgue.

If you are a pathologist or laboratory administrator who has never heard of us, there is no shame in that. It seems as if all pathologists' assistants must explain their existence on a daily basis. We joke that even our families fail to understand what we do, noting that the only aspect anyone is interested in is "cutting up bodies."

If you work with a pathologists' assistant, learn more about his or her experience, expertise, and potential as a highly trained specialist beyond simply grossing. If you want to learn more, the American Association of Pathologists' Assistants website (pathassist.org) includes abundant information about our profession.

Most of all, thank you to those in pathology who acknowledge our daily efforts to make the pathologists' jobs and lives easier. A content pathologist is the sign of a competent and successful pathologists' assistant.

Death Under Scrutiny

How a new national system of medical examiners can support patient safety

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

As of April 2019, the UK has implemented rollout of a national system of medical examiners to increase patient safety and support bereaved families – a step forward that I believe will provide increased accountability, sensitivity, and credibility to the processes surrounding a death.

What is a medical examiner? These doctors are senior physicians from a range of disciplines including pathology, primary care, acute medicine, and many other specialties. They act as independent doctors in the review of deaths. Why has the UK's National Health Service (NHS) decided to employ medical examiners? Three independent inquiries into NHS failings – the Shipman Inquiry, the Mid-Staffordshire NHS Foundation Trust Public Inquiry, and the Report of the Morecambe Bay Investigation – recommended that certificates for cause of death should be scrutinized by an independent doctor.

I was a medical examiner in the pilot scheme at the Royal London Hospital and saw firsthand how valuable the role was, not only as support for those certifying deaths, but also – and most importantly – for loved ones and families. I heard details, occasionally worrisome, but far more often deeply gratifying, about the services we gave to patients during their treatment and at the end of their lives. I fed back to the teams involved and was happy to see that either things improved as a result, or the staff were appropriately congratulated. I helped junior colleagues learn more about death certification and to feel supported in the learning process. Evidence from pilot sites showed that bereaved families valued the opportunity to ask questions and discuss concerns about the death of their loved one with an independent doctor.

Medical examiners are a key part of the drive to improve patient safety. When issues with care are identified by families, or by the examiner during scrutiny of the records, they can be fed into governance systems in the organization providing care or escalated to a Coroner. Positive feedback for staff and organizations is also part of the process! Learning from the examiner system is key to a culture of continuing safety improvement, and will link to other programs aimed at learning from deaths and to established systems, such as structured judgment reviews.

The other broader aspect of the examiner's role is to help ensure high-quality data on causes of death through accurate certification. Such data helps in monitoring the "health" of the population, and feeds into local health planning and national public health. We cannot plan future health services without accurate data on what is causing death in our population!

As lead medical royal college for medical examiners, the Royal College of Pathologists is firmly committed to the patient safety and public health benefits this program will bring. We are providing support for doctors who wish to take on this important new role by delivering training and ensuring medical examiners have a collective voice through our medical examiner committee. We have also created resources for organizations that are planning to set up a medical examiner system.

The system will be rolling out across acute and community services, starting in the acute setting; although some services are already operational in primary and community care. The range and number of these "full-service" systems will increase, and we will continue to encourage this spread to ensure that everyone can benefit from the new system of medical examiners – and perhaps, one day, other countries will be able to learn from this example.

Leading the Way to Success

Leadership and management skills are vital to keeping our place at the strategic table

By Dan Milner, Chief Medical Officer at the American Society for Clinical Pathology, Chicago, USA

The leadership fellowship Bethany Williams describes in her interview with The Pathologist (1) is a refreshing look at a novel program – one that may be a voice for change in the profession of pathology and laboratory medicine. More than just an informatics fellowship, this unique program appears to be the first of its kind to focus on the tools and skills of leadership and management, which are much needed in our discipline.

It is unfortunate that essential leadership and management skills are not generally taught in pathology training models. All too often, "leadership" is confused with "title" or "position." In academic medicine, the system has historically promoted individuals due to age, publication productivity, or grant funding. These accomplishments, although impressive, are not necessarily indicators of true leadership and do not in any way suggest that a person is capable of managing. This is true for microbiology, cytopathology, molecular diagnostics, and every other aspect of pathology and laboratory medicine.

Another common fallacy is that "the one person who knows" should be in charge. I remember well when informatics came into being and several of my senior faculty suddenly became "informaticians." Next, we started recruiting residents who wanted to do informatics. Now, of course, it is a vital branch of our enormous tree – a specialty in its own right with a clear curriculum and obvious role in the practice of pathology. But the skills of the people entering this field are, by and large, computers – not leadership or management. To assume that, because someone is the only person in your institution who understands a computer, they should be in charge of informatics (or IT) is a mistake. The same naturally holds true for any subspecialty in our field, and for any laboratory in the world.

Pathologists and laboratory professionals are often underappreciated and do not get a seat at the table for major strategic planning. But that is not because what we do is unimportant; in fact, our work is arguably one of the most important aspects of a healthcare system! The reason we often lack input into important plans is that we do not use leadership and management skills to demonstrate our value within the system, present it to those who are not familiar with pathology and laboratory medicine, and strategically plan its contribution to the whole. It is not enough to step up to the table as an expert and espouse the value of what you do every day; personally, I have found that actually often turns the C-suite off.

Strategic leadership planning requires selflessness, accountability, transparency, compromise, an ability to see the whole system, and the skills to reach solutions that achieve a common goal. It is true that not everyone can be in charge, but that doesn't mean that not everyone can have, understand, and use the teachable skills of leadership and management. It doesn't matter how you parse situations – whether by role, goal, personality, or any other approach that works for you. What matters is that you think like a manager when parsing those situations and tackling those goals. Through fellowships that hone such skills, people like Bethany Williams will gain the ability to think this way in informatics – and beyond.

Reference

1. *M Schubert, "Leading by Example", The Pathologist, 53, 50 (2019). Available at: https://bit.ly/2ZD8ml6.*

The Biggest Piece of the Puzzle

Delivering excellent patient care through big data

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

As laboratory medicine practitioners, we're always looking for innovative ways to improve our practices. Whether it's remodeling the lab based on spaghetti diagrams, configuring our workspaces according to Lean best practices, or educating the clinical care team through consultation, our end goal is to ensure we deliver excellent patient care as efficiently as possible. However, perhaps the biggest piece of the efficient laboratory puzzle is nonverbal: leveraging big data to drive quality laboratory results and improve the lab ecosystem, thereby enhancing patient care and benefiting the entire healthcare system.

"Leveraging our data is not a future thing. It's a now thing."

"Big data" is a term that gets thrown around a lot, but what does it mean for pathology and laboratory medicine? Every report you generate, every result you turn out, every culture you finalize, every bag of blood you send to the floor for transfusion – all of that contributes to the data the lab generates each year. It's estimated that around 10 billion laboratory tests are performed each year in the US. To put that in perspective, lab tests are ordered at three times the rate of imaging studies. These assays range from cord blood analysis on newborn babies to strep throat screens on children to postnatal workup on new mothers to colonoscopy biopsies to end-of-life palliative care. It's not hard to believe that 70 percent of medical decisions are reached due to laboratory test results. These results – this mountain of data we generate each year – are big data.

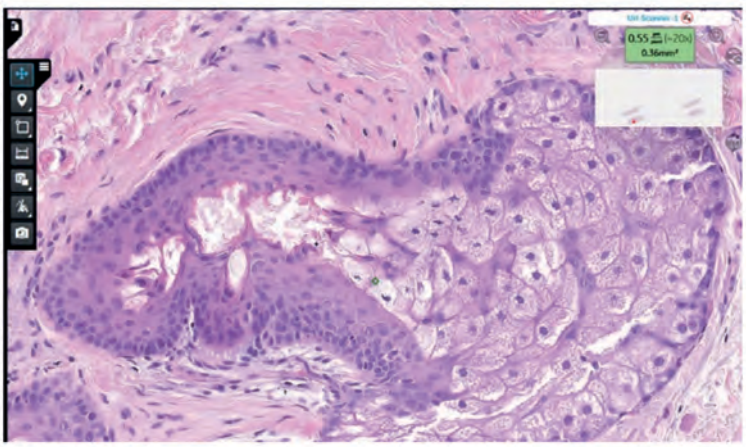
Where can the data we generate each day lead us? We can analyze test usage to not only refine our test menus, but also design electronic requisitions that reduce incorrect or redundant test orders to help ensure we reach our "right test on the right patient at the right time" goals. Laboratory test usage data can also help allocate more resources to the busiest shifts or departments so we can make better use of our most important assets and improve employee retention.

We can analyze call center data – what questions do clinicians call the laboratory with, for example – to design and generate user-friendly lab reports. We can also use STAT turnaround time data and critical value incidence rates to improve processes for communicating with the clinical care team. And we can analyze workflow patterns and benchtop organization to ensure we're making the best use of our space and staying up to date with Lean best practices.

Leveraging our data is not a future thing. It's a now thing, and the only limit to the possibilities is your imagination.

1 Million Reasons

In a quiet, yet purposeful way, the world of pathology changed with little fanfare on February 22, 2019 – a change that will allow pathologists to positively impact the lives of people all over the world.



This change was put in motion at the Ohio State University (OSU) James Cancer Center, when Inspirata and the OSU pathology team scanned the 1,000,000th tissue image to form the largest library of whole slide images (WSI) in the world. Forming the most extensive tissue image resource for cancer research and laying the foundations of accelerated clinical care, this monumental achievement established the new era of digital pathology as real.

Every patient's battle with cancer begins with their diagnosis. With the advent of slide scanning devices, pathologists are using whole slide images (WSI) for primary diagnosis and treatment effectiveness assessment, as well as conferences, tumor boards, and case sharing. Furthermore, researchers have been using whole slide images to interrogate many aspects of histology with deep learning and artificial intelligence, which was not previously possible using traditional analog-based pathology.

A founding reason – accelerated care

Accelerating time to initial diagnosis, time from diagnosis to treatment initiation, and even early treatment pathway assessment is becoming an increasing priority in cancer care. To accelerate both clinical and research needs, Inspirata has built the world's largest WSI library. In the emerging era of digital diagnosis and artificial intelligence, access to a large volume of digital data becomes more important than ever. Less than one year ago, Inspirata announced that their digital pathology system was used to make the first-ever primary digital diagnosis in the US, heralding a new era in cancer diagnostics. The company created the world's first comprehensive high-throughput scanning facility at OSU, which has now scanned over one million whole slide images in less than 18 months.

The undertaking has included scanners from multiple vendors, full-time staff supplied by Inspirata, comprehensive planning, standard operating procedures, project governance, workflow review, communication and stakeholder engagement activities, system integrations, file storage, and IT support. This historic accomplishment has demonstrated Inspirata's ability to scan and support large digital pathology implementations while simultaneously creating imaging data that are now speeding up clinical and research efforts.

An efficiency reason

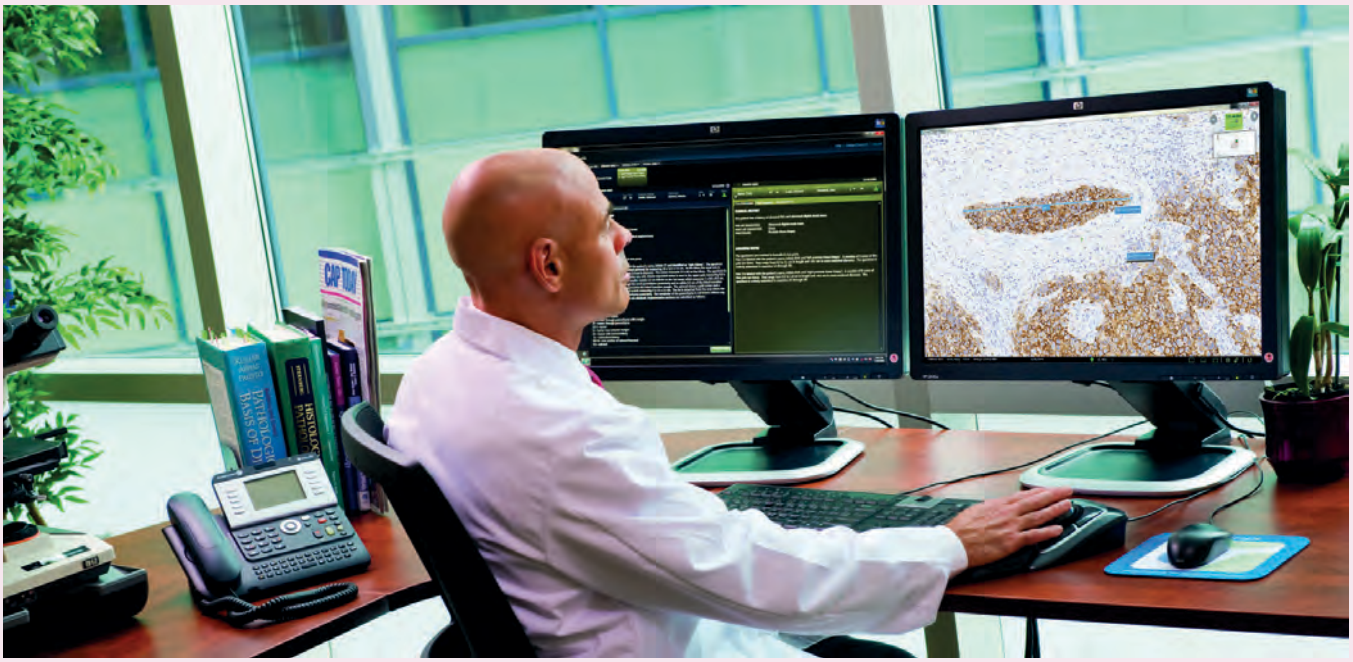
Pathology continues to feel the strain of more cases per pathologist. Now, coupled with large WSI libraries, pathologists can access priors at a touch of a button, perform quantified image analysis, and even offer patient hours wherein the pathologist can offer to view a patient's sample and engage in a far more interactive role in the patient's experience. Never before have pathologists had such a direct ability to impact patient care.

What has been required is a hub to the pathology ecosystem. Dynamyx™ brings each of the valuable aspects of digital pathology together in a single accessible and easy-to-use workflow, giving pathologists all over the world a reason to adopt Dynamyx™ digital pathology.

A million reasons

The advancement of artificial intelligence and deep learning technologies make WSI libraries even more important and valuable. The extraction of critical data and patterns from WSIs ushers in a new era of scalable and accelerated research opportunities. A million WSIs provides real reason to get excited.

"Accelerating time to initial diagnosis, time from diagnosis to treatment initiation, and even early treatment pathway assessment is becoming an increasing priority in cancer care."



Anatomy of Dynamyx™

Data Mediator

Dynamyx™ provides an agnostic architecture that permits integration with almost any slide scanner, AP-LIS/LIMS, and image analysis platform, allowing pathology departments to pursue a multi-vendor approach. As scanning technology continues to advance, hospital consolidation continues to proceed, and vendor performance waxes and wanes, pathology departments can protect their investments by using Dynamyx's broad vendor integrations.

The Data Mediator leverages Inspirata's market-leading Enterprise Service Bus (ESB) to enable a diversified vendor strategy. The Data Mediator is the backbone of our workflow management toolsets, facilitating the flow of images and connecting data between scanners, laboratory systems, and best-of-breed algorithms that enhance the pathology workflow.

Knowledge Hub

Dynamyx™ brings all of your data together into a seamless workflow accessible via our Tissue Diagnostics Knowledge Hub. Here, Inspirata applies our deep experience in digital pathology workflow and value-added analytics to develop the methodology and technology needed to offer a comprehensive pathology platform. The heart of the Inspirata Knowledge Hub is artificial intelligence; it enhances the pathologist's ability to accumulate, augment, and disseminate knowledge from a customizable suite of algorithms, reference materials, and AI-driven tools.

These innovative assays are a key business driver for the utility of digital pathology and the adoption of this emerging technology. Digitization of large libraries of WSIs facilitates a quantitative approach to evaluating disease recognition and progression. Our Knowledge Hub puts the power of these tools in the hands of your pathologists.

API Garden

Dynamyx™ boasts an "open" architecture designed to enable customers to arrive at their preferred blend of laboratory technologies. Inspirata is committed to accommodating the nuanced requirements of each individual customer by providing an "API Garden" that allows each pathology department to continue to build upon their digital pathology capabilities at a pace that makes sense for their organization.

The API Garden leverages Inspirata's deep partnership capabilities with AP-LIS/LIMS information systems, image analysis tools, and even reference material and quality assurance strategies.

Conferencing Hub

Dynamyx™ facilitates the sharing of WSIs through its Conferencing Hub, allowing pathologists to achieve qualified diagnoses with peers anywhere in the world. Users can share in real time or by sending cases. The Dynamyx™ real-time collaboration allows an unlimited number of users to access, comment on, and annotate a slide at the same time, regardless of their physical location. Furthermore, entire cases can be shared in an identified fashion with approved users or de-identified for any collaborator. These cases include the WSI and the clinical history, gross images, and other pertinent diagnostic information. Driving collaboration elevates the impact and importance of pathology on the entire cancer care process.

Know Your Strength

Women tackle gender-specific career issues in pathology and lab medicine

In many respects, laboratory medicine is a trailblazing field. Not least among its achievements is an unusually welcoming environment for women, who now outnumber men as new practitioners in the field (1). However, does the influx of women into one of many traditionally male-dominated fields signal that all is well? Unfortunately, not by a long shot.

Despite equivalent relative value units (RVUs, a measure of the value of physician services), there are still fewer women than men in senior academic and clinical positions. And among those who do make it to the top, the pay gap between women and men is actually increasing (2). So why, in an apparently enlightened age of equality, do these differences still exist? And what other unique issues do women in pathology and laboratory medicine face?

Hoping to gain some insight, we asked you to share your questions about women's career issues in the field. The answers come from an international panel of women – all of whom are navigating highly successful careers in various laboratory medical disciplines.

Elizabeth Montgomery is Professor of Pathology, Oncology and Orthopedic Surgery at Johns Hopkins School of Medicine in Baltimore, USA.

Suzy Lishman, CBE, is Consultant Histopathologist at North West Anglia NHS Foundation Trust, UK, and immediate past president of the UK's Royal College of Pathologists.

Marilyn Bui is President of the Digital Pathology Association; she is also President of Medical Staff, a Senior Member of the Department of Anatomic Pathology & Sarcoma, Section Head of Bone and Soft Tissue Pathology, and Scientific Director of the Analytic Microscopy Core at Moffitt Cancer Center, Tampa, USA.

Debra Graves is Chief Executive Officer of the Royal College of Pathologists of Australasia, Fellow of the Royal Australasian College of Medical Administrators, and Fellow of the Australian Institute of Company Directors.

Sherrie Perkins is Chief Executive Officer of ARUP Laboratories and Professor of Pathology at the University of Utah School of Medicine, Salt Lake City, USA.

Diana Kremitske is Vice President, Operations, Diagnostic Medicine at Geisinger Health System, Danville, USA.

As a woman, what is your biggest challenge?

Luis Humberto Cruz Contreras (@luishcruzc)

EM: The challenges I face are the same as those faced by men: meeting deadlines, doing the best I can with an overwhelming academic schedule, handling my clinical duties well, and keeping my temper in check when there is a lot going on. Of course, I am constantly treated as a secretary – when I answer the phone, I am always mistaken for one and asked to provide secretarial services. This is annoying, wastes time, and does not happen to my male colleagues – but it is inconsequential. I am also still subjected to moronic explanations of topics about which I am quite knowledgeable, which is tiresome but – again – inconsequential. When my children were small, things were different; then, my biggest challenge was the chronic, debilitating exhaustion of dealing with work, the needs of the children, and domestic chores.

SL: I think women are often underestimated in the workplace, so the biggest challenge is getting the opportunity to demonstrate what you can do. Once you've shown how capable you are, people are likely to ask you to do more.

MB: You have to know and believe you are good enough. When that happens, you no longer seek approval from others to feel confident. It is in our nature to think from our hearts. Be compassionate and sympathetic, but keep a cool head when dealing with the root of the problem. When building a supportive network, choose strategic partners who will help you reach your full potential.

SP: My biggest challenge was always in striking an appropriate work-life balance while maintaining the respect of my colleagues – many of whom had non-working spouses. It was often hard for me to clearly articulate the value I brought and make the request for appropriate recognition or pay.

Studies show that the odds are often stacked against us for achieving equal promotion, equal pay, and equal respect. What are some tips for success in leadership roles?

Dana Razzano (@Dr_DR_Cells)

EM: Sadly, the reality remains that women have to work harder and be better to get the same recognition as men – and this is not always easy. This construct is slowly changing, but it will take a few more generations. When I began medical school in 1980, there were substantially more men in training than women. It struck me, as a junior attending reading pathology journals, that the few women on the editorial boards were all heavy hitters like Sharon Weiss and Elaine Jaffee. Many of the men, on the other hand, were unknown junior colleagues of the editor (always a man). I do not think that the editors of these journals were trying to be sexist; they simply felt more comfortable promoting junior male colleagues than female ones.

It has been wonderful to see editorial boards fill with women, but there are still few female journal editors – not least because the job is fun and the men in those roles have yet to retire! New searches, however, currently favor men. Some series, however, do have gender parity. For instance, I am the Editor in Chief of the new series of the Armed Forces Institute of Pathology (AFIP) Fascicles, published by the American Registry of Pathology – and there is also a new series of Wolters Kluwer books that I co-edit with Christina Arnold and Dora Lam-Himlin.

In 2019, women still lag behind in promotion, pay, and leadership positions. For us, the path still consists of working harder than men to achieve the same ends – but, slowly, the outlook is changing.

SL: I think it is vital that women put themselves forward for leadership roles throughout their careers. You can start small, as a student representative or committee member, for example. I've found that the first step is often the hardest – but once you're involved, you get to know people, gain a better understanding of the challenges and your own strengths and weaknesses, and can look out for further opportunities.

MB: Being in a leadership position does not equal being successful. A successful leader is measured by mastering the art and science of motivating people to achieve a common goal. It is true that there are fewer women in leadership positions. Our goal is not simply to increase the number of women leaders, but to be successful leaders. I don't believe leadership should start with the goal of "being the boss." Rather, I see it as the natural result of putting your heart, soul, and talent into something bigger than yourself – something you believe in – to earn those opportunities.

DG: Maybe I am lucky, but I have not experienced such problems in my career. I think one of the reasons is that I have never thought it would be an issue; I just assumed I would get where I wanted to be if I put in the hard yards.

SP: Although we have made great strides in becoming leaders over the past 20 years, women continue to face challenges in being chosen and accepted in leadership roles. Some of this comes from the perception that we are not as dedicated (perhaps due to family issues or lack of interest). I think many of these perceptions are changing as men become much more engaged in childcare and typical female/male workplace stereotypes are broken down, but many women still suffer from not being aggressive enough in seeking out mentorship and leadership opportunities.

Often, if we don't succeed with the first opportunity, we stop looking for experiences that will help us develop in our careers. Many women feel that, if we are not perfect, we are not good enough – yet fail to recognize the value of learning from mistakes and uncomfortable experiences. I have done many things over the course of my career that, in retrospect, were great in teaching me lessons about how to be a good leader, even though they felt like dead ends or like I was over my head at the time. One needs to look at the positives for each experience, but not be afraid to say no when

an assignment is not a good fit or won't help develop new skills.

I also find that women are somewhat reticent to ask for equal pay or promotion in comparison to male colleagues. Somehow, the fear of tooting your own horn or bragging never seems to stop most men in the field, but is a major hurdle for women (who tend to just "get on with it" without asking to be appropriately rewarded). Unfortunately, if you don't speak up, you will often be overlooked in favor of more vocal colleagues.

The most important pathway to success is the hard work of daring to seize new opportunities, even if they may seem uncomfortable. A great mentor to help you navigate new situations is also very valuable. In my case, a supportive spouse who shared in child-rearing, celebrated my successes as equal to his own, and was willing to occasionally compromise on issues was key to my success.

DK: It's no secret that women are underrepresented in healthcare leadership roles. A recent online commentary noted that only 16 percent of healthcare leadership roles are held by women (3). In another online article in the Harvard Business Review, it is stated that only 6 percent of women are in department chair roles (4). Why are there so few women in healthcare leadership roles? The reasons are many – and they're worth exploring to develop solutions for change.

The women leaders I know have earned respect by exhibiting confidence and demonstrating a continual desire to learn – not only through training, but also through immersive experiences – and to apply that learning to become better at what they do. They have been tested, persevered, and continued to seek out growth opportunities to attain leadership roles.

In addition to routine leadership skills, I offer a few tips for success:

- Make your career goals known to your mentor, offer ways to achieve them, and ask for support.
- Be a great leader (whether formal or informal) for your department by bringing clarity to goals and helping staff see how their role connects to larger goals.
- Maintain a strong network of connections internal and external to your organization and demonstrate the impact of your work to these connections.
- Move forward despite any challenges. Never stagnate.

How well do people worldwide accept women as lab directors?

Suraksha Rao B (@suraksharaob)

EM: It depends on the laboratory and the director herself. It may require extra work for a female director to command the same respect as a man; after all, it usually takes time and a demonstration of consistency and capability for a woman to achieve the respect that a man is immediately granted. We all need to teach our sons and daughters to respect leaders, regardless of gender, for the coming generations. These issues are all societal and can only change gradually.

SL: I have never experienced a problem with this in the UK and know many excellent female lab directors. Job descriptions shouldn't change depending on the gender of the director, so the work should be the same. If there's pressure on a female director to take on roles not usually done by someone in that post, she needs to be clear from the beginning that those activities are not part of her job description.

MB: In the US and Europe, people are more accepting of woman lab directors. Gender does have some effect, but leadership style has much more.

SP: I think that women are well-accepted as lab directors in many countries, although not universally. In my own experience, the gender of the director does not affect the functioning of subordinates in the lab, particularly if the leadership is appropriate and even-handed.

What impact do you expect the feminization of medical careers will have on the future of our profession?

Stefania Landolfi (@steland011)

EM: The pay will go down, of course. The quality will improve.

SL: Experience in countries and professions where this has already happened suggests that feminization of the workforce reduces its stature and rates of pay, particularly if there are other roles dominated by men. However, it has also led to improvements in working conditions, many of which both men and women enjoy. It is increasingly common for men to work less than full-time, and a good work-life balance is becoming desirable and attainable for all.

In medicine and other professions, women are taking on leadership roles and inequalities are decreasing. As the number of women in senior positions increases, the number of male-dominated jobs will decrease. Our aim must be for women to have the opportunity to work in all professions at all levels, helping us move toward a future where status and pay reflect not the gender of the person in the role, but their contribution and hard work.

MB: There are more women in medical schools. The number of women going into pathology is surpassing men, which will make it easier for the next generation of pathologists to find role models – and for society to accept women as leaders in the field.

SP: I think that feminization is already having a strong positive effect on issues such as work hours, alternative work paths (such as job sharing), and other issues that positively affect work-life balance and the practice of medicine. However, we continue to see erosion of reimbursement and pay despite the relative prestige and high satisfaction value of a career in medicine. Women will need to emphasize the value of this career choice to maintain appropriate pay.

What concrete steps are departments taking to look at female progression and compensation?

Yael Heher (@yaelheher)

EM: I cannot speak for all departments, but ours has studied time to promotion, absolute number of full professors, and transparency around compensation equity – and taken steps to change inequalities. This was probably prompted by laws concerning pay parity rather than by any virtue on anyone's part. The review was also initiated by women who pointed out the inequalities and pressed the issue. However, in countries without pay parity laws, women have to band together and loudly ask for reviews of such matters. In some places, reviews can be prompted when individuals gather as much data they can,

present those data to the administration, and publicly ask for clarification. Not many universities offer job sharing initiatives for anyone, male or female, but most physicians can organize flexible hours on an individual basis working with colleagues.

SP: Many departments are recognizing that women are an essential part of the medical field and are offering more flexibility to meet the demands that childbearing places on a career. Many of our male colleagues are also becoming more interested in work-life balance, helping to bring these issues to the forefront. As competition for high-quality academics of all genders increases, programs are recognizing the need to provide equality and flexibility. I see more and more accommodation for scheduling flexibility, pausing of the "promotion clock" to allow for maternity leave and other issues without penalty, and addressing gaps in pay. Though much work remains to be done, these changes have led to greater numbers of women at higher ranks and leadership positions over the years.

What resources are there to fund and invest in scientists with atypical career tracks – specifically, women taking time off for their small children and then re-entering science?

Liliana H. Mochmann

EM: The reality is that this is still a tough area. In the past, it was a kiss of death to take time off – and it still is if one wholly leaves the workforce when one has small children. Currently, the best approach is to scale back for those diaper years with a supportive PI, but it is still better not to scale back and, instead, to simply endure sleep deprivation for several years and become a master of time management. This is the strategy that my successful female colleagues with grant-funded laboratories and children have used. After all, men don't take time off, and you are competing with men. Lucky women in science have partners who are fully engaged in child-rearing, but most are not so fortunate.

If you think like the colleagues giving out grant money, you'll want to fund someone who is always working. That is why, ideally, one should have small children as young as possible – while a student, for example – to be on a level footing once competing for grants as a PI. There is still no real mechanism for taking several years off and being a leader in science. The best strategy is thus to initially link to a supportive lab and never take the plane off the runway to the hangar – even if it needs to sit on the runway for some time before taking off.

MB: Our hospital has a daycare on site. We also have a program that pays for babysitters so that parents can have an evening off or go to work when the kids are off from school.

SP: I think that the emergence of "team science" has helped, but it continues to be difficult to maintain a high-level scientific career and leadership without the extensive support of the institution (helping to bridge funding gaps), extraordinary effort by the woman to maintain continuity and relevance during years away from full-time work, and a degree of luck in funding. I think flexibility is important as your situation changes.

Pregnant pathologists should minimize exposure to chemical and biological agents. How can we safely perform our work in the laboratory?

Marta Garrido (@martiponi)

EM: Take universal precautions extra carefully and do your work in ventilated areas. Doing gross work in a ventilated hood is ideal, as is a mask with a filter. However, it depends on the types of samples you are handling.

MB: The workplace should be willing to accommodate pregnant pathologists by either assigning them duties free of such exposure or providing ways to shield them. Taking care of each other is just as important as taking care of patients.

SP: It is important to make use of all appropriate safety protections and do whatever possible to minimize exposure. If you feel uncomfortable, perhaps working with colleagues to redistribute workloads for a period of time in a fair and equitable manner may help minimize risk.

DK: Workplaces that handle chemical and biological agents should have a safety plan that includes tactics to minimize exposure to hazardous agents. A good safety process will include audits of personnel

and procedures when handling hazardous materials to determine compliance and areas of vulnerability to safety. Consult with a safety officer for your organization to discuss your personal situation and any specific concerns in the work environment.

I do not currently have children, but would like to in the future. Could you comment on your experiences with being pregnant while working in the lab and your work-life balance as a mother and a pathologist?

Lacey Durham (@laceydurham)

EM: There is nothing easy about having kids and working, and there is no easy time to do it. The key is a partner who is as engaged in parenting as you are – and if you don't have that, you just have to push yourself like crazy! However, there is a positive side. You have to get yourself very organized to handle kids and a consuming career. You have to take care of little things immediately; if you don't, more will appear. Learning this skill makes you ready to be very productive once children become more self-sufficient over time; you become more efficient than those without kids, or those who have someone else to care for their kids. Not allowing yourself to be a "helicopter mother" also helps.

Because there is no great time to have kids, my own view is to do it sooner rather than later. Get the kids out of diapers while you are a medical student or resident – when someone else is still ultimately responsible for the lab or patients – and you will have more time when you become an attending. When you are younger, you can also better handle the sleepless nights with infants. Of course, life does not always make this an option. If you are older, you can better afford household help! No matter what you do, you will work your backside off on all fronts, but become more efficient than most because you have no choice.

MB: It is a privilege, honor, and joy to be a mother. Helping my daughter reach her full potential personally and professionally is my top priority in life. When she was growing up, it was a struggle to balance life and work. As professional women, we need to realize that we may not always be able to have it all. At certain points in your life, work may take precedence; at others, the reverse may be true. Having a strong support network of family, friends, and colleagues is important no matter what stage you are at.

DG: Many of our trainees and young fellows combine working in pathology with motherhood. It seems to work well, but they say they need to be very organized and have assistance. Access to part-time work and training also helps.

SP: Being pregnant while working full-time – and, subsequently, having two small children – was one of the biggest challenges in my career. Having a supportive spouse who shared in household duties and took over when I needed to travel or be at work was really important and is a big part of why I am successful today. I also learned that being perfect both at home and at work was an impossibility; choosing what was most important on each particular day helped to maintain sanity and made sure that neither work nor home efforts became too unbalanced. The ability and willingness to pay others to help was essential, even though finding good people was sometimes a challenge. I also became a master of multitasking and learned to finish jobs and move on, rather than always striving for perfection and never finishing. Although I am really proud of my career, my family and my children remain my biggest and most lasting accomplishments.

How we can reduce the gender pay gap?

Nigar Anjuman Khurram (@NigarAKhurram)

EM: This can only be fixed by speaking up very loudly and en masse. Women are shy about asking for more pay and pointing out

disparities. Do it. Ask your male colleagues who are at the same level what they are paid and, if something seems off, point it out to whomever you need to. In countries where such discrimination is not legal, the powers that be may fear legal action and fix it. This happened to me in the early 1990s; I was told by my chairman that I was being paid a lot less than a male colleague with a slimmer CV because I had a husband.

SL: A lot of work is being done in the UK at the moment, led by Professor Dame Jane Dacre, to better understand the gender pay gap in medicine and what can be done about it. An interim report of the review (5) has found that men not only dominate senior positions, they also earn around 17 percent more than women in hospitals and 33 percent more in the community. The difference varies across medical specialties, with women overrepresented in lower-paid specialties. Although not mentioned by name, I would not be surprised if this included pathology. The final report, which will include recommendations to address the gender pay gap, will be published in September 2019 and is eagerly awaited.

MB: Transparency in pay between men and women should be public information. Institutions should have internal policies to bridge this gap. Our institution has a gender-neutral pay scale for faculty that is based on work experience and merit.

DG: I am not aware of such pay disparities in Australia, but they could exist. Most pathologists are employees either in the public or private sector. Public sector wages are usually based on awards that do not differentiate between men and women. More women do work part-time in Australia but, increasingly, men are opting for this too.

SP: One needs to be careful with "average" data, but if a woman is working at the same level as a male colleague, she needs to be vocal and firm in demanding equal pay. One must be sure to have accurate data, but clearly demonstrating equal amounts of work and experience will provide a strong argument for equal pay.

How can we promote genderblind peer review in pathology journals? Are positive discrimination policies needed to close the existing gap?

Laura G. Pastrián (@DraEosina)

EM: Several pathology journals have initiated blind review without any names or institutions listed. This seems like a great idea to reduce many types of bias, including gender bias. We can all work to promote blind reviews by suggesting this to journal editors we know!

Others may disagree but, in my opinion, affirmative policies directed at gender only serve to hold women back more. In my opinion, such policies legitimize the marginalization of women and create resentment. Sometimes, my institution offers luncheons for female colleagues. To me, these "ladies' luncheons" suggest that women, for some reason, need "extra help." We don't have men's luncheons – although some might argue that all the important meetings are men's luncheons! Such events often feature a female speaker on a scientific topic. Just invite her as someone from whom all can learn regardless of gender! No one wants to be invited to speak because of gender rather than skill and talent. The key is spotting the talent and creating opportunities. There are plenty of top tier women we should promote.

SL: I think that current policies should be applied fairly and everyone encouraged to put themselves forward for opportunities when they arise. Women often hold back, thinking that they're not good enough for a role. We need to get over our impostor syndrome and recognize what we have to offer. Selection panels should be trained in principles of equality and diversity and include independent members.

MB: We should promote review processes in which author information is blind to prevent bias. Similarly, if an institution is recruiting – for example – a new department chair, the committee should include women members and qualified women candidates should be considered.

DG: I do not think positive discrimination is a good idea. Women can achieve without such policies; in fact, I would personally feel uneasy about succeeding as a result of such a policy. I would rather do it on my own merit.

SP: I have never personally found gender discrimination in peer review to be an issue, but with many journals increasingly blinding reviewers as to authorship, it should become less of a potential problem.

What are the experiences of women of color working as clinical laboratory professionals?

Dana Bostic (@ThatLabChick)

EM: My colleagues who are women of color tell me that they are subjected to small, seemingly insignificant indignities on a daily basis. Each individual one is inconsequential, but the sum total becomes really tiresome and annoying. Being mistaken for members of the housekeeping or clerical staff is a recurrent theme. This does not happen to any white male colleagues, but African-American male colleagues are often taken for orderlies and parking attendants (if they are outside), which must be similarly tiresome. As noted above, I am simply mistaken for a secretary and subjected to explanations of topics on which I have ample expertise – and my colleagues of color are doubly treated to the latter, along with other aggravations.

MB: Do not let how society perceives you discourage you. If you are truly an effective leader who is doing the right things for the right reasons, anyone in their right mind will eventually see your value. Otherwise, it is their loss.

DG: Australia is a very multicultural society and we don't have a lot of problems in relation to this. If there are, appropriate mechanisms should be used to deal with the issue, as it is not something that can be tolerated.

Many lady doctors in India are given less credibility than their male counterparts – sometimes even called "Sister," the term for nursing staff. How can we address this?

Hasan Faheema (@histolover)

EM: That happens to a certain extent everywhere, including here in the US, and is one of the indignities that simply will have to change over time. You can only keep introducing yourself as "Doctor X" and politely repeating it and repeating it. If someone calls you "Sister" or "Nurse," keep saying, "I am Doctor X, your physician. Do you need something from your nurse? I will be happy to find them for you."

SL: It sounds like this reflects wider issues in society, not just challenges for women in medicine. I would just correct anyone who used the wrong title – but I'm sure it's more complicated than that!

SP: I was often mistaken for a nurse earlier in my career. I think gentle education as to your position and role, acting the part of physician, and not accepting the stereotype being forced on you are important approaches. However, these cultural stereotypes are difficult to overcome and it is often a long education process for patients, staff, and colleagues.

How can we organize mentorships for women? At the moment, we have to find them for ourselves.

Bamidele Farinre (@bamiprecious)

EM: That is always true, even for men. Some places assign mentors, but that only works if both parties are compatible in the first place. You have to seek advice and people will give it! No one is going to come to you and say, "Please let me help promote your career." You have to look for colleagues whom you admire and find a way to work with them.

SL: Some organizations do allocate mentors to new appointees but, in my experience, it's better to select your own. Choosing a mentor is about more than just finding someone doing what you'd like to do in the future; there's got to be an emotional connection. Organizations should support mentoring by providing training and opportunities for pairs to match up without being proscriptive. I would encourage everyone to find a mentor and not to hesitate to ask someone to take on the role. Most people are pleased to be asked and glad of the opportunity to support others.

MB: Our institution has a Women in Oncology program that pairs mentors with mentees. In that context, I meet with a colleague monthly to discuss issues that are important to professional development. I think this is a great initiative; in fact, my colleague and I actually discussed this and other reader-submitted questions with great enthusiasm. Ours is a two-year-old program, but other institutions have similar arrangements with a much longer history and measurable results.

DG: Mentors are a fantastic resource to assist anybody in their career. Generally, that relationship is something people source themselves but, if seeking a mentor, you can often ask your colleagues, friends, or professional organization to suggest suitable people. At the Royal College of Pathologists of Australasia, we have a mentoring policy and will help our fellows find a suitable mentor if they wish.

SP: I think that the value of having a good mentor is becoming more readily recognized and many institutions are trying to facilitate the process. I have had many mentors over the years, each bringing insight into different aspects of my career ranging from academic success to handling work-life balance to signing out cases efficiently. My best mentors have not been in formal situations, but have been people who were willing to talk, share experiences, and encourage. I think that being willing to seek and accept advice is the underpinning of great mentorship, but

one must realize that one person cannot fulfill all needs, and the amount of effort mentors put in can vary widely. Seeking out a mentor who can give you advice in a specific situation is often much more valuable than an "assigned" person who may not be a good match for your needs.

How can we change the perception that pathology is a good choice for women not because "it is the most compatible with being a physician mom," but because "it is the most rewarding career path for those who love to teach, mentor, work in a team, and do great medicine?"

Fabienne McClanahan Lucas (@DrFabLucas)

EM: Keep repeating what you just said! Put it all over social media. Tell medical students about it. Be hot stuff yourself!

SL: I think this is a challenge for the specialty in general, and much is being done to address it. We are all aware of the stereotypes surrounding pathology and have heard the comments about "not being proper doctors" or "being nerds with poor communication skills." We need to highlight the importance of pathology in healthcare and the range of fulfilling careers in the specialty to school students, the general public, other healthcare professionals, and policymakers. The better pathology is understood, the more likely people are to want to join the field because of the fantastic range of opportunities it offers. But I wouldn't knock the benefits of a good work-life balance for everyone!

MB: We need more successful women pathologists to share their passion and achievements – and the sheer joy of practicing pathology – with medical students to help them make wise career choices.

SP: I think that our actions and the demonstration of what a great career pathology provides are essential. We must stress our importance in patient care and as educators of physicians, rather than content ourselves with coming in and doing our work (often in the basement). This requires a willingness to engage with healthcare teams, serve on committees that include a wide variety of healthcare professionals, and freely offer mentoring to others. Being an active member of a healthcare team and providing value through expertise – not just providing a result – is an excellent way to engage.

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Go with the Flow

Advances in flow cytometric immunophenotyping for leukemia and non-Hodgkin lymphoma diagnosis

Laboratory medicine professionals involved in the diagnosis of leukemia and lymphoma will be familiar with the immunohistochemistry (IHC) techniques used to spot these diseases. It's likely that they are also familiar with flow cytometric immunophenotyping (FCI), an approach that – although less common – carries significant advantages.

In 2013, the FDA held a workshop that brought together laboratorians dealing with the complexities and expense of laboratory-developed flow cytometric tests (LDTs), clinicians relying on correct diagnoses to drive discovery and individual patient treatment, and regulatory agencies concerned with the safety risk posed by non-standardized assays. As a result of that workshop, Beckman Coulter Life Sciences pursued a de novo pathway to bring to market first the original five-color ClearLLab assay and, ultimately, ClearLLab 10C.

Each ClearLLab antibody combination is designed to characterize expected normal cells in a sample, while simultaneously highlighting and characterizing aberrant cells. Every tube contains CD34 and CD45 for the detection of blast populations and their cells of origin, and the tubes' design also allows maturation sequences to be identified, a key method for detecting abnormal populations. The ClearLLab 10C system's standardized instrument setup, 10-color control material, and analysis templates reduce the learning curve and make FCI more readily available to laboratories. Mike Keeney, Coordinator for Investigational Hematology and Associate Scientist at the London Health Sciences Center, and Jeannine Holden, Chief Medical Officer and Vice President of Scientific and Medical Affairs at Beckman Coulter Diagnostics, discuss the advantages of this approach.

How does flow cytometry improve on IHC for leukemia and lymphoma testing?

Mike Keeney: Flow cytometry plays a pivotal role in the diagnosis and follow-up of patients with leukemia and non-Hodgkin lymphoma (NHL). Its advantages over IHC include the ability to test a variety of small samples (including fine needle aspirates and body fluids), "gate out" cell fragments and debris from analysis, examine 10 intracellular or surface antigens simultaneously, detect level of antigen expression, and resolve multiple hematopoietic malignancies in the same sample.

IHC still has an important role to play in Hodgkin lymphoma and in situations where bone marrow aspirate results in a suboptimal sample. In addition, IHC preserves the architecture of the sample, which can aid the differential diagnosis of several lymphomas. However, a key advantage of flow cytometry is the speed at which samples can be analyzed. A stat result can usually be provided within hours, whereas the requirement to fix, decalcify, and embed the bone marrow in wax adds a significant delay.

Jeannine Holden: The fundamental advantage of FCI over IHC is FCI's capacity to simultaneously assess numerous markers. Whereas IHC can generally only assess one or two markers at a time, commercially available clinical flow cytometers can easily assess 10 at once, identifying co-expression of any combination of markers in a single tube. By repeating certain markers across several different tubes (antibody redundancy), the findings can be extrapolated to generate an even more detailed immunophenotype for essentially every single cell in the sample, while simultaneously assessing each cell's relative volume and cytoplasmic complexity. Finally, FCI can distinguish subtle differences in antigen density, permitting distinction among various normal and pathologic cell types that are difficult or impossible to perform with IHC.

This fundamental difference is the basis for two other advantages: small sample size and small target size. Whereas the serial sections required for detailed IHC quickly consume the small biopsies common in hematolymphoid malignancies, FCI generates a detailed immunophenotype on the first round of testing using a relatively small number of cells. Because the phenotypes of normal cells are reproducibly preserved within and between patients, FCI can distinguish and characterize aberrant cells that represent only 1 percent of the total sample* – and, because of its speed, neither antigen degradation due to tissue processing nor antigen retrieval is a concern (1).

FCI is the standard of care in the US for hematolymphoid malignancies, and in Europe and the rest of the developed world for patients whose disease presents primarily in the bone marrow and/or peripheral blood. Lymph nodes and tissues are increasingly studied with FCI in these geographies as well.

How does the ClearLLab 10C system improve efficiency and reduce error?

JH: By eliminating most of the manual steps involved in staining and/or reagent cocktail preparation, ClearLLab 10C minimizes manual pipetting errors in these steps – as well as reducing the risk of repetitive motion injury from reagent pipetting. From a laboratory efficiency perspective, ClearLLab 10C eliminates the need for panel design and its shelf-stable reagents eliminate the need for cold shipping and cold storage. The waste generated by wet reagent handling is no longer an issue, and low- and high-volume laboratories can use the same system and scale kit orders appropriately as their volumes grow.

MK: Because most flow cytometry laboratories use their own LDTs, it's difficult to compare results across centers. Additionally, the level of expertise in choosing the right antibodies and fluorochromes for leukemia and lymphoma immunophenotyping is challenging and requires highly trained personnel – especially as the number of colors increases to as many as 10. The time

spent validating different antibody clones, preparing and validating cocktails, and ensuring that cocktailed reagents do not degrade is significant. The ClearLLab 10C system standardizes the flow cytometry approach from instrument setup and compensation to 10-color control material and analysis templates – areas where many labs without flow cytometry experience struggle.

How does it improve standardization and validation of results?

JH: Unlike previous attempts at LDT standardization, intra- and inter-laboratory standardization among ClearLLab 10C users is straightforward and does not require direct coordination. The pathologist can consequently concentrate on analyzing and interpreting the data, rather than worrying about whether the assay design was robust or if deviations from manual laboratory protocols may have introduced new artifacts.

MK: With one fixed set of reagents, validation is reduced to comparison with current reagents or lot and verifying quality control results.

What is significant about the antibody panel at the heart of the ClearLLab 10C system?

JH: The ClearLLab 10C system employs 10-color reagent combinations of antibodies designed to characterize both normal and aberrant cells. The normal cells, or "normal internal control," are the key to FCI for hematolymphoid malignancies. The more detailed the normal immunophenotype, and the more familiar the pathologist with both the normal immunophenotype and characteristic deviations typical of various malignancies, the easier it becomes to recognize even subtle aberrations. To that end, the ClearLLab 10C system includes a casebook of normal samples as well as some common hematolymphoid malignancies to help users gain familiarity with expected staining patterns.

MK: The antibody combinations in the ClearLLab 10 C system have been designed to identify the majority of leukemia and NHL cases seen in standard practice. The reagents are formulated in a dry-down format that can be stored at 18–30°C for 12 months without degradation. This allows a full year's supply of reagent to be ordered as a single lot and stored on the shelf. This single lot of reagent can be validated once received; then, no further validation is required other than monitoring quality control samples and internal populations in samples under investigation.

The ClearLLab 10C system has four targeted tubes: one to characterize B cells, one for T cells, and two for myeloid. Each tube covers one lineage and shows the maturation sequence in each cell line, making it easier to detect "different from normal" changes. I've found that, because the system comes with fixed antibody combinations and standard analysis templates, pattern recognition is easily acquired. This kind of consistency can lead to quick and accurate detection of an abnormal population. The analysis templates cover all main cell populations, making it unlikely that an unexpected secondary abnormal population would be missed.

How does the system conform to the 2006 Bethesda guidelines?

JH: The 2006 Bethesda Guidelines (2) described a common set of antibody specificities that had been used for the characterization of hemolymphoid neoplasms for approximately 10 years at that point and are still in use today. Due to the variability among vendors as regards antibody clones, fluorescent tags, and cytometer design, the Bethesda participants could not agree on consensus standardized panels. The lack of clinical flow cytometers that could assess more than five or six markers simultaneously at the time was a significant barrier, as most of the participants had preferred combinations that didn't agree perfectly with those of other participants. With the more recent availability of 10-color flow cytometers, this barrier has largely disappeared. ClearLLab 10C incorporates a core set of antibodies and some more recently described markers, using strategic antibody redundancy to permit cross-tube comparison.

MK: The guidelines were an attempt to find consensus on hematological disease types and the antibody panels most effective in defining those conditions. All of the antibodies that met consensus in the Bethesda guidelines are included in the ClearLLab 10C system. Additionally, the B cell tube contains CD200, which – although not in the guidelines – is an excellent discriminator between B-CLL and mantle cell lymphoma. The addition of TCR γδ to the T cell tube is useful for detecting mature T cell malignancies that may express this receptor (3).

How do systems like this change the work of laboratory medicine professionals?

JH: On a day-to-day basis, ClearLLab 10C users should expect to spend less time on error-prone manual tasks and more on value-added work, such as data analysis and interpretation. From the research perspective, cases studied with ClearLLab 10C, even if done in different laboratories in different places, should generate comparable results.

MK: Consistent antibody combinations enable retrospective analysis of patterns that may not have been obvious on initial diagnosis. If new data appears linking such information to different disease states, it will be much easier to review previous cases due to the consistent antibody combinations in the ClearLLab 10C system.

** This number depends on how different the aberrant immunophenotype is from the normal cells, the number of events collected, and the number of informative markers in the tube.*

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A Disease With Many Faces

For patients with triple-negative breast cancer, insight into the tumor's molecular subtype and microenvironment can have significant effects on outcome

By David R. Hout

Patients with triple-negative breast cancer (TNBC) experience a wide range of treatment outcomes – from rapid recovery with minimal therapy to highly resistant and recurrent disease. However, with what appears to be a single diagnosis, why are the response rates so different? The truth: TNBC is not, in fact, a single entity. Rather, it is a plethora of different subtypes distinguished by their molecular expression profiles.

The value of subtyping

The treatment of triple-negative breast cancer (TNBC) has been challenging due to the absence of well-characterized molecular targets and the heterogeneity of the disease. TNBCs comprise up to 20 percent of all breast cancers (up to 45,000 women diagnosed in the US each year). This type of cancer occurs more frequently in young and African-American women and has higher rates of metastatic recurrence and poorer prognosis than other breast cancers, with a five-year survival of only ~30 percent (1–3). A critical unmet need to improve the outcome of women with TNBC lies in the development of diagnostic methods that address the heterogeneity of disease and differentiate molecular subtypes possessing unique biology, molecular genetic features, and therapeutic targets.

"A critical unmet need to improve the outcome of women with TNBC lies in the development of diagnostic methods that address the heterogeneity of disease."

The Pietenpol group originally molecularly classified TNBC into six distinct subtypes, each with unique biologic features and specific signaling pathway deregulation signatures (4). To accomplish this feat, retrospective gene expression data from Vanderbilt-Ingram Cancer Center (VICC) clinical trials was analyzed, as well as 21 publicly available datasets from eight countries (3,247 breast cancers in total). This worldwide dataset included nearly 600 TNBCs, which were used to classify the disease into two basal-like (BL1, BL2), mesenchymal and mesenchymal stem-like (M, MSL), immunomodulatory (IM), and luminal androgen receptor (LAR) subtypes. In addition to further validating these TNBC subtypes using The Cancer Genome Atlas (TCGA) data, the VICC group developed "TNBCtype," a web-based subtyping tool for TNBC tumor specimens using GE metadata and classification methods (5).

Importantly, evidence supportive of the clinical utility of TNBCtype has already been demonstrated, based on the ability of the algorithm to predict differential responsiveness to the current standard of care (taxane- and anthracycline-based chemotherapy) for TNBC. Subtyping analysis of 130 patients who received

At a Glance

- *Triple-negative breast cancer has a wide range of potential outcomes*
- *With six different molecular identifiers, a "one-size-fits-all" treatment approach is implausible*
- *Molecular subtyping is vital to determine the best treatment for each patient*
- *The ideal test should be cost-efficient, high-throughput, and feature a rapid turnaround time*

neoadjuvant taxane and anthracycline-based therapy revealed that the BL1 subtype has the highest pCR rate at 52 percent, whereas BL2 shows the lowest with none at all (6). Clinical responses to both neoadjuvant treatment arms found BL2 to be significantly associated with poor response. Recently, a refined subtyping tool reduced the original Pietenpol 2,188-gene expression algorithm to 101 genes while retaining the ability to subtype TNBC tumors similar to the original algorithm and to predict patient outcomes (7). This newly refined assay also displayed the capability to identify more than one subtype – called a dual subtype, with a primary and potential secondary subtype – in any given patient, which should better reflect tumor heterogeneity. The assay also separately classifies each patient as either IM-negative or IM-positive to provide possible insight into the tumor immune-microenvironment. Additionally, the 101-gene model also demonstrated the significant association of the BL1 subtype with improved response (7). Ultimately, it appears that BL1 patients may benefit from standard chemotherapy, whereas BL2 patients may not benefit – but still experience unnecessary and sometimes harmful side effects. In addition, the BL1 and mesenchymal categories are also most closely associated with a *BRCA1*-like status, meaning that they may respond well to PARP inhibitors (8).

Learning about LAR

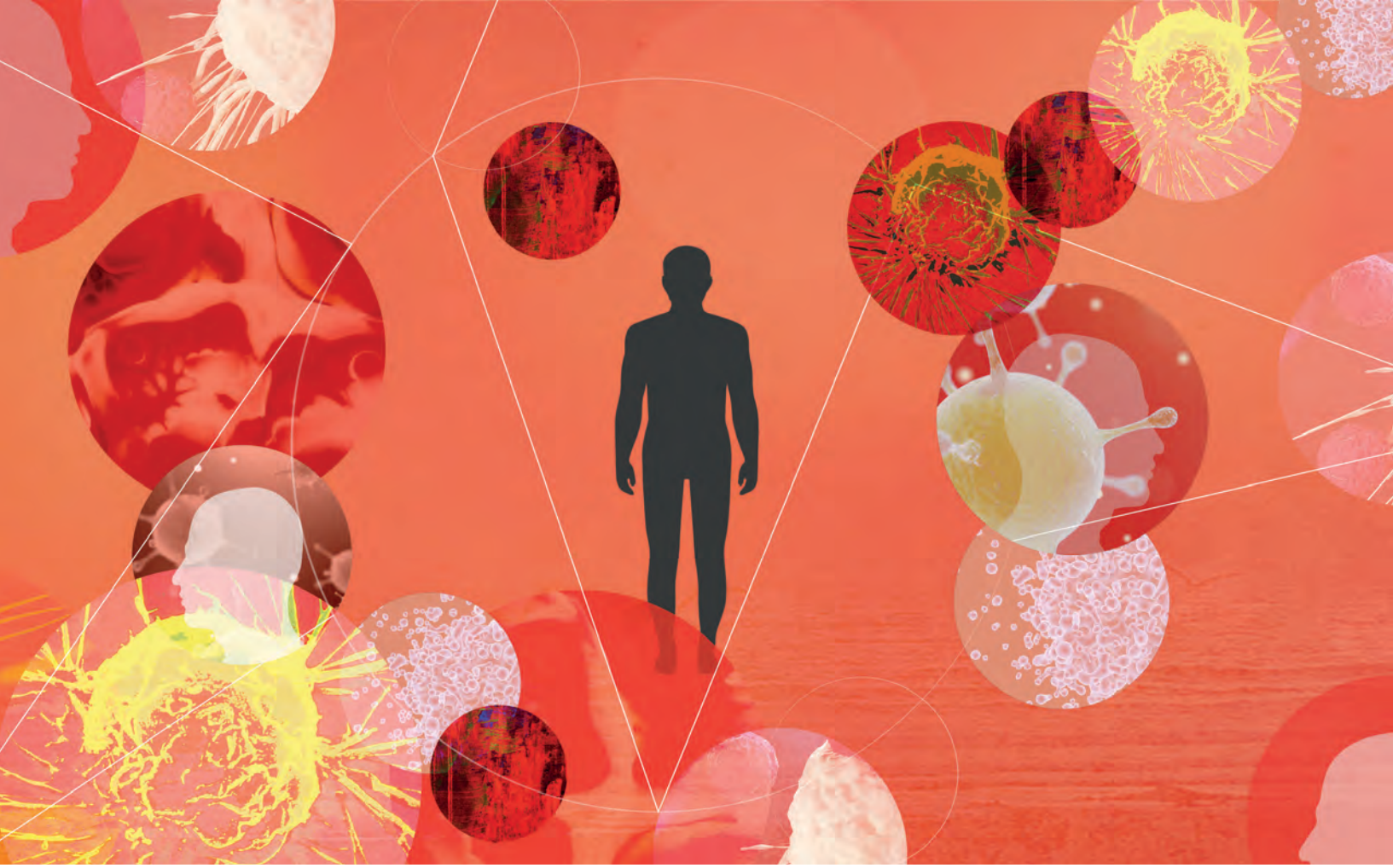
The LAR subtype is enriched for hormonally regulated pathways and is dependent on androgen receptor (AR) signaling. Although AR can be expressed in multiple molecular subtypes of TNBC, the LAR subtype has the highest level of AR expression. It is predominantly subclassified in the non-basal subgroup and represents a novel subtype of TNBC with a distinct prognosis that offers an opportunity to develop targeted therapeutics. Cell lines of this subtype, the growth of which is driven by AR signaling, are uniquely sensitive to AR antagonists (4). LAR tumors and cell lines also have a high frequency (~40 percent) of *PIK3CA* mutations that confer responsiveness to PI3K inhibitors (9) and may benefit from PI3K inhibitor treatment.

LAR tumors appear to respond poorly to conventional chemotherapy. A pCR rate of only 10 percent following sequential taxane and anthracycline neoadjuvant therapy was reported (6), clearly demonstrating the need for LAR TNBCs to be distinguished from other subtypes so that physicians can use specific treatment approaches. Because the AR is a potent mitogenic driver of the LAR subtype (10), and because previous data indicate that LAR cell lines and xenografts are sensitive to AR antagonists (4), these patients may benefit from simultaneous targeting of AR and the PI3K/mTOR pathway – a combination known to be synergistic in AR-dependent prostate cancer cells. This and other corroborating data should prompt clinical trials to confirm the efficacy of AR antagonist therapy in LAR TNBC.

Immuno-oncology's potential

Although it seems that an antibody to detect PD-L1 would be the obvious biomarker for an immune checkpoint inhibitor, this biomarker has not always provided a desirable objective response rate with the various agents (11). Therefore, various alternatives, including DNA mutations and gene expression signatures, are being explored. A recently published case report used the 101-gene assay as a potential immuno-oncology diagnostic to identify a patient who tested negative for PD-L1 by IHC, but as IM-positive by TNBCtype (12). The patient, who had already received exhaustive chemotherapy, had few other treatment options. Partially based on the positive IM result, the patient was approved for pembrolizumab treatment – and, after four treatment cycles, experienced a complete radiologic response.

It has been shown that the presence of the immune-suppressive T regulatory cells (Tregs) in the tumor microenvironment play a role in the escape of immune surveillance. A meta-analysis using the ratio of CD8+ cells to FoxP3+ cells (as surrogates to the ratio of activated T-cells to Tregs) gave a more impressive hazard ratio for overall survival than CD8+ cells alone (13). In relation, our collective data show that the M subtype – named for its high expression of genes associated with the epithelial-to-mesenchymal transition (EMT) – appears in only 9 percent of patients who have a single subtype, compared with 80 percent of patients



"The clinical utility of subtyping in patients treated with immunotherapies is currently being established, but will need further validation."

who have a dual subtype. The inverse relationship between the M subtype and positive IM status can be seen using either the 2,188-gene algorithm or the 101-gene algorithm. This holds true even when M is one of dual subtypes and another subtype has a higher correlation coefficient (14).

The M gene expression signature is also enriched for genes associated with the extracellular matrix (ECM) and the TGF-β signaling pathway (4). Given that the secretion of TGF-β is an anti-inflammatory mediator that inhibits dendritic cells and T cells (15), the EMT may represent an additional immune escape mechanism whereby the TILs lose their aggression toward the tumor independent of PD-L1 inhibition. This supposition has at least one observation to support it; a group of melanoma patients resistant to PD-L1 inhibitors expressed a subset of genes associated with EMT and ECM, both of which are characterized by the TNBCtype M signature (16). Interestingly, this study noted that the genes that distinguish the basal subtypes – BL1 and BL2 – from mesenchymal tissue in breast cancer are downregulated in the resistant patients.

The MSL subtype is the exception to the above rules. It appears to correlate with cellular heterogeneity and has been shown to result from the presence of tumor-associated stromal cells. (17).

Why subtype?

A diagnostic test that addresses disease heterogeneity and differentiates molecular subtypes possessing unique biology, molecular genetic features, and therapeutic targets is a critical – and currently unmet – need that could improve the outcome of women with TNBC. Algorithms such as TNBCtype have already proven their clinical utility in the molecular characterization of TNBC patients, based on their ability to predict differential responsiveness to the current standard of care (taxane- and anthracycline-based chemotherapy). Potential downsides of RNAseq methodologies could include the robustness of the assay and requirement for batch sample testing, an issue addressed by the assay's demonstrated ability to test a single sample.

In many studies, individual biomarkers have been shown to be fairly reliable predictors of patient outcome – but they are not universal, and researchers have observed lower sensitivity compared to molecular methodologies. For this reason, my colleagues and I currently recommend a testing approach that has the capacity to categorize patients into multiple subtypes and includes the IM classifier; ideally, the test should include primary and secondary subtypes to better reflect tumor heterogeneity and elucidate treatment pathways in patients with dual subtypes. Importantly, such a test must differentiate basal patients into BL1 and BL2, because these two distinct subtypes respond differently to various levels of care.

To reach full clinical utility, TNBC molecular subtyping tests need lower cost, faster turnaround, and higher throughput – all of which can be achieved by streamlining them and finding alternatives to RNA sequencing platforms. Next-generation sequencing (NGS) targeted panels can help with streamlining; better yet, placing each subtype onto a qPCR panel could drastically reduce the cost of the test and better position each subtype for companion diagnostics in the event that a specific therapy aligns with response in a specific subtype. For example, the IM and M calls are currently being validated against NGS to determine concordance so that they can be used as a separate qPCR assay for immuno-oncology. We have already observed that the IM subtype can identify patients who are PD-L1 negative, but respond to immunotherapy (12). We also believe that, because the M subtype contains genes in the TGF-β pathway, it may exhibit immunotherapy resistance. The clinical utility of subtyping in patients treated with immunotherapies is currently being established, but will need further validation.

When these tests do enter the clinic, I anticipate they will initially be offered at central, CLIA-certified laboratories. Pathologists and laboratory medical professionals will have an additional three to five slides cut from the same biopsies taken for ER/PR/HER2 testing and ship those to the testing laboratory. Shortly thereafter, the medical professional will receive a subtyping report to inform the patient's care. This could be standard therapy, an immuno-oncology treatment, or an anti-androgen therapy. No additional reagents or instrumentation would have to be introduced into the clinician's normal workflow. It's still some time away from becoming a routine test, but I am optimistic that molecular subtyping of TNBC will lead to optimized treatment and, ultimately, better outcomes for patients with every subtype of the disease.

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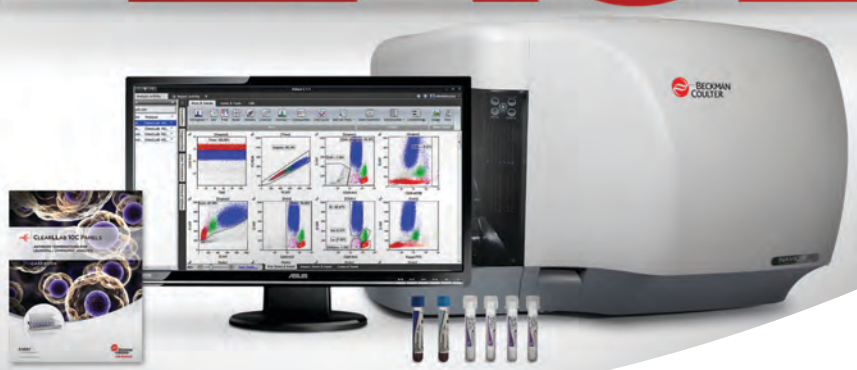

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An Inside Look at the CNS

CSF cytokine profiling can offer a faster, less invasive way to distinguish between cancer, infections, and autoimmune processes in the brain

By Danielle Fortuna and Mark Curtis

A patient presents with neurological symptoms – perhaps headache, numbness, or functional difficulties. It's clear that this is an urgent situation, but the patient obviously can't be treated appropriately without knowing the underlying cause of their symptoms. But even the most basic questions – for example, "Is the problem a brain infection or cancer?" – can be time-consuming and require a brain biopsy to answer.

The immune system has a fascinatingly precise and fairly reproducible response to various tissue threats: a cytokine cascade. By examining the cytokine patterns in the cerebrospinal fluid (CSF) of various central nervous system (CNS) diseases during my residency training in pathology at Thomas Jefferson University Hospital, my colleagues and I are essentially decoding what the body has already figured out. Based on the presence or absence – and relative levels – of these immune mediators, the cytokine profile reveals what the immune system has probably encountered. The faster we can make such a diagnosis, the better the outcome, and our new test allows rapid triage of these diseases to assess the most appropriate next steps in care. It's a big-picture approach to diagnosis; instead of asking the direct question ("What is it?"), we are instead asking, "What is happening?" by observing how the environment reacts. We are learning a tremendous amount by looking at CNS diseases from this perspective and, after validating this work with large sample sizes, we will be closer to helping patients in real time.

At a Glance

- *Current tests for problems of the brain and spine can be invasive or require significant time investment to obtain results*
- *Patients with neurological symptoms often can't wait for an answer – so they're treated based on early evidence*
- *CSF cytokine profiling is rapid and performed on spinal fluid samples routinely obtained from patients with serious CNS disorders*
- *Performing such a procedure early in a patient's presentation can optimize treatment and spare the patient unnecessary additional tests*

Making the differential diagnosis

The current standard of care for diagnosis of a tumor involving the central nervous system (CNS) is a brain biopsy, followed by histopathologic analysis of the tissue sample. But even cases deemed likely to be a brain tumor prior to biopsy are sometimes found to be not a neoplasm but a neuroinflammatory process (either a CNS infection or an autoimmune disease). A brain biopsy is an extremely invasive process. If the pathologic process can be determined in another way (for example, if the patient's cytokine profile suggests an infectious agent rather than a tumor or an autoimmune process), then we can spare the patient a brain biopsy and instead perform further testing for the specific pathogen (see Clinical Case 1).

Another common disease, CNS lymphoma, often goes undiagnosed following CSF cytology, flow cytometry, and B cell clonal analysis. The clinical and radiologic differential for CNS disease that turns out to be lymphoma often includes both infection and autoimmune disorders. CSF cytokine profiles may

"The immune system has a fascinatingly precise and fairly reproducible response to various tissue threats: a cytokine cascade."

Clinical Case 1

A young teenager was admitted to the hospital with signs and symptoms of severe encephalitis. The clinical suspicion was viral encephalitis. Analysis of serum, stool, sputum, and CSF for a variety of pathogens including enterovirus was negative on multiple samples from each site. Brain biopsy was performed and revealed encephalitis, and PCR of the brain tissue was positive for enterovirus.

We characterized the CSF cytokine profile of enterovirus in an earlier paper (1). If more in-depth CSF analysis, including cytokine profiling, had been performed in this case, the pattern might have suggested a viral infection. The patient might have been spared an invasive brain biopsy and treatment with approved antiviral agents might have been initiated earlier.

prove helpful in such cases prior to biopsy.

To identify a CNS disease state as infectious, you may find CSF parameters including cell count, protein, and glucose concentrations valuable. But some pathogens, such as the human parechovirus (HpeV), do not elicit a marked cellular response, so the virus as a cause of illness in a patient may be missed. HPeV is the second most common cause of meningitis in neonates worldwide, so the ability to rapidly and accurately identify it is important – a task with which an inflammatory CSF cytokine profile can help.

Other options

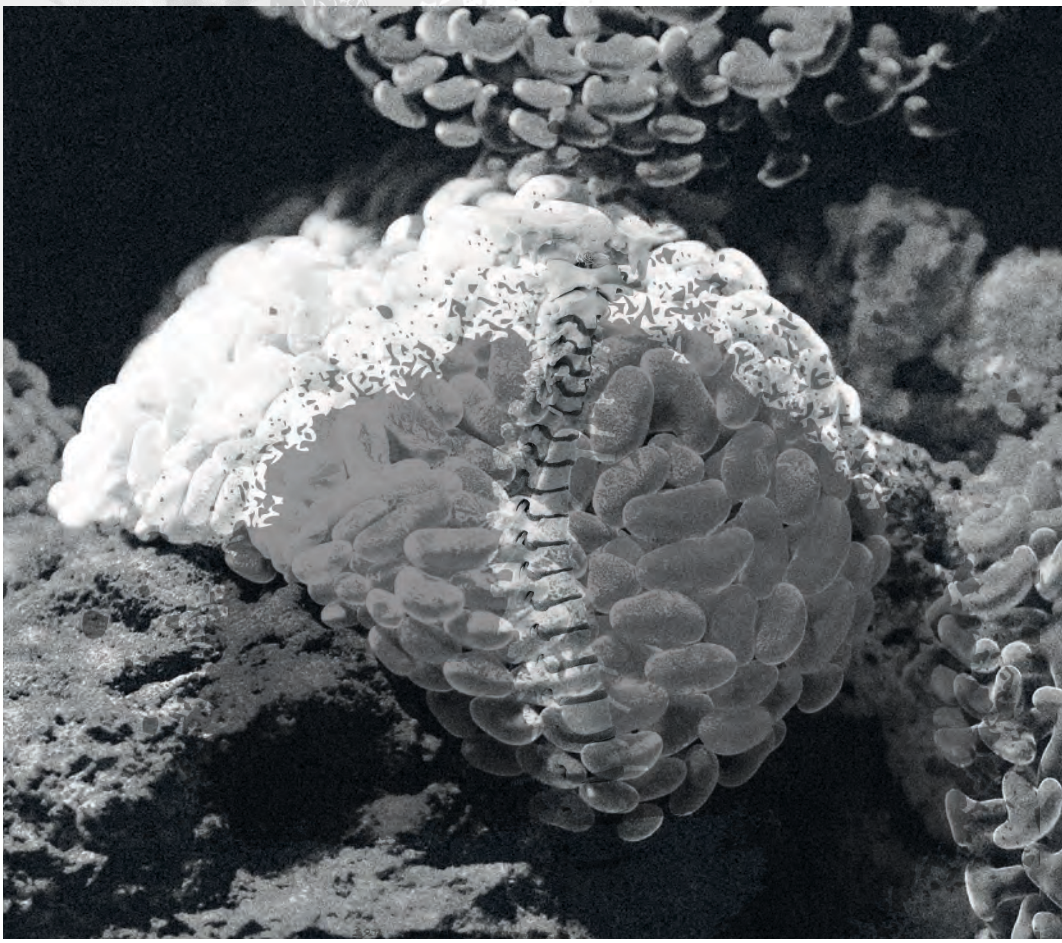
There are a number of ways to investigate suspected infectious disease in the CNS – but none of them is without its downfall. There can be overlap in terms of CSF cell count, glucose, and protein concentrations between CNS infections and other brain and spinal cord diseases. Rapid special stains and smears to discern bacterial and fungal organisms in the fluid can be helpful, but may be negative. Identification of an infectious organism after growth in culture can take days or longer for positive results. PCR for viral infections is rapid, but only works if testing for the causative virus. Molecular techniques to identify viral pathogens are extremely powerful, but require clinicians to know the precise virus that they are looking for – and these assays can still return a negative result (see Clinical Case 2). Additionally, only the more common CNS viral pathogens are usually included in tests, limiting our ability to diagnose patients with rare or emerging CNS infections.

Cytokine profiling can identify patients who need urgent therapy, assist with treatment selection, and direct additional testing. Therefore, analysis of the CSF sample obtained when the patient comes to the hospital – or at any time during their admission – could allow us to treat each patient's affliction in the fastest and most appropriate way.

How it works

Analyzing the body's cytokine response to infections and other pathologic CNS processes is tapping into the central nervous system's innate immune system response to cellular injury – be that an

"In experimental animal models, pro-inflammatory cytokine levels are elevated as soon as two hours after exposure to pathogenic bacteria."



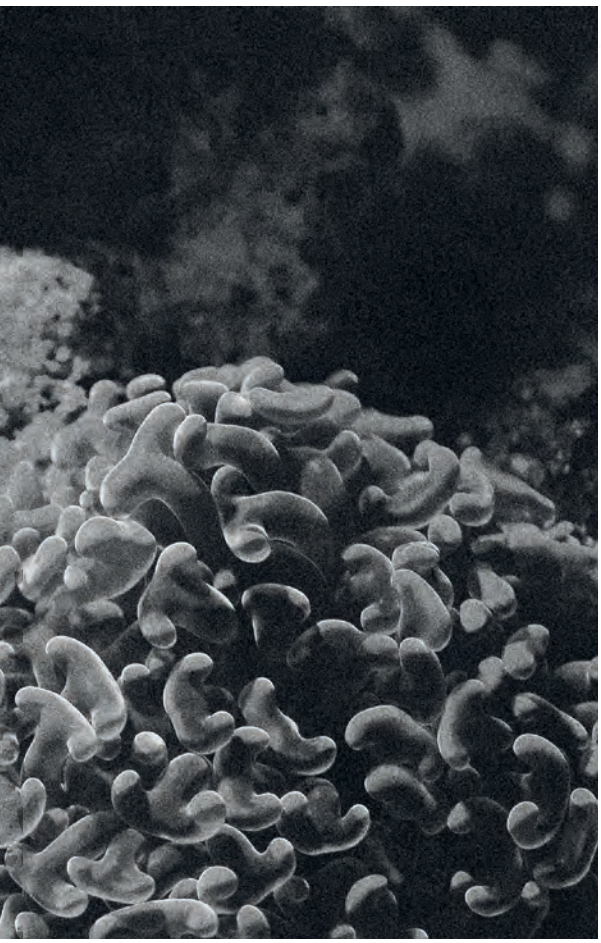
infectious pathogen, a neoplasm, or an autoimmune disorder. The measured cytokine profile reflects how the immune system is responding to a particular insult at the time the CSF is obtained.

The fluid is obtained via lumbar puncture as part of the clinical workup of a patient for a possible CNS disorder. In our new study (2), cytokine levels (pg/mL) were measured in undiluted patient CSF using human cytokine/chemokine magnetic bead panel plates on a multiplex assay instrument. The test requires a total 100 µL of CSF for running samples in duplicate, and samples are run with appropriate controls and standard curves. Each time we completed the run of a 96-well plate, the data was transferred automatically to an Excel file for further analysis.

Each run analyzes 41 cytokines, with results available for review within two hours. In experimental animal models, pro-inflammatory cytokine levels are elevated as soon as two hours after exposure to pathogenic bacteria. We previously detected markedly elevated CSF cytokine levels with virus-specific changes in samples obtain within several hours following onset of symptoms of meningitis in neonate and infant patients with CNS viral infections. Why such young patients? Children are especially susceptible to meningitis and encephalitis – and even when they display symptoms of severe illness, they are not able to tell the clinical team how they feel (for instance, if their neck feels stiff or the light hurts their eyes). The threshold for performing a lumbar puncture in these very young patients is therefore much lower than in older patients, so it's a common procedure when a baby arrives in the emergency department with symptoms that may be sepsis or meningitis. The ability to quickly determine whether symptoms represent a CNS infection or a systemic process could potentially save children's lives.

Moving into the mainstream

In many clinical situations, it is important to know as soon as possible whether or not a patient who presents with acute or recent onset of neurologic disease has an infectious CNS process. For example, patients coming to the emergency department with new-onset seizures and a CT or MRI negative for mass lesions or cerebrovascular event may be worked up extensively for infectious disorders. The workup may include tests for infections (viral, fungal, and bacterial) and autoimmune processes – the latter of which are investigated using CSF analysis for autoimmune antibodies. This test in particular is expensive, but those for infectious disease also consume time and resources. A CSF cytokine test performed early in the patient's care may



"A CSF cytokine test performed early in the patient's care may help determine which specific tests should be ordered."

help determine which specific tests should be ordered for the patient, improving overall utilization management.

In some cases, early analysis of CSF cytokines might spare a patient an unnecessary biopsy if they indicate a treatable infectious process when the clinical and radiologic differential also include a metastatic tumor or a glioma. Even in patients who have already had a biopsy, CSF cytokine analysis can be helpful. The histologic findings in biopsies from patients with autoimmune encephalitis can be indistinguishable from those of viral encephalitis. A cytokine profile that points toward (or away from) an infectious process can help the neuropathologist decide which immunohistochemical stains and molecular tests to perform on the biopsy tissue.

Our next step is to formally validate the use of CSF cytokine profiles to distinguish infectious from noninfectious CNS disorders by analyzing a much larger number of patient samples. We also plan to expand our analysis to include additional infectious pathogens and a wider range of noninfectious processes. Further studies will include additional cytokines that might help us identify profiles that can distinguish not just bacterial from fungal infections – not just viral from non-viral infections – but even distinguish between virus types. We would eventually like to obtain FDA approval for our test and partner with a manufacturer of cytokine analysis systems to develop an instrument ideal for the efficient analysis of patient samples in an acute setting.

Hopefully, our future analysis of cytokine profiles in a wider range of infections – including rare and emerging CNS infections and noninfectious processes – will reveal important information about the pathogenic mechanisms of these disorders. For example, CSF analysis in patients with new-onset seizures in the absence of either infection or mass lesion may reveal important information about possible immune factors in epilepsy.

Clinical Case 2

A young adult in his early 20s presented with signs of cerebellar dysfunction. MRI revealed a contrast-enhancing mass in the cerebellum, thought by radiology and the neurosurgeons to be a malignant neoplasm. Brain biopsy showed an inflammatory process – but no tumor. The patient improved with just supportive therapy.

Although it was not used in clinical decision-making, CSF cytokine profiling in this patient revealed a profile suggesting a viral infection. A validated CSF cytokine analysis test might be helpful in such patients in the future and allow them to avoid the stress of potential misdiagnosis with a CNS malignancy.

Danielle Fortuna completed the work described above while at Thomas Jefferson University and is now Assistant Professor of Clinical Pathology and Laboratory Medicine at the Perelman School of Medicine, University of Pennsylvania. Mark Curtis is Associate Professor and Director of Neuropathology and the Residency Program at Thomas Jefferson University, Philadelphia, USA.

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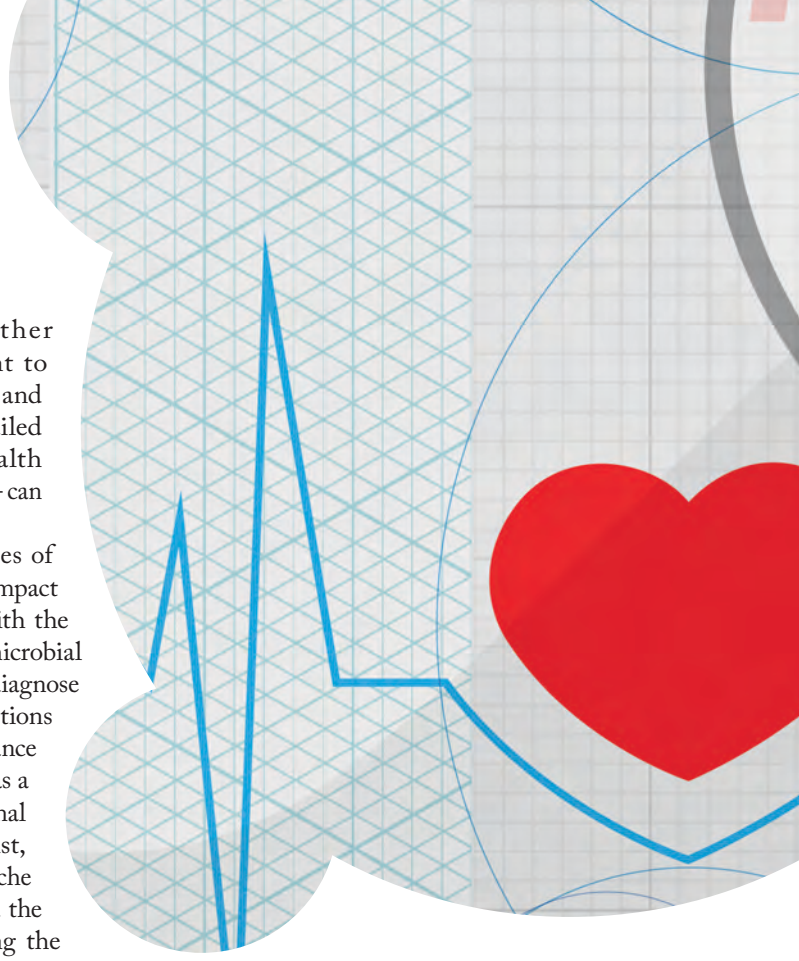


Under Pressure

When winter is coming and healthcare systems are overloaded, could health tech be the answer?

By Will Culliford

Barely a week goes by during winter when the UK's National Health Service (NHS) isn't in the headlines. Increasing wait times, more cancelled operations, and higher bed occupancy rates have led to the term "winter pressures" to define this seasonal crunch point, during which the NHS struggles amid spikes in clinic appointments and hospital admissions for illnesses such as influenza (1).

Short of resolving the long-term issues facing the NHS – funding, workforce, an aging population, and the impact of chronic conditions and comorbidities – there is little talk about how to alleviate these pressures (2). The focus is on the problems, rather than solutions.

So what can be done to help?

Collaborating on challenges

In an attempt to answer this question, a group of diagnostic specialists, clinicians, healthcare professionals, tech innovators, and policy leads from NHS England recently came together for a roundtable event to discuss how innovation and technology – widely hailed as the answer by Health Secretary Matt Hancock – can address these issues.

One of the key themes of the discussion was the impact of rapid diagnostics. With the growing threat of antimicrobial resistance, the ability to diagnose common bacterial infections takes on serious significance to global health, as well as a more quotidian, operational importance. Geoff Twist, Managing Director of Roche Diagnostics, emphasized the importance of leveraging the latest medical technology to help alleviate pressures on the NHS.

"Having reliable, actionable information is key for healthcare professionals to help them provide patients with the right treatment at the right time and discharge with confidence where appropriate," he said. "Diagnostics plays a huge part in helping relieve pressure on the NHS every day, but access is not equitable."

Diagnostic tools help clinicians and frontline staff to detect, confirm, or rule out diseases. These innovations can enable healthcare professionals to focus on the patients who need specialized care immediately. They can also save on admissions, meaning waiting times for patients should be less and availability of beds should be greater (3). However, although Twist believes that innovations "can help transform how healthcare professionals are able to manage winter pressures," he added that the key challenge lies in "spreading the latest innovations, helping to make them available where and when they are needed."

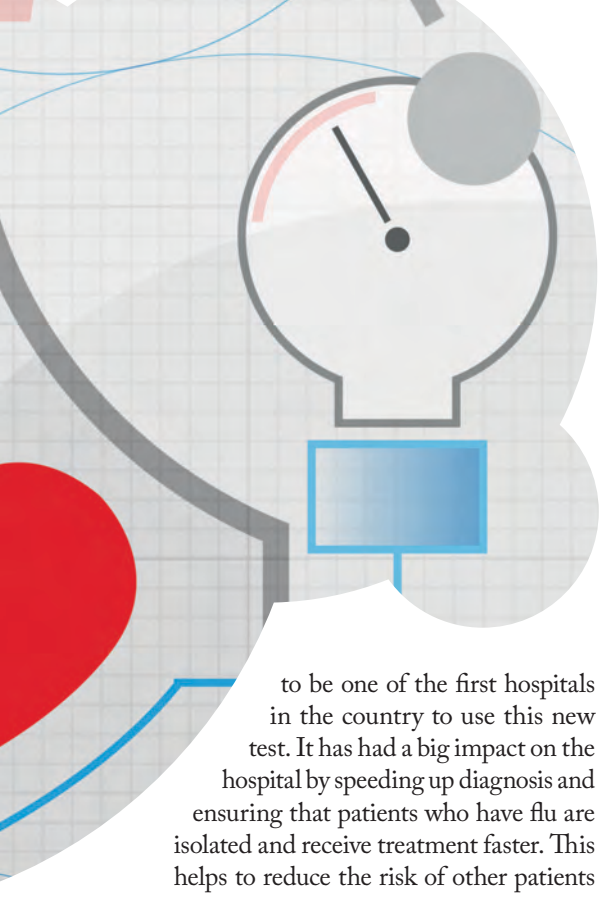
Clinical scientist Emma Meader, from Norfolk and Norwich University Hospitals NHS Foundation Trust (NNUH), spoke about a point-of-care test used to check whether patients admitted with flu-like symptoms actually had the flu. The test can detect 43 strains of influenza A and B and seven of respiratory syncytial virus (4). NNUH found that, over a four-month trial period, only 46 percent of the tests staff carried out came back positive, leading to more efficient use of side rooms and quicker diagnosis. This in turn helped save money and led to more timely treatment for patients.

Meader said, "We are delighted

"Diagnostic tools help clinicians and frontline staff to detect, confirm, or rule out diseases."

At a Glance

- *Many healthcare systems go through periods of increased pressure, particularly in the winter months*
- *Advances in diagnostic testing can reduce the number of patients receiving unnecessary care*
- *Technological assistance can support overburdened diagnostic professionals with some tasks*
- *To implement new technologies, open-mindedness and collaboration are vital*



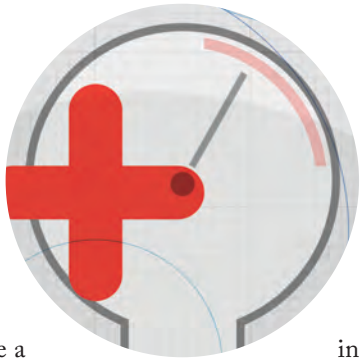
to be one of the first hospitals in the country to use this new test. It has had a big impact on the hospital by speeding up diagnosis and ensuring that patients who have flu are isolated and receive treatment faster. This helps to reduce the risk of other patients catching flu. During a challenging flu season, this test makes it easier to manage beds and side rooms, because patients who do not have flu often do not require isolation."

Democratizing technology

It's clear that technological interventions can save on time and money when both are at a premium. In the age of tech, apps that can save both are never far from the news – and they have real-world advantages.

Ben Moody, Head of Health and Social Care at Tech UK, said, "Technology can help patients in a variety of ways. There are digital apps with an increasing evidence base to monitor and treat conditions from diabetes to insomnia. Some diagnostic tests can now be done without the patient's needing to leave the comfort of their own homes, and smarter technology in people's homes can stop them needing to come into a surgery or hospital in the first place. Tech can help clinicians to record and access the information that they need when they need it, and it can help planners to predict demand and supply over a longer period."

Ultimately, Moody continued, health is a very personal sector and nothing is going to replace the contact between real people in the system. Nevertheless, technology can make the lives of everyone involved in planning, giving, and receiving care a lot easier and help patients to live happier, healthier, longer lives.



Right place, right time

Much fanfare is made of the potential for technologically enabled developments, such as AI-assisted analysis or rapid diagnostics, to transform the NHS. However, attendees at the roundtable felt the right conditions need to be in place to accommodate such advances. Some delegates felt that technologists and healthcare professionals need to be more open to collaboration and listening to one another to build greater understanding. Recommendations included the expansion of the UK's Academic Health Science Networks and the start of a collaborative exercise to develop a single set of standards for healthcare data and system interoperability (5).

The group also discussed the difference between diagnostics and pharmaceuticals and the lack of priority sometimes afforded to testing over treatment. It was felt that diagnostics evaluated by The National Institute for Health and Care Excellence, which are shown to be cost-effective and confer clinical benefit, should be given equal status to pharmaceutical products in their evaluation, recommendation, and funding mandate.

At a time when the NHS has only just pledged to get rid of its fax machines, it is understandable that people may be skeptical of novel technologies – but it's these technologies that promise a better future for healthcare systems. There is definitely more that can be done to make the NHS better integrated and more interoperable, so that key data can be shared to inform all parts of the system. The ability to predict and respond to spikes in demand for care should also be a priority, so as to avoid periods of great pressure such as the one perennially experienced over the winter months.

Listening to the professionals working at the coal face of the NHS alongside those aiming to make their lives easier, it is clear that a new, collaborative way of working is needed to build sustainable, innovative healthcare systems.

Elliot Jones, a researcher at cross-party think tank Demos, says, "There are so many promising innovations and technologies out there waiting to be harnessed for the health of the public." The next step is leveraging these to address some of the short-term pressures and ensure that healthcare systems and industry work together to build systems that are fit for the future.

Will Culliford is a Senior Consultant who works with a range of clients in the life sciences and healthcare sectors at Lexington Communications, London, UK.

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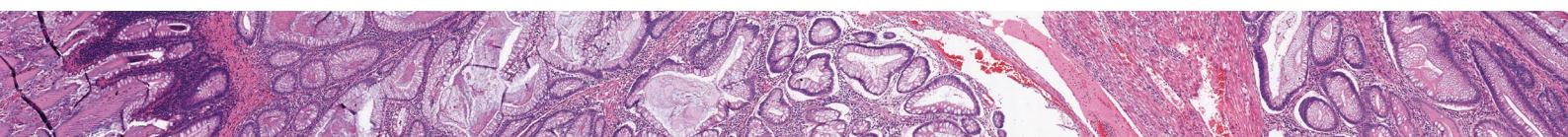

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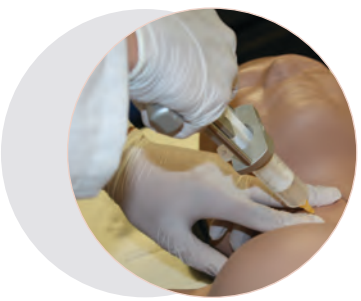

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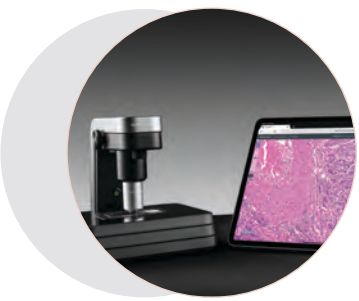

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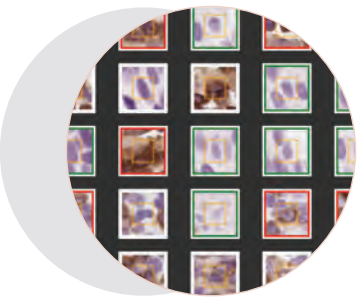

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Solving the Big Problems

Sitting Down With… Stephen Quake, Lee Otterson Professor of Bioengineering and Professor of Applied Physics at Stanford University and co-President of the Chan Zuckerberg Biohub, Stanford, USA

Did you always plan to work in bioengineering?

My career in bioengineering actually unfolded accidentally. I originally trained in physics, but I was always interested in the boundaries between physics and biology, and particularly in the development of new measurement techniques. And that led somewhat naturally into my role in the bioengineering department – I was recruited to help build and lead it.

You have been involved in a number of different projects – which has been your favorite?

I like to measure my work in terms of its impact and, in that regard, I think my research on noninvasive prenatal testing (NIPT) is some of the most significant thus far. Previously, invasive techniques, such as amniocentesis, were used for prenatal diagnosis in pregnancies at risk of single-gene disorders. However, building on the discoveries of Mandel and Metais in 1948 that cell free DNA exists in the blood, and then of Dennis Lo and colleagues in the 1990s who showed definitively that fetal DNA circulates in the mother's blood, we developed the first noninvasive diagnostic test for Down syndrome and aneuploidies. We have also been able to monitor the developmental gene expression program and sequence the genome of the fetus noninvasively.

The reason I felt compelled to develop these noninvasive tests wasn't chance; it was derived from my own experience of becoming a parent. When I saw my wife and unborn daughter go through amniocentesis, I was thinking, "Jeez, we're risking the life of our baby to ask a diagnostic question; that doesn't seem right." Now, versions of this test are available around the globe – in 2014, approximately one million women received some form of NIPT. Amniocentesis rates are plummeting as a result, meaning that the test is saving thousands of lives each year.

How hard is it to develop diagnostic tests using circulating tumor DNA?

It depends on the stage of the disease for which you're developing the test. Many companies are trying to commercialize the great academic work that has been completed – for example, on mutational burden – and they are making good progress; there are a few tests now on the market. My own research has focused on the epigenetic properties of tumors and how they're reflected in the blood. From there, you can gain a great amount of information about the biology of the tumor, such as its tissue of origin.

"I always give them the same piece of advice: identify the big problems and seek a solution."

Another part of our work (which we stumbled into accidentally) is the use of circulating cell-free DNA (cfDNA) to monitor the microbiome. When we were working on using cfDNA to reveal information about organ transplant rejection, one of my postdocs realized that not all of the DNA he was sequencing was human. He eventually worked out that some of the cfDNA in the blood is derived from the microbiome, which is a phenomenon that can be used as a tool for the diagnosis of infectious disease. I think this is a really cool application that holds a great deal of promise.

What are your next targets?

I'm excited about the work we're doing in preterm birth. After more than half a decade of shoulder to the wheel we've finally cracked it open with the introduction of a cell-free RNA test that detects, with 75–80 percent accuracy, whether a pregnancy will result in premature birth. Despite great promise, we're actually at the beginning of that story – although we have a proof-of-principle technique, we need to complete much larger studies to validate the results for clinical use. I also think there is great potential for the application of cell-free RNA tests to cardiometabolic disease. This area of research is only in its infancy, so there is much work to be done.

How do you see diagnostics changing in the future?

I believe we're going to see a big shift in the coming years; patients will become directly engaged with test selection and viewing the results and play a more active part of the diagnostic process. Patients won't settle for simply receiving wisdom but will instead pepper their physicians with questions. I don't know anyone in this age who, once given a diagnosis, doesn't go straight to Google to discover more. The whole process will fundamentally change – and the medical establishment will need to factor this shifting dynamic into the way they interact with patients in the future.

Reflecting on your own career, what advice would you give to others?

I've been lucky enough to have a very fortunate and blessed career; although it has had its twists and turns, there isn't anything that I would want to go back and change. When I speak to young people at the start of their careers, I always give them the same piece of advice: identify the big problems and seek a solution; life is too short to solve small problems.

THE FIRST FDA-APPROVED CDx FOR TNBC

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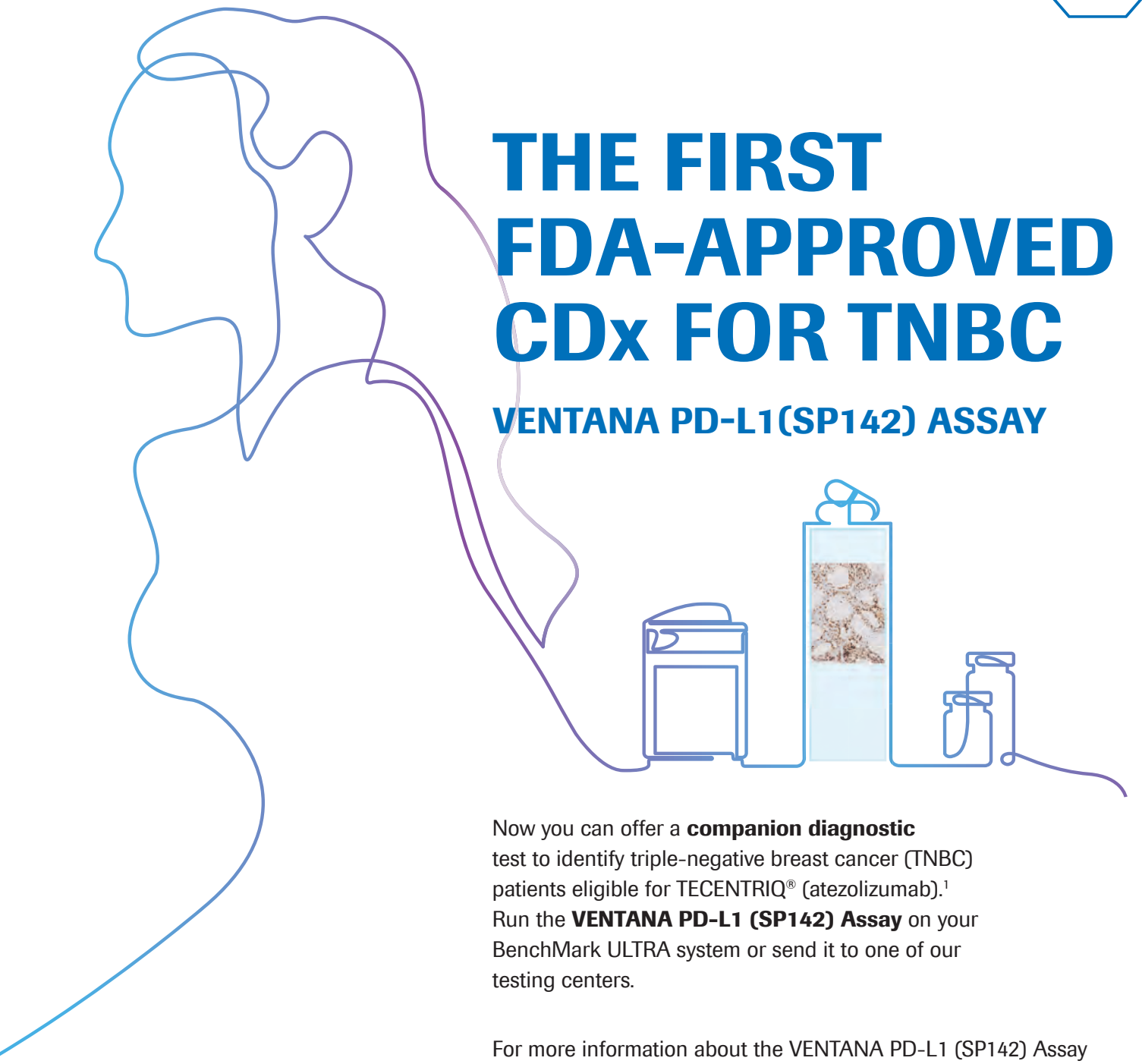

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[1] VENTANA PD-L1 (SP142) Assay approved as first companion diagnostic to identify triple-negative breast cancer patients eligible for treatment with TECENTRIQ® in combination with ABRAXANE®.