APRIL 2015 # 07

the Pathologist

Dubious Diagnoses?

A recent paper highlighting disagreement between pathologists on breast biopsies has tarnished the field and left women feeling anxious. We dig deeper.

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Online this Month

"I would say a hospital that doesn't understand the value of pathology is never going to succeed at delivering value based care or accountable care."

This month, we sit down with Michael Prystowsky, Professor and University Chairman of Pathology at Montefiore Medical Center and Albert Einstein College of Medicine, New York, USA (page 50). Head over to our website to read our more in-depth interview, and hear why Michael believes that any hospital that undervalues pathology could face serious repercussions.

"By not valuing the diagnostic expertise of the pathologist, the administrator focused on cost per test can delay initial diagnosis and impair management of patients with chronic diseases resulting in ineffective care, poorer clinical outcome and ultimately higher costs."

Read our in-depth interview online now: thepathologist.com/issues/0415/701

The Pathologist Live at USCAP 2015

1. *2.*

3. *4.*

1. #USCAP new branding announced #USCAP2015
   9:31 PM - 25 Mar 2015

2. Inexpensive concept explained for fluorescent microscopy at this morning's practice changers session #USCAP2015
   3:33 PM - 24 Mar 2015

3. How SMILE makes a #diagnostic decision #USCAP2015
   8:59 PM - 24 Mar 2015

4. It's been a good day at #USCAP2015!
   12:10 AM - 24 Mar 2015

Last Month's Top Tweets @pathologistmag

Variation between specialist #uropathologists in reporting extraprostatic extension after radical #prostatectomy:
http://bmj.co/1BtFfvT
12:00 AM - 30 Mar 2015

Where is the next generation of #pathologists?!
http://bit.ly/15kmmT7
11:00 PM - 1 Apr 2015

#Liquidbiopsy could herald the dawn of a new era in #diagnosis - here's why:
http://bit.ly/1CB9Uez
12:00 PM - 5 Apr 2015

#Molecular testing of #endometrial #biopsy could improve #IVF:
http://bit.ly/1Irtdbr
7:45 PM - 18 Apr 2015

New guidelines on #colorectalcancer #moleculartesting:
http://bit.ly/1FqPtVl
7:30 PM - 11 Apr 2015

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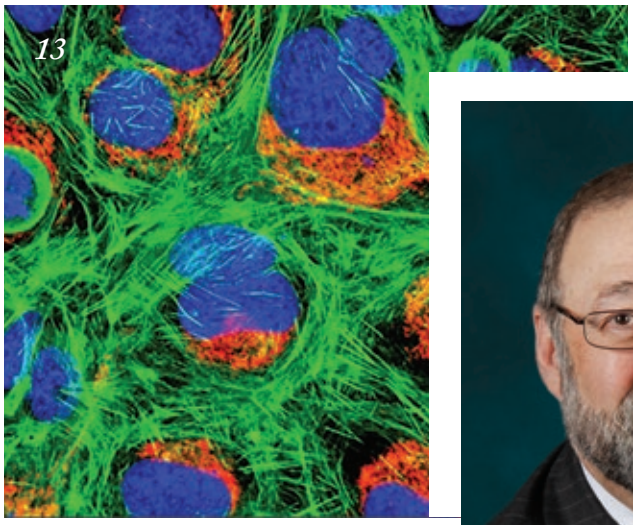

In Practice

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Sitting Down With

the Pathologist

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Stop the Press!

Can negative media reports open up a good opportunity for pathology?

Last month, JAMA published a paper that created waves. The study – "Diagnostic concordance among pathologists interpreting breast biopsy specimens,"(1) – cites its primary objective as quantifying "the magnitude of diagnostic disagreement among pathologists compared with a consensus panel." If you get the sneaking suspicion that the outcome was unlikely to be positive, you're not wrong; disagreement was reported in around 25 percent of cases. Unsurprisingly, discordance was highest in those cases deemed as "borderline" diagnoses of atypical hyperplasia and DCIS. Though the results are pretty damning on the face of it, the lack of commonality between the study methodology and real-life conditions was not given sufficient attention. For example, the pathologists who took part were unable to solicit a second opinion; not only is that commonly practiced, it's expected.

Nonetheless, the story was inevitably spread via many media channels in the medical profession and beyond. Even more worryingly, there have also been reports on the dwindling number of women attending breast cancer screening in some countries; better education on the risk of misdiagnosis being cited as a factor. It is clear that pathology is gaining a bad reputation from some of this publicity – unjustifiably.

We talk regularly of the need for pathologists to communicate with those outside of their profession and to educate on the value of pathology. Sadly, most consumer attention tends to be generated when things apparently "go wrong". The press will always pick up on the most impactful and newsworthy element of a piece of research. And let's face it, pathologists disagreeing on diagnoses is a pretty shocking and saleable story.

But perhaps this situation can be flipped on its head and used to pathologists' advantage. Why not get out there and talk about your role, in particular its criticality to a patient's health, and defend against some of the research that has negatively represented pathology to the public and your medical peers? In response to the JAMA piece, we did our own digging around and bring you the story from different perspectives in this month's cover feature.

Don't let negative comments go unanswered on Twitter, Facebook or LinkedIn - better still, write a blog about the bias introduced by reporters and link to as many sources as possible. In other words: take control.

Fedra Pavlou
Editor

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Kenneth Bloom

An early adopter of information technology, Kenneth developed the first commercial telepathology system during his residency. Creator of the Pathology Information System at Rush Medical Center, he also helped design the hospital's Tumor Registry and Surgical Information System. His career spans more than 30 years, including key positions in start-up companies, University-based medical centers and commercial laboratories. An author of more than 50 peer-reviewed articles, he has also served as principal investigator of more than a dozen clinical trials. Currently, he is President and CEO of Clarient Pathology Services, and Chief Medical Officer of Clarient Diagnostic Services, where his lab evaluates over 100 breast cancers daily.

On page 22, Kenneth refutes claims by a JAMA study that pathology breast cancer diagnoses are often inconsistent.

Matthew Smith & George Burghel

As principal clinical scientist at the molecular pathology diagnostic service, University Hospitals Birmingham NHS Trust in the UK, Matthew has worked for the past nine years in clinical genetics laboratories, specializing in molecular pathology, which has included working on a number of next generation sequencing projects, focusing on solid tumors.

George was awarded a PhD in cancer genetics from the University of Sheffield, UK, before completing a three year clinical scientist training programming with Yorkshire Regional Genetics Services. He is now working as a higher specialist trainee clinical scientist at the Manchester Centre for Genomic Medicine in the UK.

Matthew and George explore the progress and applications of next generation sequencing on page 30.

Michael Misialek

Michael currently serves as Associate Chair of Pathology at Newton-Wellesley Hospital, Newton, MA, USA, and Medical Director of the Vernon Cancer Center, and practices in all areas of pathology in a busy community hospital. "I'd like to tell women that recent studies should in no way dissuade them from breast cancer screening. Patients are healthier when pathologists are involved with their care. Many pathologists already regularly meet with patients – let's open the doors for all of us to invite our patients to meet us."

Michael discusses the backlash against breast cancer screening on page 24.

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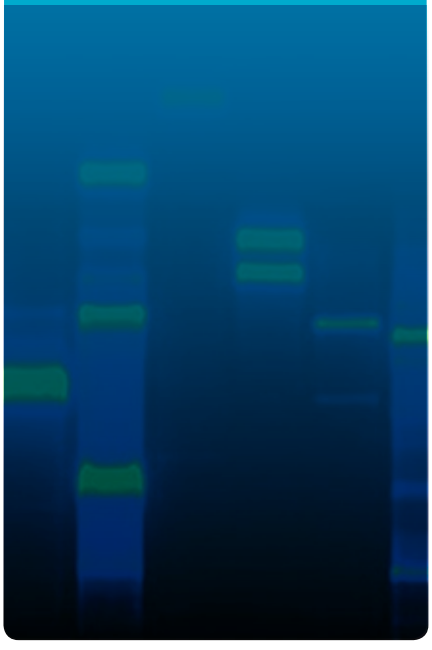

Tumor Only Sequencing Could Be Misleading

Many hospitals sequence patients' tumor genomes to personalize their treatment – but without sequencing normal tissue, this can harm rather than heal

Sequencing the tumors of cancer patients is an increasingly common practice among healthcare providers. The testing is done in an attempt to personalize each patient's therapy as much as possible – but it may actually be negatively impacting treatment.

The reason, according to a study by scientists at the Johns Hopkins Kimmel Cancer Center (Baltimore, MD, USA), is that many hospitals and companies that sequence patients' tumor genomes fail to sequence normal tissue as well, meaning that they can't easily distinguish cancer-related mutations from those that have no deleterious effects (1). Without the ability to fully understand what's going on inside a tumor and what genetic alterations are causing it, attempting to use tumor sequencing information to direct treatment may be inappropriate or even harmful. The study analyzed sequencing data from 815 patients with a wide variety of cancers, filtering out well-known germline mutations. Looking only at tumor sequences, researchers discovered 382 mutations. After comparing those sequences to the patients' normal germline genomes though, they found that an average of 249 of the mutations – over 65 percent – were part of the patients' normal background genetic variation.

But not all mutations can be therapeutically targeted. When the researchers limited their search to "actionable genes," for which targeted treatments have already been developed, they found that many of those changes were also part of patients' germline genomes, resulting in "false positive" sequencing results for nearly half of patients. This, warns principal investigator Victor Velculescu, could lead to inappropriate therapy for patients in whom these changes are normal. In a press release from Johns Hopkins Medicine (2), he explains that personalized therapies, which are aimed at the unique genetic changes that drive individual tumors, depend on accurate assessment of those tumors' genomes. As his study shows, though, not all genetic changes in tumor tissue are directly related to the cancer. In order to determine which types of treatment will work for which patients, it's important to consider every factor – and that includes comparing their tumor sequences to the genetics of their normal tissue.

Of course, implementing this knowledge in a clinical setting isn't as easy as just acknowledging its necessity. Sequencing normal tissue alongside tumor samples doubles the cost of testing – currently several thousand dollars to sequence tumor tissue alone – and the amount of work required to collect, prepare and analyze samples. But the benefits of sequencing normal tissue extend beyond a single patient; understanding more about which mutations are directly related to cancer can increase our overall understanding of the disease and allow us to discover new genes that increase the risk or severity of disease. Ultimately, normal sequencing could help us to better identify cancer patients at greater risk of refractive disease, or screen the general population for people at risk of developing cancer in the future. *MS*

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Hitting the Mark

New US guidelines for colorectal cancer testing highlight the importance of molecular markers

Draft guidelines designed to address the evaluation of molecular markers in colorectal cancer (CRC) have been released by a partnership of US pathology and oncology societies (1). The group hopes that the multidisciplinary guidance will provide useful recommendations on everything from sample collection to diagnostics and follow up, with a stated aim of improving and optimizing personalized care for patients.

Sponsored by the American Society for Clinical Pathology (ASCP), the College of American Pathologists (CAP), the Association for Molecular Pathology (AMP), and the American Society of Clinical Oncology (ASCO), each society was represented by a co-chair. A panel of over 25 different experts in oncology and pathology was also involved – a truly collective effort.

So why were the guidelines needed? "While other CRC guidelines have been published, they tend to focus on one marker or a small panel of markers for one specific clinical use, unlike the collaborative multidisciplinary approach for this guideline," says Stanley Hamilton, the CAP co-chair of the project. "This guideline addresses all current molecular markers that can impact treatment decisions for patients with CRC. To date, there isn't an evidence-based guideline that's quite as all-encompassing and patient-centered as this one."

Recommended

Marker	*Use*
RAS mutational testing – including *KRAS* and *NRAS* ("expanded" or "extended" *RAS*)	Should be performed for patients being considered for anti-EGFR therapy
BRAF V600 mutational analysis in conjunction with deficient mismatch repair/microsatellite instability	Should be performed in colorectal carcinoma tissue of patients with metastatic CRC, for prognostic stratification
Deficient mismatch repair/ microsatellite instability testing	Should be performed in all patients with CRC, for prognostic stratification and to identify cases of Lynch syndrome

No Recommendation

Marker	*Use*
BRAF V600 mutational status	Insufficient evidence to support this marker as predictive of response to anti-EGFR inhibitors
PIK3CA	Insufficient evidence to recommend *PIK3CA* for therapy selection outside of clinical trials
PTEN analysis using IHC or FISH	Insufficient evidence to recommend *PTEN* for therapy selection outside of clinical trials

Table 1. Recommendations made by the ASCP/CAP/AMP/ASCO guidelines on which molecular marker tests should be performed on patients with CRC.

The document provides guidance for pathologists on which molecular markers to use for which patients (see Table 1), as well as recommendations on appropriate sampling and testing methods, turnaround times, and test prioritization.

The draft guidelines were made available online from March 30 to April 22, 2015, in order to allow comments from the healthcare community, with feedback welcomed.

The guidelines also acknowledged testing methods still under development; "Given the rapid evolution of the field, we have 'future proofed' the document with a research section that acknowledges molecular markers and tests on the horizon. We intend to review these recommendations regularly," says ASCO co-chair, Carmen Allegra. *RM*

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Buying the Hype

As consumer genetic testing becomes cheaper and easier to access, medical professionals worry that unregulated Internet marketing may steer patients in the wrong direction

To most medical professionals, the questionable nature of consumer genetic testing seems self-evident. Unfortunately, that isn't the case for members of the general public, who – without an advanced education in molecular biology or oncology – lack the ability to critically evaluate the marketing of those kinds of tests. It's a major concern, then, that the Internet marketing of these services is unregulated; commercial testing companies can make whatever claims they choose, which leads to wide variation in how their services are presented to the public. As a result, many physicians are concerned about the challenge this variation poses both to them in lifting the veil of confusion for their patients, and to the patients themselves, who are trying to make the best possible decisions for their own care.

A new study from the Dana-Farber Cancer Institute (Boston, MA, USA) has determined that websites advertising personalized cancer testing offer genetic tests whose value in clinical guidance has not been shown (1). Stacy Gray, lead author on the report, says, "Over 85 percent of the websites that marketed tumor testing marketed at least one or more tests that really have not been proven to improve patients' outcomes. That means that there are many different types of tests on the Internet – some of them helpful and some of them not yet known to be helpful." Even the tests that have clinical value aren't always presented correctly – most Internet copy emphasizes the purported benefits of the tests while downplaying their limitations (1). "Websites marketing personalized cancer medicine tests, services or clinical care were much more likely to endorse the benefits of personalized cancer care than the potential limitations. For example, important issues such as the possibility of test failure or the fact that providers and labs often face a lot of uncertainty as they try to interpret complex genomic data were infrequently mentioned."

Marketing claims made by the websites include such statements as, "We want you to have the peace of mind that comes from knowing you are doing everything you can to maximize the success of your treatment and limit treatment side effects as much as possible," or, "Why use your body to investigate a drug's effectiveness, when we can garner the results safely and in a timely manner? (2)" Even more worryingly, some suggest making or modifying treatment plans developed by the patients' care providers, saying, "If you want the peace of mind that comes from knowing that you are doing everything possible to beat your cancer with the least amount of side effects and the shortest recovery time possible, let [our company] prepare a [personalized plan] for you." Or even claiming, "Our team has helped patients become aware of, and gain rapid access to, innovative treatments that were not initially prescribed by their oncologists. (2)" It's possible that these often unfounded claims may actually have a detrimental effect on patients' care if they promote products or treatment pathways not recommended by doctors.

Gray feels that another major risk is patients having unrealistic expectations if they believe many of the online claims. "If patients see interesting information online," she warns, "they should definitely ask their doctor about it. And given the disproportionate claims of benefit and promotion of tests that may not be beneficial, we would urge clinicians and patients to critically evaluate online personalized cancer products."

Recently, the US Food and Drug Administration has stated its intention to begin regulating genomic testing more broadly – a promising step forward for a market whose information is as yet unsupervised by any such agency. But even if such regulation does materialize, as consumer genetic testing becomes more popular and more affordable, it will become increasingly important for medical professionals to assist patients in determining the best way forward for their own treatment. *MS*

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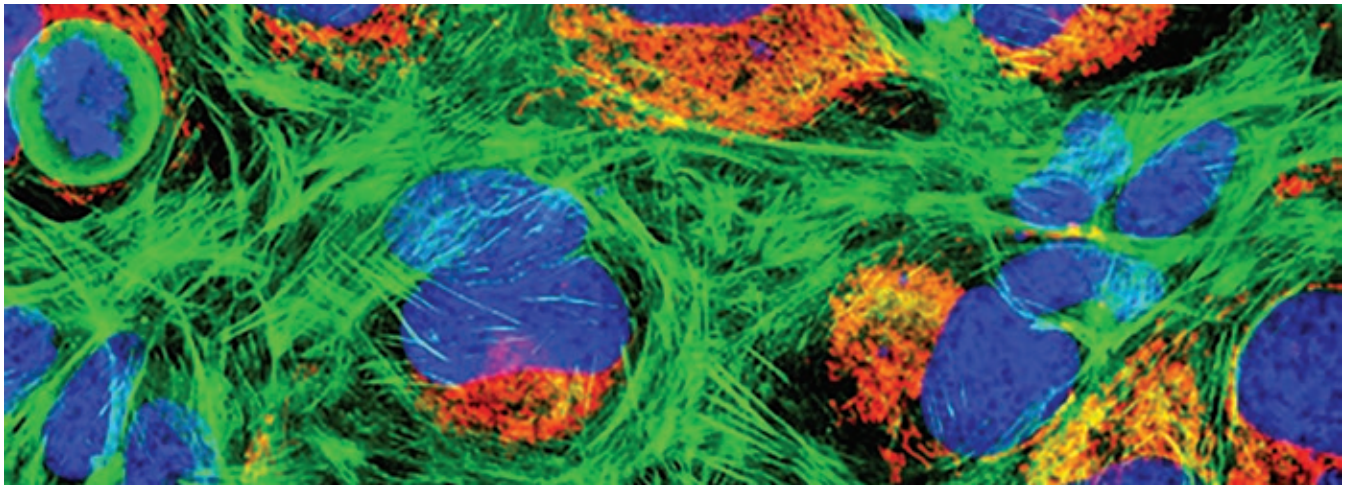

Clamping Down on Mistaken Identity

Mislabeling and contamination of cell lines in labs are well-known issues, but often nothing is done about them; journal publishers are getting tough

Errors with misidentification and contamination of samples and cell lines is a big problem and it's a widely known one too. Not only does it affect data integrity and scientific reproducibility, but outside of research, it could result in a misdiagnosis; a worrying consequence that all pathologists would wish to avoid at all costs. In spite of this, not enough is being done to avoid it, in particular in research labs. Some journal publishers, however, believe it's time to force an end to the "ignorance is bliss" approach and tackle the problem head on.

Nature and Nature research journals, for example, from May onwards will ask authors of submitted manuscripts to check that "they are not working on cells known to have been misidentified or cross-contaminated, and will ask them to provide more details about the source and testing of their cell lines," (1). Some specialist journals, such as the International Journal of Cancer, are also systematically asking for authentication.

Nature journals started to ask the question back in 2013; of those cell-line based papers published, only 10 percent of authors said they had authenticated the cell line and, worryingly, almost one-third said the cell lines had been gifted from another laboratory.

Addressing this issue might seem obvious, but until recently, tests to check the contents of cell lines were complex and time-consuming. In a bid to address this, scientists at biotech firm Genentech have created a cheap and efficient way to identify cell lines (2). Using standard tests to distinguish cells by short, repeated DNA sequences, the team gathered profiles for cell lines from seven databases and created a clean list of existing cell lines after cross-referencing all profiles (they narrowed a collection of 8,577 DNA profiles to 2,787 unique ones). The firm has uploaded its data to the US National Center for Biotechnology Information, and it's also working to make it more widely available. They also compared variations in single nucleotides of DNA in order to profile cell lines. In a Nature press release (3), Jon Lorsch, head of the US National Institute of General Medical Sciences says, "The fact that Genentech has chosen to invest in dealing with this problem gives a clear signal that it needs to be dealt with."

More needs to be done to highlight the extent of this issue though. The Global Biological Standards Institute, for example, has launched a social media campaign, #authenticate, to publicize the problem of misidentified cell lines. And in next month's issue, we speak with members of a working group of the European Federation of clinical Chemistry and Laboratory Medicine (EFLM) about the work that they are doing to eliminate preanalytical sample errors, so look out for it in the May issue of *The Pathologist*… *FP*

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In a Swipe of a Swab

Researchers believe a simple oral swab test could overcome the limitations of standard sputum testing methods for tuberculosis

Dilutions of mycobacterium tuberculosis H37Ra, a nonvirulent strain, were tested in the Cangelosi Lab. Photo credit: Sarah Fish, University of Washington, USA.

Although mortality rate has seen a big decline, pulmonary tuberculosis (TB) remains the second biggest killer from a single infectious agent: according to WHO, 9 million people fell ill with TB in 2013, 1.5 million died from it (1). While a diagnosis is usually done using microbiological, microscopic, or molecular analysis of sputum, this form of test has its challenges. Given the global burden of TB, it's clear an alternative is needed. And researchers from the Universities of Washington, USA and Cape Town, South Africa, think they might have found it – in a test that involves using a $1 cheek swab.

Bacteria like to stick to surfaces, which inspired the team to conjecture that TB pathogen cells can be found attached to the inner surfaces of the mouths of people with active disease. "The swab is used to gently scrape the interior of a person's cheek and the material collected by the swab is then tested by a standard PCR test for *Myobacterium tuberculosis* DNA," explains lead author of the associated paper (2), Gerard Cangelosi. "One of our collaborators, Lisa Jones-Engel, showed the method can work in veterinary applications, which was what prompted us to try it out in humans. This is an example of a "One Health" approach to improving human healthcare," adds Cangelosi.

So how did they go about testing the hypothesis? The team collected three swabs each from 20 subjects with active pulmonary TB and from 20 healthy controls. Those samples were then tested using a PCR-specific to the *M. tuberculosis* IS6110 insertion element. And the result? At least two positive swabs for 18 of the 20 test subjects (90 percent); all healthy control samples were negative. "This initial proof-of-concept project used a small sample set," says Cangelosi, "and the results suggest that the method can be used for the most common form of TB, but large samples are needed." He believes if larger samples continue to show promise, the method may facilitate TB case finding in several ways, including improving identification of people with active TB in large numbers before they have a chance to spread disease to others; so "active case finding," a long-sought goal in TB control. It could make it easier to diagnose TB in remote settings too, and it may also make it easier to diagnose pediatric TB.

Why is an alternative actually needed? Sputum has several limitations: it's difficult for some patients (especially children) to produce, its viscosity restricts test sensitivity, and its production requires patients to cough, thus posing a threat to healthcare workers.

The advantages of an oral swab are clear: it's fast and easy to collect, samples are easier than sputum to analyze, and they pose a lower risk to others. "We consider it unlikely that our method can totally replace sputum testing. However, it may simplify TB diagnostic and screening tasks that are not currently easy with sputum analysis. And possibly, it may enable active case finding strategies that are not possible with sputum analysis," explains Cangelosi.

What's next for the team? They'll repeat the proof-of-concept study in a larger subject sample in South Africa and the USA. They also plan to demonstrate efficacy in pediatric patients. If all goes according to plan, "We will then work to develop point-of-care testing methods that exploit the unique advantages of oral swabs," Cangelosi confirms. *FP*

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Cancer's Common Core

Genetic flaws shared by all metastases of a single prostate cancer may be the key to personalized treatment

In a landmark study by the International Cancer Genome Consortium (ICGC), scientists believe they have discovered the common genetic faults at the root of individual prostate cancers.

The ICGC Prostate Cancer UK group analyzed the genomes of tumor samples in 10 patients, allowing them to map the genetic changes that occurred as the tumors grew, metastasized and developed treatment resistance (1). They found massive genetic diversity between cells even when taken from different sites in the same prostate – but despite this diversity, the researchers were able to show that metastatic prostate cancer cells all share common mutations unique to the individual patient. In a Cancer Research UK press release (2), study author Ros Eeles said, "We found that all of the cells that had broken free shared a common ancestor cell in the prostate. The common faults we found in each man could potentially offer new targets for treatment." Principal author Steven Bova agrees, saying, "The diversity we've found suggests multiple biopsies might be needed to identify the 'trunk' of the cancer's tree of mutations – we need treatments that target these core weaknesses to destroy all cancer cells in a clean sweep."

Eeles also reported that she and her group gained a much broader view of prostate cancer as a whole by studying both the original tumors and the cells that had metastasized. They discovered new information about the way prostate cancer spreads through the body (see infographic), using genetic evidence to show that the cells that initiate metastasis continue to travel through the circulatory system seeding additional tumors. However, Eeles adds the caveat that "once cancer cells have spread, they continue to evolve genetically, so choosing the most effective treatments will remain a key challenge." For a disease that kills over 300,000 men worldwide each year (3), any step toward better treatment is welcome. *MS*

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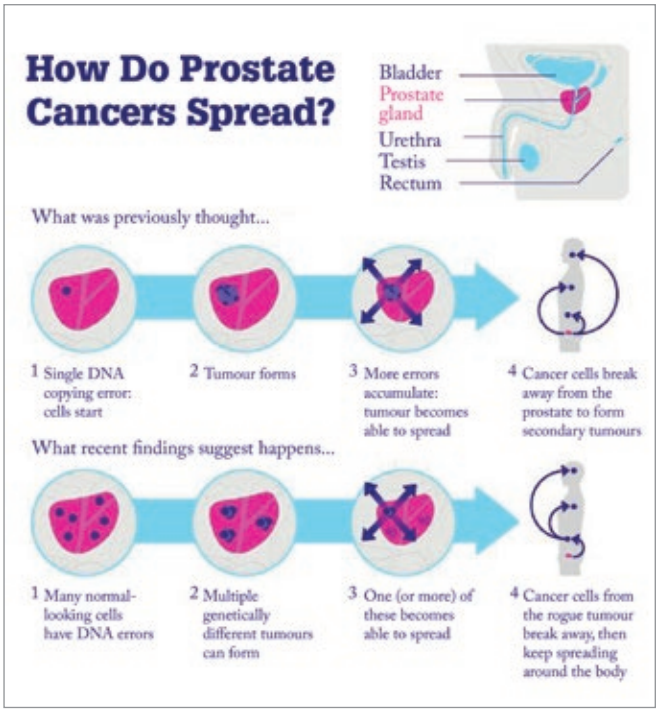

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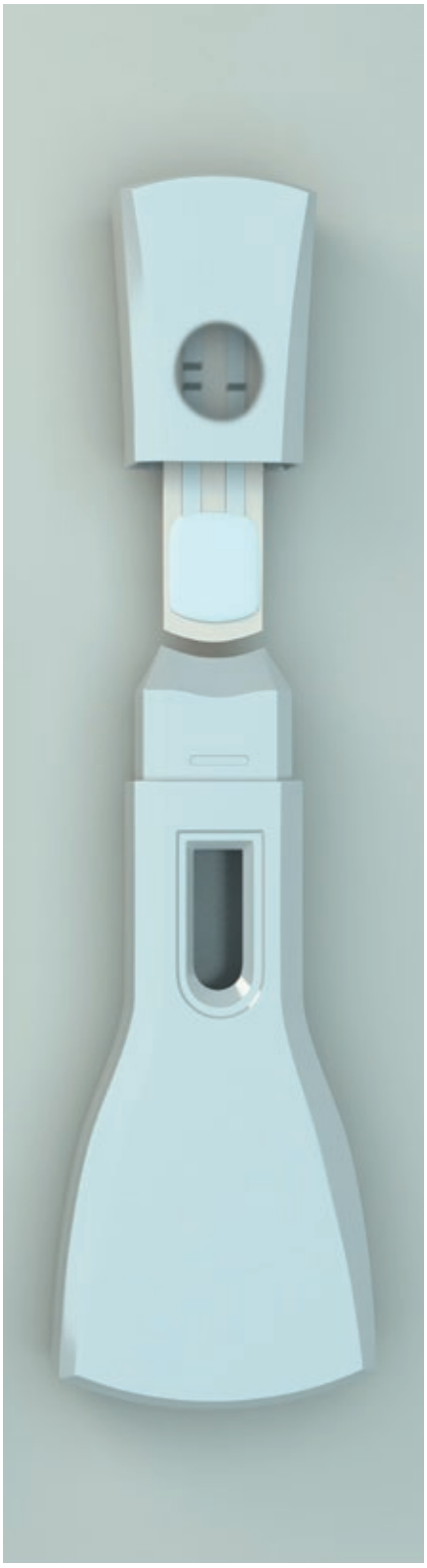

Nanoparticle Nephrology

A new device combining nanoparticles with pregnancy testing technology may provide rapid, inexpensive kidney disease diagnosis and monitoring

Chronic kidney disease (CKD) is estimated to affect 8 to 16 percent of the world's population (1). In the United Kingdom alone, it's suggested that there may be over 1 million people who suffer from undiagnosed CKD (2) and who, as long as their disease goes unrecognized, will continue to miss opportunities to improve their health outcomes. The factors underlying this lack of diagnosis are multifaceted, but in areas where testing is lacking or difficult to access, the engineers at Bio Nano Consulting (London, UK) think they have a solution.

They've developed a medical device, which combines nanotechnology with a pregnancy tester (see photograph). The quantitative electrochemical lateral flow assay (QELFA) uses nanoparticles to test the protein content of a patient's urine and delivers quantitative results in seconds via a digital readout on the handheld device. Doctors can even link it to the computers in their surgery via mobile technology, allowing them to track a patient's disease progress over time without requiring repeated clinic appointments. The QELFA device is still in the early stages of development, but results so far have been so accurate that a patient trial program is currently being designed, and the developers hope to have the final product available within the next five years.

Helen Meese, head of materials at the Institution of Mechanical Engineers, says that the drive to develop kidney disease technology is "to provide simple-to-use, yet accurate medical tools that will not only aid in the diagnosis of disease, but enable the patient to be engaged in their treatment in a straightforward way using recognizable technology." She hopes that simplifying the diagnosis and monitoring process for patients will reduce the mental and physical stress of dealing with illness. It will be helpful for doctors, too – at the moment, there is no device physicians can use for day-to-day monitoring of kidney disease. Increasing their ability to receive rapid updates on their patients' conditions will improve care in both ongoing chronic disease and acute kidney failure.

Meese anticipates that rapid, low-cost tests like this could save the UK's National Health Service millions of pounds for a disease with a current cost burden of over £1.4 billion (3). They anticipate that the test will cost around £10. It's not just the cost of the test that is reduced with devices like QELFA, but the need for late-stage or emergency treatment of kidney disease sufferers. Meese also doesn't think that the QELFA device's potential is limited to kidney-related conditions. "With the increasing number of people requiring diagnosis of different types of disease, point-of-care tests such as these will become more commonplace and increasingly useful in helping pathologists, urologists and general practitioners to provide more personalized health care." *MS*

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Celiac Screening

Growth monitoring could screen children for celiac disease, enabling easier lab diagnosis

Celiac disease (CD) has a prevalence of around 1–2 percent in Western populations, but less than a third of patients receive a diagnosis. Accurate blood-based tests are available, but the idea of population-based blood screening is controversial. Many symptoms of CD, such as poor weight gain and inconsistent growth are very nonspecific; which means it can be a challenge to identify which children might benefit from blood tests. Now, Finnish researchers are working to develop a noninvasive screening method to pinpoint CD earlier, and more accurately.

Using five growth-based parameters, the researchers were able to predict which children had CD with over 80 percent accuracy. "Systematic population-based screening of childhood growth would facilitate early diagnosis of celiac disease," says co-author of the associated paper (1) Sankilampi Ulla, "as faltering linear growth may be the earliest way to detect symptomless celiac disease."

Early diagnosis of CD is linked to better outcomes, and could lessen the impact of the condition on health – and since many disorders affect growth, monitoring could potentially improve the diagnosis of other disorders too. Ulla and her team now intend to perform a prospective study to further validate the screening method. *RM*

Reference

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Credit: Andrew Kilianski

Assemble the MinIONs

A pocket-sized DNA sequencer powered by a USB connection could bring disease differentiation capabilities to remote locations

UK researchers are working on a technology which will potentially be able to offer whole genome sequencing in a tiny palm-top device, with high accuracy. Diagnosing infectious disease in remote areas, especially during outbreaks, is an ongoing challenge for researchers and physicians, and the minION sequencer has the potential to offer sequencing on the go with just a laptop and a sample.

Developed by Oxford Nanopore Technologies, the sequencer was given to several research groups for alpha testing (1). One of the groups reported that the device was able to identify viral and bacterial species from samples within six hours, identifying *E. coli* down to species level, and separating three poxviruses down to strain level, despite two of the viruses (vaccinia-MVA and vaccinia-Lister) having 98 percent similarity – a promising result.

Powered and operated using a USB connection to a laptop, minION contains protein nanopores through which single DNA strands pass, detecting the bases present using their distinct electrical signals. Since it is easily portable and relatively low in cost, it could potentially be used in inaccessible locations without lab access, in order to identify disease.

However, with its current 30 percent error rate in identifying individual bases, there is still room for improvement. In the current experiments, amplicon sequencing was used to aid identification of the microbes. But it is hoped that, as the technology evolves and matures, sequencing will become more accurate, and the device will have applications for both infectious disease control, and clinical genetics. *RM*

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Dubious Diagnoses?

Recent media attention on diagnostic discordance has patients shying away from cancer screening – but are they justified?

By Michael Schubert

The messages are everywhere around us – campaigns for breast cancer screening, for prostate cancer testing, for gynecological exams, for colonoscopies. Patients are warned to stay ahead of the potential risks by making sure they have regular checks. Though there's plenty of dissent in the medical community about cancer screening – who should get it, when it should be done, which methods are most reliable – it's hard to deny that early testing can save lives. But how reliable is this screening, and how much does success depend on the pathologist behind the test?

Diagnostic disagreements

A recent report in JAMA has drawn a lot of attention for its investigation of diagnostic concordance between pathologists interpreting breast biopsy specimens (1). The authors of the paper attempted to quantify the degree of disagreement between diagnoses provided by different pathologists for the same specimens. To do so, they generated a set of 240 excisional or core needle breast biopsy specimens randomly selected from pathology registries affiliated with the Breast Cancer Surveillance Consortium. From each biopsy, new slides were prepared in a single laboratory for consistency, and the best of those slides was selected by consensus panel for inclusion in the set of test cases. Specimens exhibiting atypia and ductal carcinoma in situ (DCIS) were oversampled, as were cases from women either in the 40-49 age category or with mammographically dense breast tissue. These types of samples were emphasized because age and breast density are key risk factors for both benign breast disease and cancer, and because atypia and DCIS are often more difficult to diagnose or appear "borderline" between multiple diagnostic categories – so the researchers predicted that there would be more discordance between different pathologists' conclusions.

The cases were first reviewed by a panel of three experienced, internationally recognized pathologists who were blinded both to previous interpretations and to one another's conclusions; at this point, the pathologists were in unanimous agreement on the diagnosis of 75 percent of cases. After resolving the remainder of cases by consensus, the 240 slides were randomly divided into four test sets and distributed to pathologists in the United States (all of whom had at least one year of experience interpreting breast specimens and intended to continue for at least one additional year) for interpretation. Slide examples for each diagnostic category can be seen in Figure 1. The invited participants received one hematoxylin and eosin-stained slide for each case, as well as information on the type of biopsy and the patient's age. They were not given any diagnostic definitions or specific instructions; rather, they were asked to evaluate the cases as they would in their standard laboratory practice.

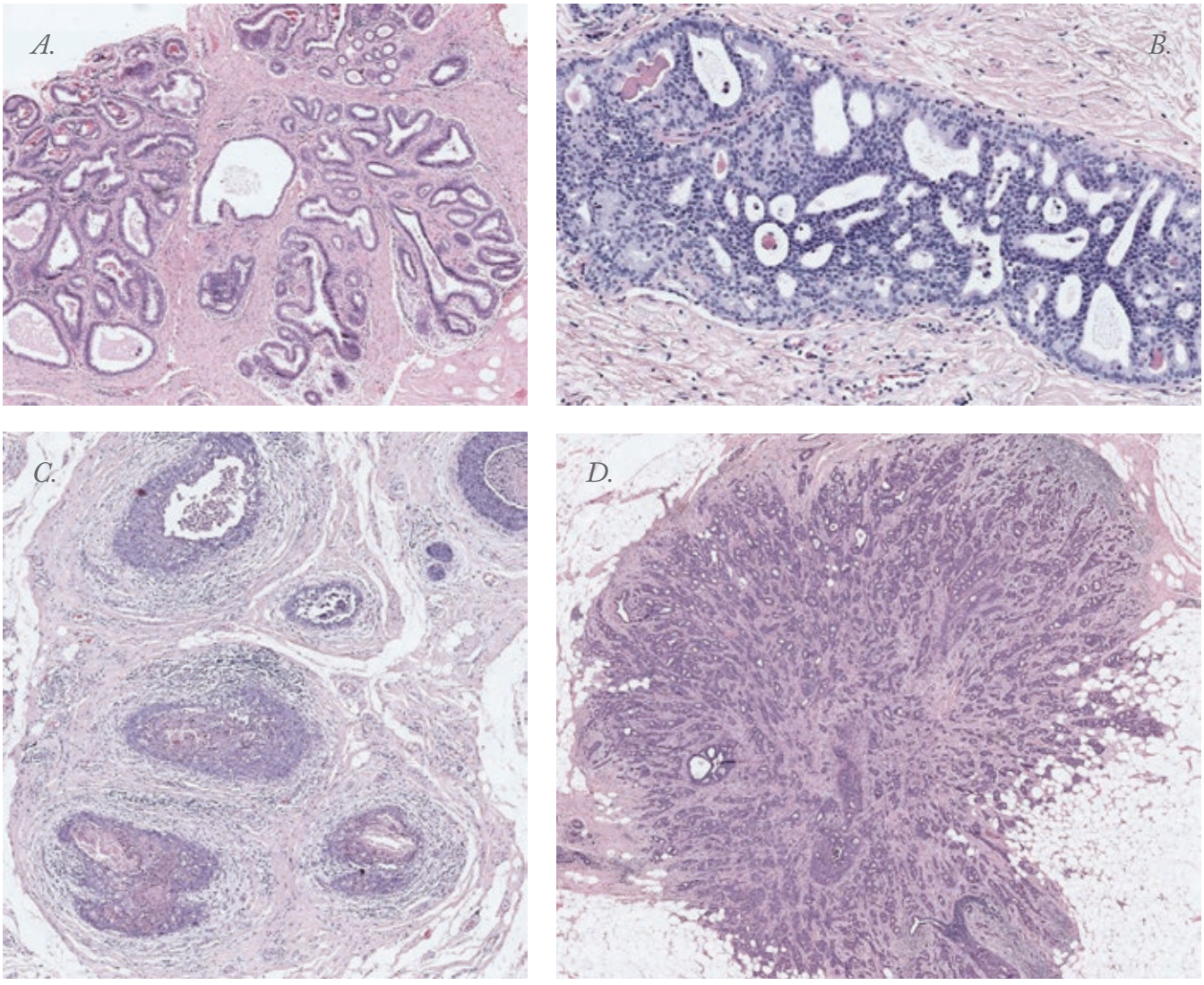


Figure 1. Slide example for each diagnostic category assessed in the JAMA(1) study. A) Benign without atypia; B) Atypia; C) DCIS; D) Invasive carcinoma. DCIS, ductal carcinoma i*n situ*. Credit: University of Washington, USA.

Of the 6,900 total interpretations in the study (115 pathologists reviewing 60 cases each), participants agreed with the consensus reference diagnosis 75.3 percent of the time – but the agreement varied widely depending on the type of specimen. Concordance for invasive breast cancer cases, for instance, was high (96 percent), but low (48 percent) for atypia (Figure 2). Discordance was higher when pathologists reported that a case was "difficult" or "borderline," requested second opinions, or lacked confidence in their own assessments.

A key finding in the JAMA study is the variability of pathologist interpretations. Though the danger of underinterpreting a case is clear, it's less obvious how overinterpretation (which, in the study, occurred in 3 percent of DCIS cases, 17 percent of atypia cases, and 13 percent of benign breast tissue specimens) can cause harm. Unnecessary medical intervention, additional incursion of costs and the possible detrimental psychological effects of a cancer diagnosis are all potential consequences. But knowing the level of discordance between pathologists and the risks associated with overinterpretation may cause anxiety and uncertainty among women who undergo breast cancer screening. It may even discourage them from receiving

the appropriate monitoring (see section on "Prompting patient participation"). But what exactly is "appropriate" monitoring – and who determines how much is too much?

Testing: who, what, and when?

Some suggest it should be the physicians and researchers with the greatest knowledge and understanding who determine "appropriate" levels of testing – but even when offered the chance to reduce the amount of unnecessary screening, practitioners may not take it. Acknowledging estimates that as much as 30 percent of healthcare spending may not go toward improving patient health, a study published in JAMA Oncology (2) investigated regional imaging rates for both breast and prostate cancers. The researchers conducted a retrospective cohort study to look at how closely the American Society of Clinical Oncology (ASCO) recommendations against imaging to stage cancer in patients with low-risk disease were followed.

Patients were considered to have low-risk breast cancer if their disease was *in situ*, stage I, or stage II; low-risk prostate cancer included patients with stage T1c or T2a disease, a Gleason score of six or less, and a PSA level below 10 ng/mL (see The Pathologist's previous feature on the value of PSA testing, (3)). ASCO's Choosing Wisely guidelines (4) recommend against positron emission tomography (PET), computed tomography (CT), or radionuclide bone scans for patients meeting these criteria – but physicians continue to order them anyway. In the JAMA Oncology study, the overall rate of inappropriate imaging for breast cancer was 41.8 percent, while for prostate cancer it was 44.4 percent. There are a number of factors that might cause a clinical practitioner to order a test that isn't recommended; for instance, a doctor might take a "better safe than sorry" approach by preference, a patient might request imaging, or fears of malpractice might prompt an unnecessarily high level of caution.

It's true that best practices for care in staging cancers are different to those in screening for them, but in both cases, clinicians may be ordering unnecessary tests, and neither patients nor practitioners benefit from the results. Tests that aren't needed for medical care cost doctors' time, healthcare systems money, and patients their peace of mind – especially when the people responsible for reading the scans might disagree in their interpretations.

Prompting patient participation

Not everyone wants to put the decision-making power in the doctors' hands. Some advocate for patients' rights to choose whether or not they want to be screened for cancer. And in fact, a first-of-its-kind study in The Lancet recently found that women who are better educated about the risks of breast cancer screening are less likely to want to take part in screening programs (5). The randomized controlled trial involved 879 Australian women aged 48 to 50 (the age at which screening commonly begins in Australia and in other countries with similar programs). Those given information on overdetection were found to have a less favorable attitude toward breast screening and, as a result, significantly fewer intended to be screened when compared with controls. Nonetheless, overall attitudes toward screening remained positive. The majority of the women also reported that they had not been aware of the facts surrounding overinterpretation before the study.

"Women who are better educated about the risks of breast cancer screening are less likely to want to take part."

"Recent international reviews have called for better, more balanced information to be provided to women when they are invited to breast screening", said Jolyn Hersch, lead author of the Lancet study. She added, "Overdetection is considered one of the most important downsides, but most women are unaware of the risk. Screening can detect inconsequential breast cancers, leading to overdiagnosis and overtreatment. And this treatment can include surgery, radiotherapy, hormone therapy, and chemotherapy, all of which have side effects." An article published in JAMA Internal Medicine shows that most patients overestimate the benefit of interventions, but underestimate the potential risk (6) – but studies like the JAMA and Lancet ones regarding breast cancer screening seek to change that.

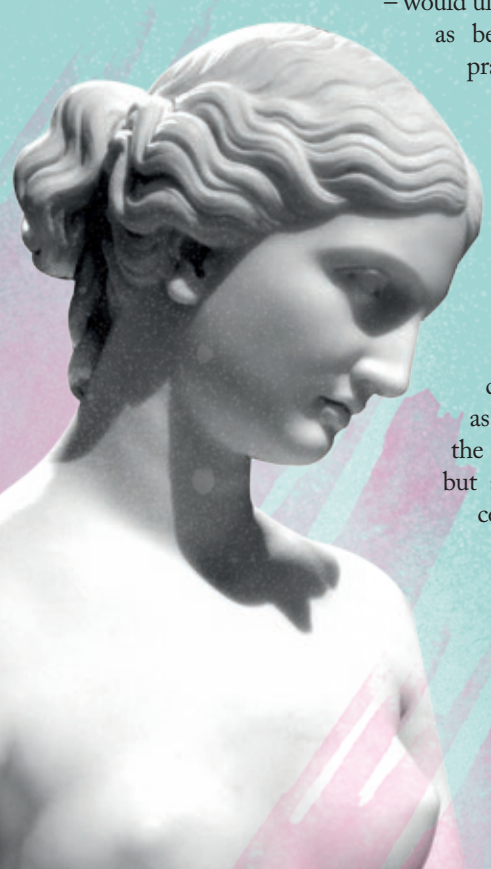
And it seems that the message is being heard. Recent statistics from the UK's National Health Service show that the number of women attending breast screening in the country has fallen for the third year in a row. Media attention given to the hazards of screening (7,8) could be partly to blame. The Lancet study's authors believe that patients should be provided with all of the information, so that they can make their own decisions about screening. Hersch explains that the current breast screening

Not Reflective of Clinical Practice

By Kenneth Bloom

Although the JAMA article (1) claims to have identified a lack of consistency in pathologists' breast cancer diagnoses, this doesn't reflect actual clinical practice, where the rate of discordance is significantly less. Pathologists are physicians and, as such, make diagnoses based on all available information, including clinical information, radiologic findings and all of the available pathology material. Communication with the submitting physician is common, as is confirmation of all malignant diagnoses by a second pathologist and a more comprehensive workup of atypical cases, including recuts, immunohistochemical stains and second opinions when necessary. This means that virtually all cases with a diagnosis of invasive cancer, DCIS or atypia are seen by more than one additional pathologist.

There were 216 cases that were called as benign without atypia by the expert consensus panel in the JAMA paper, and 19 (8.8 percent) of those were called as atypical, DCIS or invasive carcinoma by the individual pathologists. Since all of those cases would have been reviewed by a second pathologist, along with all pertinent clinical information, I would guess that most – if not all – would ultimately have been called as benign in actual clinical practice, or at least sent out for a second opinion if the second pathologist could not convince the first that the initial diagnosis was in error.



More problematic, in my opinion, are the 20 (9.2 percent) of 217 cases which were called as benign without atypia by the individual pathologists, but atypia or DCIS by the consensus panel. If the reviewing pathologist thought these cases were truly benign, it's unlikely that they would be reviewed by a second pathologist. I'd hope that the clinical and radiologic data would have tipped the pathologists off, but otherwise, these cases would have been missed. Atypia and low grade DCIS are non-obligate precursors to cancers. Based on long-term follow-up data, only about a third of DCIS patients eventually develop breast cancer after many years– so although the diagnosis wouldn't have agreed with that of the consensus panel, no immediate harm would have come to the patient. If an invasive tumor did then develop, it would likely be detected on follow-up screening procedures.

There are several reasons for inconsistency in pathology diagnosis. Surgical pathology is in large part taught through mentorship – the pathologist sits at the microscope with an attending pathologist and learns by reviewing slides with them over the course of several years. Residents read textbooks and peer-reviewed literature as well, but tend to model their style and diagnostic criteria after those of their mentor. While most criteria are relatively straightforward, some involve descriptive words like mild, round or uniform, that are subject to interpretation. Slight differences in tissue thickness or the staining protocol used by a lab can influence a descriptive call, and for some diagnoses, not every pathologist defines diagnostic categories the same way. As new diagnostic and therapeutic modalities are introduced, the significance of a false positive or a false negative diagnosis may be altered, and diagnostic criteria may be modified accordingly.

Our laboratory evaluates more than 100 breast cancers every day, and we rarely see a slide where we disagree with a cancer diagnosis. In the rare cases when it does happen, it's almost always the result of having the wrong slide sent to us for analysis. Based on 10 years of this experience, I'm confident that overdiagnosis of invasive breast cancer is very rare in clinical practice. Even in the JAMA study, no cases of invasive breast cancer were called benign or atypical, and only two cases – those with microinvasive disease – were called DCIS. Surgical excision alone would be considered appropriate treatment for this minute focus of invasive breast cancer. Overdiagnosis of breast cancer was also rare in this study, but would likely have been caught on review by a second pathologist.

Pathologists should be aware of borderline lesions and should not be afraid to seek second opinions in difficult cases. Review of all atypical and cancer diagnoses by a second pathologist should be a routine part of pathology practice. In all cases, the key to good medical practice and trustworthy diagnoses is communication!

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The opinions and views of Dr Bloom are his and do not necessarily reflect the views or opinions of either Clarient, GE or its affiliates.

programs aren't perfect, and can do both harm and good. "The national breast cancer screening program in Australia states that its aim is to reduce illness and death from breast cancer. The evidence suggests that breast screening does lower the number of women who die of breast cancer, but whether it reduces illness overall is questionable, because of the effects of overdetection. This is why it is so important to give women evidence-based, accessible information, so that they can decide what is best for them personally."

Educating for empowerment

There's no question that patients should have the final word on their own health care. But unfortunately, it isn't as straightforward as educating them about the benefits and risks so that they can make informed choices. As every physician – and especially pathologist – knows, medicine is as much an art as it is a science, and evaluating the pros and cons of breast cancer screening isn't as simple as adding and subtracting the evidence.

Given the media attention the new JAMA study on diagnostic discordance has received, it's reasonable to worry about the effect on patients. In an editorial, Nancy Davidson (University of Pittsburgh Cancer Center, PA, USA) and David Rimm (Yale University School of Medicine, New Haven, CT, USA) wrote, "An undesirable short-term outcome from the study by Elmore et al. will undoubtedly be heightened anxiety among women who undergo breast biopsy and concern among their physicians about the accuracy of the pathologic diagnosis (9)." Patients may opt out of screening even when it would be advisable, or may place less faith in the diagnoses reached by pathologists, prompting second opinions and additional testing that burden the healthcare system even more.

That isn't the way Davidson and Rimm think the results should be interpreted, though. Their editorial continues, "This study confirms that the majority of diagnoses […] are readily and accurately made by practicing pathologists." They agree that cancer screening isn't a perfect solution – the JAMA study identifies areas where process improvements are needed, and that there are ambiguous cases in which a second opinion would be valuable. But patient anxiety, and decision-making based on that anxiety, may not be necessary. After all, the study was conducted under conditions quite different to those in a pathologist's daily work – only one slide per specimen, no second opinions or outside consultation, no requests for additional tissue, and no clinical information or imaging findings other than the patient's age. Even the caseload was unrealistic, with large numbers of slides showing atypical hyperplasia and DCIS – borderline situations that comprise only a small fraction of those seen in day-to-day practice (see sidebar, "Not Reflective of Clinical Practice").

Michael Misialek, associate chair of pathology at Newton-Wellesley Hospital (Newton, MA, USA) writes, "While the study's findings may not be surprising to physicians who understand the challenges of diagnosing complex breast cases, news of the article could lead to unnecessarily heightened anxiety for patients and the public as breast cancer is a highly publicized and pervasive disease (10)." He adds, "The study

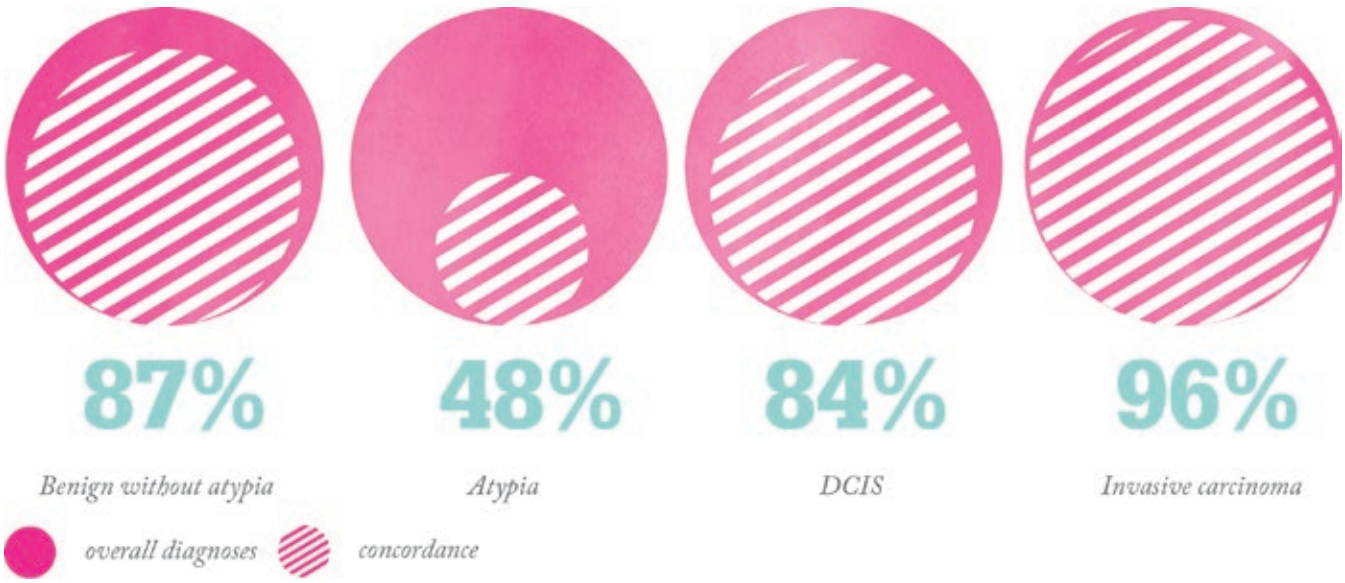
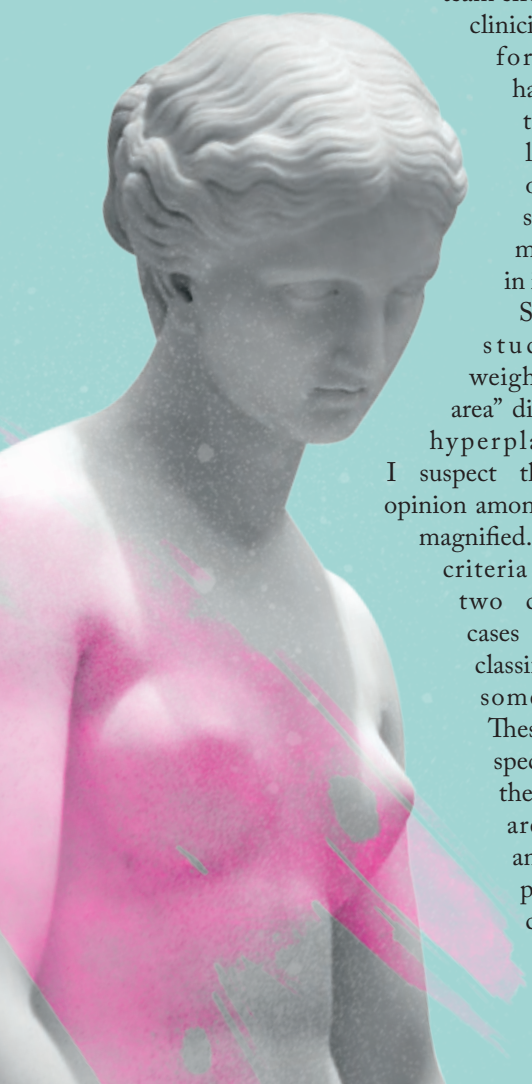


Figure 2. Diagnostic concordance among pathologists interpreting breast biopsy samples (1).

Collaborating on Cancer Care

By Michael Misialek

The major challenge in diagnosing the potential for breast cancer at the premalignant stages lies in recognizing it. In many cases, needle biopsy does a good initial job by allowing the pathologist to properly triage the patient and identify a lesion that's better examined with an excisional biopsy. Practices that don't do secondary prospective review of problematic cases face an additional obstacle to diagnosis; this is critical for high quality work and I would personally consider it mandatory. A robust quality management program that includes specific criteria for mandatory prospective review of complex cases – things that will result in significant clinical impact – is imperative to render quality, reproducible diagnoses. One final challenge that may exist for some practices is the lack of a "team effort" by collaborating clinicians. It's imperative for pathologists to have access to other treating clinicians like radiologists, oncologists, and surgeons. No field of medicine can practice in isolation.



Since the JAMA study was heavily weighted towards "grey area" diagnoses of atypical hyperplasia and DCIS, I suspect that differences of opinion among pathologists were magnified. Despite diagnostic criteria separating these two categories, many cases prove difficult to classify and even experts sometimes disagree. These diagnoses form a spectrum along which the lines of separation are often blurred, and the definitions pathologists use can vary depending upon their training. These "grey area" diagnoses illustrate that pathology is more than just a science – it's an art that requires experience and developing an "eye."

Pathologists have a lot of tools available for studying complex cases. Perhaps most important of all is the power of second opinions. My first step, for instance, is often showing my slides to a colleague, something that occurs countless times a day in many pathology practices. Others might start with ordering additional, "deeper" levels of slides to better evaluate the tissue. Immunohistochemical stains might also prove useful in particular cases. If, after all of these steps, a consensus diagnosis is not reached, then the case will be sent out for outside expert consultation – which again illustrates the importance of collaborative care.

> *"These diagnoses form a spectrum along which the lines of separation are often blurred..."*

The concern raised by media attention on the JAMA paper and other recent studies provides an excellent opportunity for pathologists to educate the public about our field, and about the importance of pathology in their care and education about disease. Impressing upon patients the value of pathology and stressing the need for multidisciplinary collaborative care is important. We should capitalize on this opportunity and use it not only to bring awareness to the field, but to engage patients more deeply in their own care.

I'd like to tell women that these recent studies should in no way dissuade them from breast cancer screening. We know that screening for disease is the best way to find cancer or precancerous conditions in the early stages when they are still highly curable. Patients should understand that board certified pathologists who work in accredited laboratories are excellent diagnosticians and ensure the highest quality in their care. And patients are healthier when pathologists are involved with their care. Many pathologists already regularly meet with patients – let's open the doors for all of us to invite our patients to meet us.

Michael Misialek is associate chair of pathology at Newton-Wellesley Hospital (Newton, MA, USA).

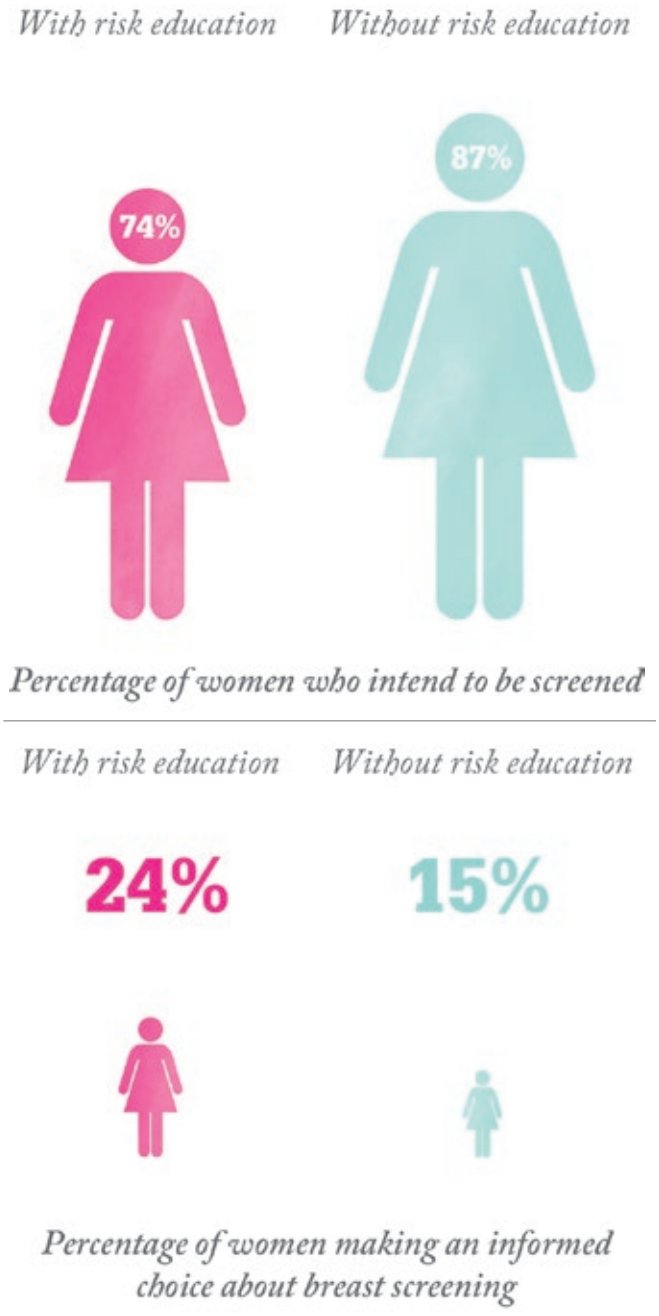
confirmed that the majority of breast pathology diagnoses, especially at either end of the spectrum (benign without atypia and invasive breast cancer) are readily and accurately made by practicing pathologists regardless of practice setting." (See sidebar, "Collaborating on Cancer Care.") Much like in the Lancet paper about overdiagnosis, it's most important to ensure that patients not only have, but understand, all of the relevant information about diagnostic concordance before making treatment decisions that can significantly affect their lives.

The source of the confusion

Oscar Bronsther, CEO and CMO of MetaStat, Inc. (Boston, MA, USA), feels that we need to do better than we have so far to treat patients as precisely as possible – not just in terms of providing better information, but in diagnostic methodology itself. In response to the JAMA study, he says, "As the disparity in diagnoses reveal, relying on traditional approaches to diagnosing cancer can lead to clinical mistakes, especially in premalignant cases. And if experts can't even agree on what cancer looks like under the microscope, they surely can't understand the underlying biology—and whether a specific cancer will become invasive."

Bronsther explains that, in his opinion, the differences in diagnoses can be traced to the "grey zone" that sometimes exists between normal and malignant results. Although both groups of individuals who examined the slides in the JAMA study – community and academic pathologists – have substantial experience analyzing biopsy results, there's still a measure of subjective judgment involved. Though the definition and morphological criteria of cancer have not changed for decades, it's inevitable that, in the absence of more detailed analysis, opinions among the two groups regarding specific slides will vary. Nevertheless, he says, "the disparity is unsettling."

There is an understandably high degree of interest in the earlier diagnosis of breast cancer and other malignancies. After all, that's why current screening programs were established – on the basis that cancers caught earlier can be addressed with cheaper, less invasive treatments. But it isn't enough simply to detect malignant tumors. Increasing the number of cancers we are able to identify without increasing our understanding of their clinical significance has the potential to result in significant overtreatment. Bronsther cautions against delivering a life-changing diagnosis such as breast cancer without all of the facts. "It is more important that we understand the metastatic potential of a tumor rather than just labeling a lesion a cancer," he says. "A tumor with little metastatic potential is very different from a lesion with significant metastatic potential."



Information on overdetection of breast cancer provided within a decision aid increased the number of women making an informed choice about breast screening (5).

Next-generation solutions

The uncertainty surrounding breast cancer screening and biopsy highlights the potential for next-generation diagnostics, which can offer more precise and personalized diagnoses. Molecular and epigenetic tests not only maximize the amount of data obtained, but can also give patients more refined knowledge of the specific challenges they face based on their diagnoses –

information Bronsther says "is crucial, because once you tell them they 'have cancer,' you've frightened them and changed their life." He's optimistic that new kinds of diagnostics can lead to more effective, targeted therapies for specific subsets of cancer patients, as well as to increased savings for hospitals and patients.

"Cancer is complicated and messy and relying on traditional criteria to establish a diagnosis potentially leads to incorrect approaches..."

Next-generation diagnostic tests have already been developed for the prediction of metastasis in women with breast cancer. Immunohistochemistry-based tests performed on biopsy tissue can tag the active sites of metastasis development; one test, for example, targets the three-cell structures necessary for metastasis (endothelial cells, perivascular macrophages and tumor cells expressing a particular chemotaxis protein) with a triple stain, and has even been able to determine whether a woman with newly diagnosed breast cancer is among the 35 percent likely to experience metastatic cancer or among those with breast tumors for whom metastasis is unlikely (11). Other diagnostic platforms quantify metastatic risk by measuring levels of prognostic markers – for instance the Mena protein, which promotes the actin polymerization and protein interaction necessary for cell migration. Tests like those are applicable not only to breast cancer, but also to other epithelial cell tumors such as colorectal, prostate and lung cancer.

"Cancer is complicated and messy," Bronsther says, "and relying on traditional criteria to establish a diagnosis potentially leads to incorrect approaches to the needs of individual patients." Better diagnostic tests will provide patients and their doctors with detailed, personalized information to accelerate the delivery of tailored cancer therapy. Next-generation tests are moving away from a morphological diagnostic approach to a more molecular one, a change that researchers hope will result in better outcomes for patients and significant savings for the healthcare system.

There's still work to be done

Regardless of the approach taken, it seems clear that pathologists and patients have some work to do. While the diagnostic discordance noted in the JAMA study is not, in fact, as concerning as the media hype would have us believe, there's certainly a need for better definitions of the various categories, and for better quality management of borderline and high-risk cases. Over- and underinterpretation are more worrying, because they may lead to unnecessary treatment or to missed diagnoses, respectively – and, as the JAMA Oncology report attested, controversy still exists about the role of increased monitoring in women with atypical biopsy results. Ideally, pathologists will embrace the idea of improving definitions and processes, consulting second opinions where necessary, and making use of next-generation testing in situations where it can offer additional insight into disease. And in the meantime, patients should be given the information and education necessary to understand the treatment decisions they, and their doctors, are making.

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Andreas Seidel-Morgenstern (left), Peter H. Seeberger (right)

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Peter H. Seeberger and Andreas Seidel-Morgenstern

Peter H. Seeberger and Andreas Seidel-Morgenstern of the Max-Planck Institutes in Potsdam and Magdeburg have been chosen as the winners of the inaugural Humanity in Science Award for developing a method for the continuous flow production and purification of cheaper antimalarial medicines using plant waste, air and light.

They were awarded with a humble prize of $25,000 during an all-expenses paid trip to Pittcon 2015 and their insightful essay will be published in a future issue of The Analytical Scientist.

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In Practice

Technologies and techniques
Quality and compliance
Workflow

A Personalized Reality

Next generation sequencing holds much promise for personalized cancer diagnosis, treatment and management, but how is this being realized and what does the future hold?

By Matthew Smith and George Burghel

Clinically actionable mutations lying within certain driver genes are central to tumor development, and hold much utility for cancer medicine. While these mutations carry diagnostic, prognostic or predictive implications, a subset are also deemed 'druggable' – able of identifying cancers that can be treated with targeted therapies acting against the subsequent protein product or disturbed pathway.

With more of these mutations coming to light all the time, this exciting field is developing very rapidly. For example, until this year inherited variants within the *BRCA1* and *BRCA2* genes indicated an increased risk of breast, ovarian and prostate cancer, but were actionable only in the sense that the disease risk could be managed (e.g. through mastectomy and oophorectomy). However, we now regard these mutations as druggable in the sense that ovarian cancers containing the mutations respond to a new class of drugs called PARP inhibitors (1).

The ability to identify such actionable or druggable mutations in tumors holds the key to personalized cancer therapy, informing clinicians and helping to guide treatments. This has many implications; patients will only receive the most appropriate treatment dependent on the underlying molecular profile of the tumor. Personalized therapy for cancer is therefore proving to be safer and more effective than traditional approaches.

A variety of genetic testing technologies are available for profiling these targets, both well-established and emerging. Since the breadth of testing is currently limited to a handful of targets, the majority of routine diagnostics utilize well-established techniques – such as Sanger sequencing, pyrosequencing and qRT-PCR – which enable tests to be turned around in a clinically actionable timeframe, and provide a cost-effective strategy. However, this is only true as long as the number of tests per individual or sample is limited, and with their restricted capacity for multiplexing applications, these techniques are not wholly compatible with ongoing trends.

As the list of actionable genetic markers and targeted therapies expands with the latest research, these types of tests are becoming less feasible. For example, in the last few years a set of actionable mutations in non-small cell lung cancer have been identified, requiring a combination of sequencing, fluorescence *in situ* hybridization (FISH) and immunohistochemistry for molecular characterization from very limited amounts of tumor material (2,3). With a reduction in cost and improvements in library preparation and sequencing, NGS now has the capability for testing larger, multi-gene panels.

Needle in the haystack

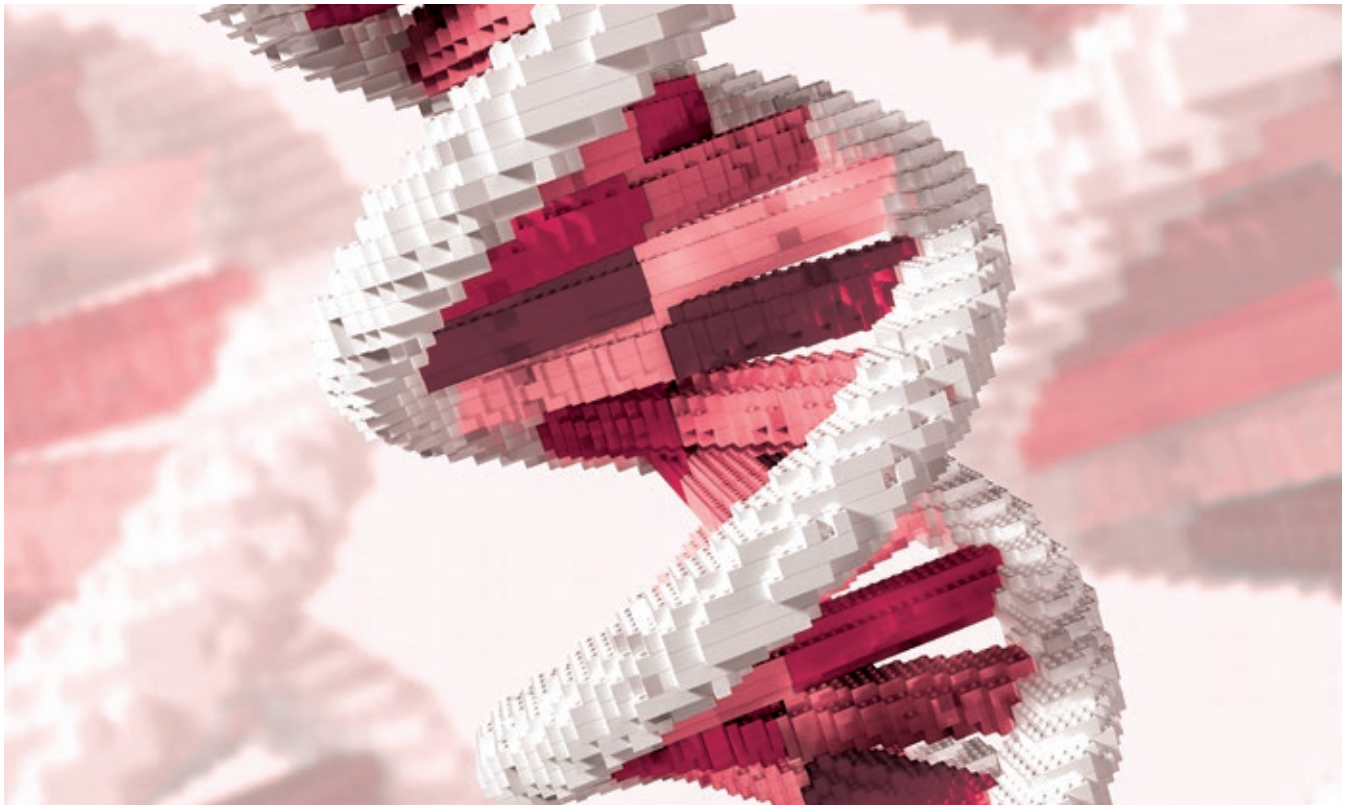
The data load generated by NGS is well-known as a bottleneck, requiring time and expert knowledge to extract meaningful results. This is particularly true within the clinical genetics workflow, where turnaround times are a major priority. As a highly efficient alternative to whole genome sequencing, targeted sequencing is well suited to the clinical laboratory. By capturing specific genomic regions of interest from DNA samples prior to sequencing, only the regions of interest are analyzed. Focusing in on relevant areas of the genome, targeted sequencing panels significantly reduce the sequencing and data load, in turn reducing both time and cost.

"The data load generated by NGS is well-known as a bottleneck, requiring time and expert knowledge to extract meaningful results."

Importantly, this approach also enables an increased depth of coverage, providing the sensitivity needed for heterogeneous samples and overcoming many of the challenges typically faced in NGS. Cancer-specific gene panels and enrichment methods are becoming increasingly popular, and a number of laboratories and commercial companies have recently developed and validated these for clinical use (see "Which Capture Method for Targeted NGS?").

At a Glance

- *Molecular tumor profiling of clinically actionable mutations using NGS guides the delivery of anti-cancer therapies*
- *Fast, efficient and cost-effective, targeted NGS is becoming increasingly embedded into the clinical laboratory*
- *Certain factors are vital for accurate clinical data, such as quality control, FFPE sample compatibility and an optimized target capture assay*
- *Targeted panels are emerging and evolving in response to the latest genetic discoveries*



Designing NGS panels

When choosing content for a new panel, the current focus of molecular pathology labs is on delivering results that can be translated into meaningful clinical action. However, this can be complex. The content of any panel is a balancing act between trying to maximize the utility of the panel with expected sample numbers and desired throughput. In general, for a diagnostic panel the focus is often very narrow, maximizing cost-efficiency and sample throughput, while limiting the amount of surplus sequencing data that, as yet, has no recognized clinically actionable relevance. Without any known effect on treatment, variants of unknown significance (VOUS) therefore tend not to be covered. The breadth of content can range from mutational hotspots through to full exons, and for each laboratory this will depend on the target genes and the clinical literature. For example, *KRAS* and *BRAF* carry mutational hotspots with well-characterized effects on drug response, and can therefore be specifically targeted. For other mutations, such as those in *KIT* and *PDGFRA* genes, which have implications for the etiology of gastrointestinal stromal tumors, diagnostic labs need to look for mutations spread over specific exons. Sometimes known as 'hot exons' exhibiting high levels of actionable mutations throughout the entire exon, these can provide a wealth of information.

Another point to consider is that investigations evolve with new discoveries, and when mutations within certain genes, such as the tumor suppressor *TP53*, become more clinically actionable, it will then become important to look for variants spread over the whole gene. However, there is a lag between discoveries in research and their clinical application. Interpreting novel variants provides a significant challenge, and requires bringing together *in silico* analysis, literature review, current drug trials and other approaches, and the panel must then be re-evaluated following the addition of any new content. Additional content must therefore be carefully considered, and provide very strong evidence for a tangible difference in patient treatment. Moving forward, one model would be to review the content after set time periods and add additional content, if required, in batches. Moreover, a particularly interesting way that targeted NGS technology has adapted in response to this challenge is with the emergence of custom panels, which enable the user to select a chosen pool of relevant hybridization probes. The flexibility of such systems facilitates researchers in investigating variants


(Source: Oxford Gene Technology, Oxfordshire UK)

With its capacity to analyze multiple genes, NGS is beginning to replace traditional single gene techniques such as Sanger sequencing, pyrosequencing and qRT-PCR.

"...a certain level of consideration is necessary in order to accommodate the particular needs of the clinical laboratory..."

relevant to their specific study, increasing the speed at which new content can be validated and decreasing the time lag from the laboratory to the clinic.

Compatibility with FFPE tumor samples

Solid tumor samples present two primary challenges. Firstly, because of tumor heterogeneity and the presence of DNA derived from non-tumor cells, a variant of interest may only occur at a relatively low allele frequency in the sample. Since detecting these is facilitated through deep sequencing, researchers are particularly interested in NGS platforms that allow considerable depth (i.e. targeted panels). In addition, the use of DNA extracted from formalin-fixed, paraffin-embedded (FFPE) tissue can present many technical challenges, impacting on both DNA integrity and yield. Due to the fixative process, the DNA can be degraded and clinical scientists often have to work with very small amounts of DNA. Because of this, a number of quality control metrics are analyzed, including the accurate measurement of low level DNA. Targeted capture methods are also carefully considered to ensure the uniform representation of all regions of interest.

Quality control for clinical application

Quality control procedures are vital to ensure accurate NGS data. All new tests undergo extensive validation initially with well characterized samples, including a variety of positive, no-mutation and no-template controls, while the laboratory based work and the bioinformatics pipelines themselves are also validated in order to estimate the sensitivity, specificity, reproducibility and repeatability of the tests. Following the initial validation, positive and negative controls are included in each assay, with the sequencing quality, coverage, depth and mutant allele frequency all

determined and data analyzed and validated by two scientists.

The test report summarizes the interpreted results clearly, and is once again checked and authorized by a second experienced scientist. Not only do the discovered variants need to be reported, but the report must also be able to verify that the reason a variant was not detected in a region of interest was because it was generally not there or below the reported sensitivity of the test, and not because of lack of sequencing depth. In addition, the challenge of tumor heterogeneity is also considered. If the test's detection sensitivity has not reached the level required to detect low allele frequencies, then this needs to be fed back to the clinician so additional testing can be performed if desired. Consideration of the latest research discoveries is also important, and published literature and known databases (such as COSMIC) are frequently used in interpretation and reporting.

The future of NGS in molecular pathology

The fundamental premise of personalized cancer therapy is to ensure the right treatment for the right person at the right time, and with the area of genomic medicine growing at an unprecedented rate, it is becoming clear that targeted NGS is playing a vital role in this. Indeed, this technology is becoming increasingly embedded within the clinical laboratory, with new panels emerging and evolving in response to the latest genetic discoveries. These panels provide the capability to detect low-level mutations from the ever increasing catalog of clinically actionable aberrations and markers for directing cancer therapy, and in fact, many of these genetic markers are already in use today. However, it is also clear that a certain level of consideration is necessary in order to accommodate the particular needs of the clinical laboratory, including the requirement for accuracy and sensitivity. Along with existing and emerging testing strategies, NGS has an extremely important role to play in future cancer characterization and treatment.

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Which Capture Method for Targeted NGS?

The type of capture method is of utmost importance for targeted NGS, and the two main approaches fall into either the hybridization or amplicon-based categories — each with its own set of advantages and drawbacks.

Amplicon

Pros

Utilizing PCR, amplicon strategies tend to be quick and easily integrated into existing laboratory workflows.

Cons

Data quality tends to be less robust when compared with a hybridization based approach, as it is very hard to determine and remove bias introduced by PCR (e.g. polymerase errors, formation of secondary structures and preferential amplification of some fragments due to differences in GC content).

Hybridization

Pros

With the ability to easily capture larger target regions, this is the method of choice for larger panels.

Cons

Traditionally, more DNA input was required, and the library preparation tends to be longer when compared with PCR-based methods. The technology has been improving, however, and advanced hybridization-based technologies, such as the SureSeq Solid Tumor Panel (Oxford Gene Technology), use extensive research validation of lower input DNA, and focus on making the whole process more streamlined.

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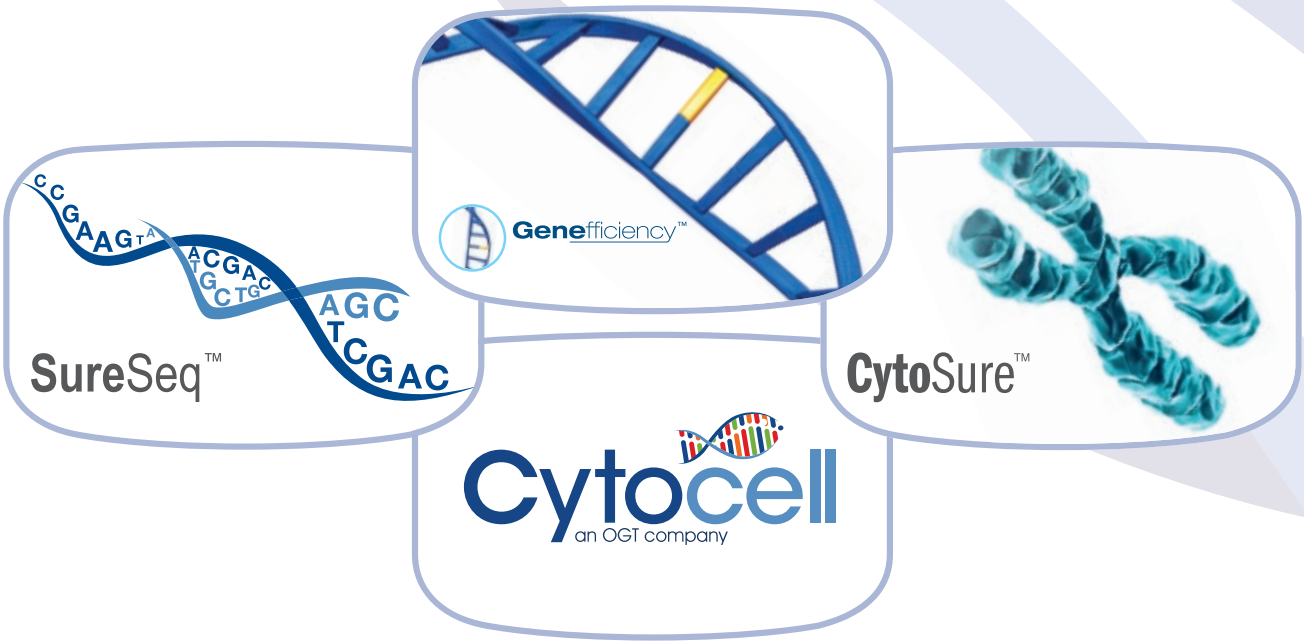

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NeuroComplexity a Diagnostic Dilemma?

Diagnosing neurodegenerative diseases like Alzheimer's can be a hit and miss process – but is a lab-based test on the horizon?

By Roisin McGuigan

Diagnosing age-related neurodegenerative disorders (NDs) is a challenge. In the clinic, the diagnosis of Alzheimer's disease (AD), Parkinson's disease (PD) and other age-related dementias relies on a mixture of clinical assessment of cognitive symptoms, brain imaging, and the measurement of proxy biomarkers. But these methods are far from ideal – the only way to obtain a definitive diagnosis of AD, for example, is by pathological examination of brain tissue after death – and it goes without saying that this has little direct application to patient diagnosis and management.

At a Glance

- *Current tests for neurodegenerative disease aren't perfect, and can lead to misdiagnosis – it is estimated that up to 20 percent of Alzheimer's diagnoses could be incorrect*
- *The race is on to develop an alternative to clinical assessment – including blood-, breath-, skin- and spinal fluid-based tests*
- *Here, we hone in on four research teams hoping to be one of the first to develop an accessible and sensitive diagnostic technique*
- *Any that succeed would have a huge impact on both clinical trial recruitment and patient management, but there is still some way to go before this becomes a reality*

The overlap of symptoms between the various forms of ND can also result in misdiagnosis – especially during the early stages of disease, or in younger sufferers, leading to inappropriate treatment and unnecessary medication (1). With an aging population and a growing number of affected patients, a more objective, lab-based method for diagnosis is becoming a more urgent research goal; so it's no surprise that research groups around the world are working on innovative new approaches for diagnosing – and differentiating – NDs. We take a look at four potential approaches, and speak to some of the researchers working to solve this pressing problem.

A breath of fresh air?

A research team from the Israel Institute of Technology appear to have found a way to identify patients with PD using only their breath – by measuring exhaled organic compounds, they were able to distinguish between patients with idiopathic PD, those with non-idiopathic PD, and healthy controls.

"The patient breathes through a device which collects the compounds in their breath," explains co-author of the associated paper (2), Hossam Haick, "these are then exposed to a nanoarray composed of sensors, combined with pattern recognition algorithms, which can be trained to recognize disease-specific breath signatures," (Figure 1).

Haick believes the test represents an improvement over current methods; "Physician evaluation is linked to high misdiagnosis rates, and expensive and risky imaging techniques will only be helpful in a limited number of specific cases. Our approach is noninvasive, inexpensive, fast and doesn't require an expert to operate, making it suitable for large scale screening of high risk populations."

Haik and lead author of the study, Morad Nakhleh, say they hope their test could be used clinically in the future – but with an accuracy of 84 percent, they plan to increase the sensitivity first. "The test will not replace pathological examination" adds Haick, "as it provides the only direct proof of disease. But we plan to validate our breath test technology and determine its potential in stratifying patients into disease subtypes."

Eventually, the group hope to study people with genetic susceptibility to PD, with the aim of early detection, before clinical symptoms appear. "This would allow us to administer preventative treatments such as neuroprotective agents, once such therapies become available," says Haick.

Cerebral clues in the skin

Meanwhile, researchers from San Luis Potosi, Mexico believe that skin could contain revealing clues about neurocognitive health, including conditions such as AD and PD. "Until now, pathological confirmation was not possible without a brain biopsy, so these diseases often go unrecognized," says study author Ildefonso Rodriguez-Leyva.

The researchers hypothesized that since skin and brain tissue have the same embryonic origins, they might also display the same abnormal proteins found in some NDs. In a small study population of 20 patients with AD, 16 patients with PD, 17 patients with dementia caused by other conditions, and 12 healthy controls, they obtained and tested very small skin samples from behind the ear, to see if they could identify altered proteins indicating AD or PD (3). They observed that in patients with PD or AD, levels of tau protein were seven times higher when compared with healthy patients and those with dementia from other, non-degenerative causes. Patients with PD also had eight times higher levels of α-synuclein protein than the healthy controls – a promising find not only for diagnosing dementia, but for identifying the underlying disease.

"More research is needed to confirm these results," admits Rodriguez-Leyva,

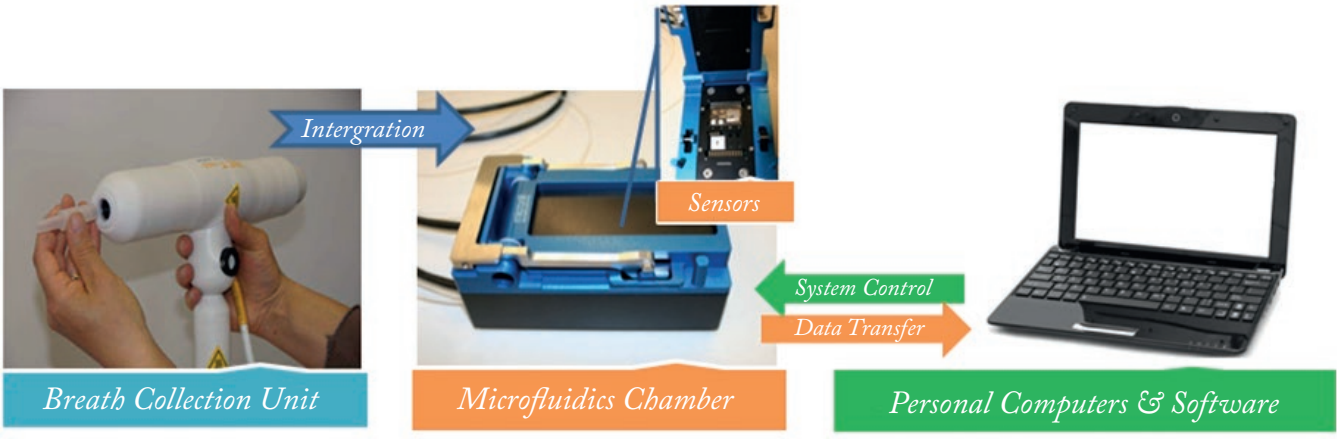

Figure 1. The envisioned breath testing system that is currently being developed. Patients breathe into the collection unit, and volatile organic compounds in their breath are detected, and analyzed to detect "breath signatures" that predict disease.

"but the findings are exciting because we could potentially begin to use skin biopsies from living patients to study and learn more about these diseases. If our findings are shown to be consistent, we could have an innovative, accessible way to support clinical diagnosis using skin biopsy. Because even in the best neurological centers, diagnosis can be erratic, and only defined by the progression of disease symptoms, or using expensive biomarkers that aren't always accessible."

In the future, Rodriguez-Leyva and his team hope to culture live tissue to enable better understanding of the mechanisms involved in the disease, and to work on the development of an autologous vaccine against protein deposits.

Cerebrospinal fluid findings

An approach that could be deemed controversial by some, owing to its invasive nature, is nonetheless showing some promise and that is in the testing of cerebrospinal fluid for the biochemical diagnosis of AD (4). The method is based on the premise that misfolded amyloid-β (Aβ) peptide oligomers accumulating in the brain, causing cellular dysfunction and damage to tissue, play an important role in the pathogenesis of AD. These oligomers have been found to circulate in biological fluids, but only in very small quantities that were difficult to detect – until now.

Researchers from the University of Texas, USA, and the University of Milan, Italy, have developed a sensitive assay for detecting very small amounts of Aβ oligomers, by creating a method for cyclic amplification of the misfolding process *in vitro*. They then tested the cerebrospinal fluid of 50 patients with AD, 39 controls and 37 patients with non-AD NDs, and achieved an impressive 100 percent sensitivity when distinguishing patients with AD from patients with non-AD ND, and high levels of sensitivity and specificity for distinguishing the different sets of patients (Figure 2).

However, even if spinal fluid testing has a high level of accuracy, lumbar puncture is a highly invasive and inconvenient test, which carries a risk of nerve damage – but the authors hypothesize that Aβ oligomers may be circulating in other fluids, and in the future, they may be able to detect the biomarker using a more routine blood test.

All in a drop of blood

Finally, there's a team that believes they could have found a way to introduce a simple blood test into AD testing. The creation of compounds that can bind to amyloid in the brain and then be detected via PET scan has been credited as a key breakthrough for AD research, and trials of anti-amyloid agents that could potentially halt disease progression are now underway. But screening for potential clinical trial participants using PET will unavoidably expose patients who are amyloid-negative and cognitively normal, to harmful radiation, especially in larger study populations. Could there be a safer alternative?

A research team from the University of California, Los Angeles (UCLA), USA, in collaboration with the International Alzheimer's Disease Neuroimaging Initiative, may have found a solution – a multimodal approach for predicting brain amyloidosis using cognitive assessment, brain imaging, and a simple blood test.

"For AD, the gold standard is always a pathology diagnosis – what is going on in the tissue, what abnormalities are we finding under the microscope? But it's not easy to access the brain and take biopsies in a living subject," says lead researcher Liana Apostolova. "So we need to look for other metrics to help us make a diagnosis. There is no perfect biomarker for Alzheimer's, so over the last five years or so, increasing

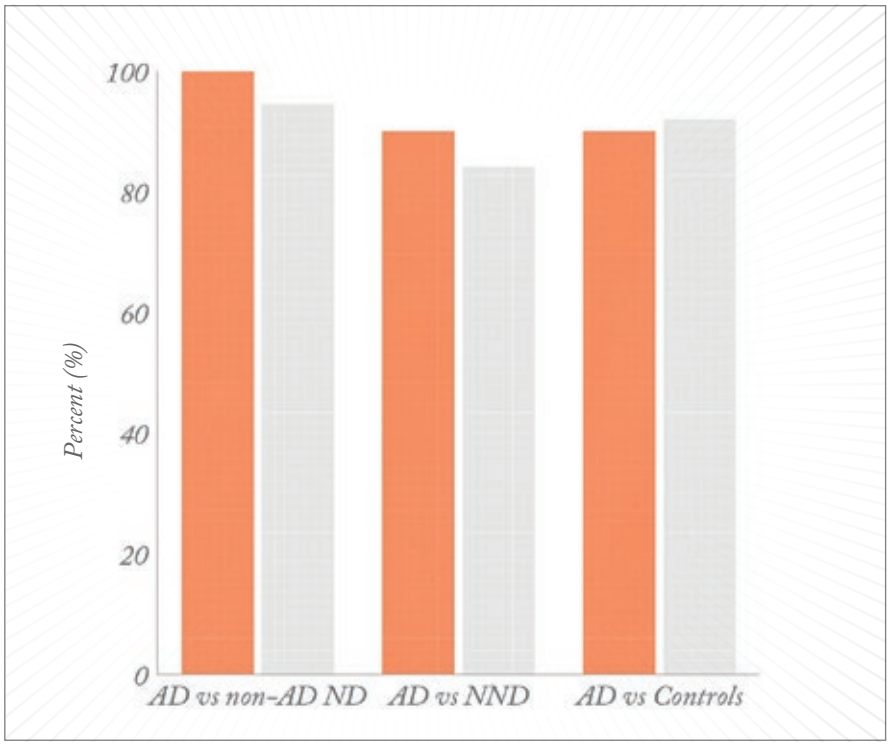

Figure 2. Sensitivity (orange) and specificity (grey) of the cerebrospinal fluid test for Aβ oligomers when identifying patients with AD versus patients with non-AD neurodegenerative disorders (ND), patients with AD versus patients with non-neurodegenerative neurological diseases (NND), and patients with AD versus controls (4).

attention has been devoted to studying several biomarkers at a time, rather than just a single one," she adds.

Apostolova and her team combined a series of measurements, including memory tests and structural MRI (information that is routinely obtained during clinical work-up for suspect AD cases), along with several blood proteins known to be associated with AD, and achieved a test sensitivity of 68 percent, and a specificity of 78 percent (5).

"People think AD is confined to the brain, but it leaves a signature in the periphery," says Apostolova, "many blood proteins change during the disease process – this means in even the most rural settings, with no PET scan available, you can get a blood draw and predict brain amyloidosis and therefore AD."

If there is wide uptake of the test, it won't only have implications for diagnosis and management of AD, adds Apostolova. "Since amyloid PET imaging has been developed, we've found that around 20 percent of patients clinically diagnosed with AD do not have amyloid deposits in their brains. So not only have they been misdiagnosed and unnecessarily treated, they may also have been entered into clinical trials when they are not suitable candidates. And increasingly, we are looking at the early and presymptomatic stages of the disease, and in these cohorts amyloid-negative individuals may make up as much as 50 percent of your study population – that's a 50/50 chance that they aren't suitable!" she emphasizes.

The creators of the test envision it as playing an important role in clinical trial design – potential participants could be pre-screened using the blood test to predict which individuals are amyloid-positive, which could significantly decrease the risk of exposing amyloid-negative patients to PET radiation. The next step? "We are continuing to look for even more powerful predictors in the blood," confirms Apostolova.

Future unknown

It is clear that a reliable, noninvasive lab test for diagnosing complex neurodegenerative diseases could be a boon for both clinicians and researchers, allowing for better diagnosis and management for patients, and in future, identifying patients in the presymptomatic and early stages of disease. It could also help researchers target appropriate candidates for their studies, and identify which patients may benefit from inclusion in clinical trials – which could, in turn, have a great impact on the development and validation of effective therapies. But with so many innovative approaches currently in the works, it remains to be seen which will make it into clinical practice.

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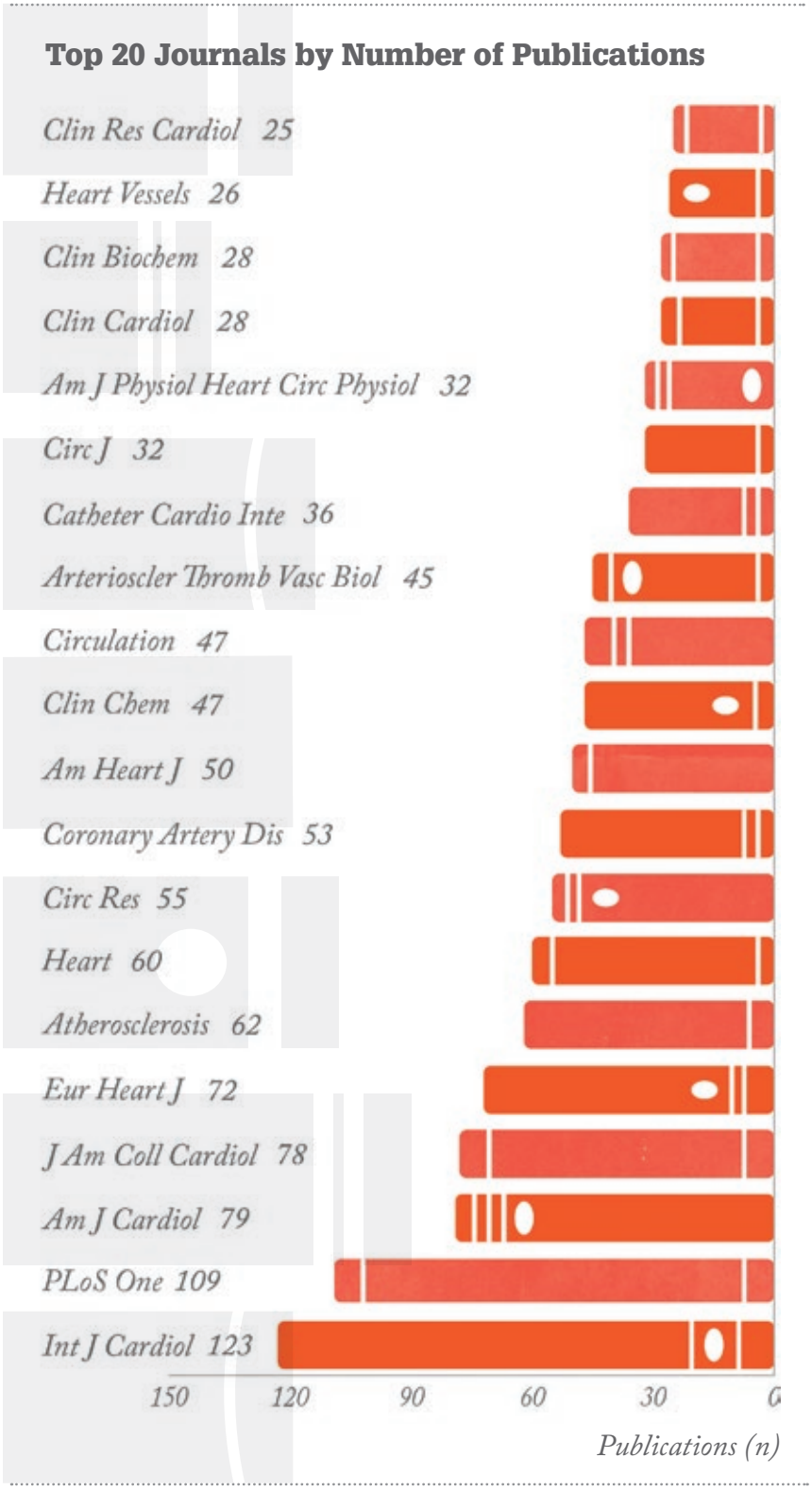
Benchmarking Biomarkers of Myocardial Infarction

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

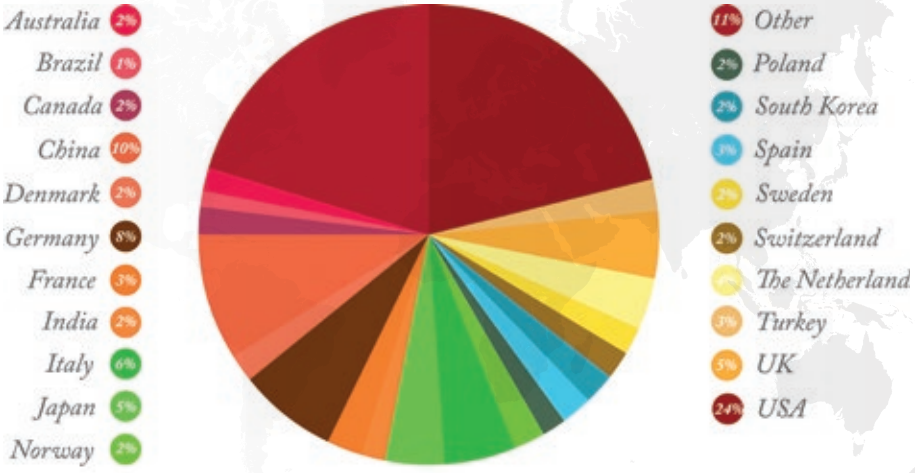
By Roisin McGuigan

Cardiac biomarkers make up a diverse range of markers used in the diagnosis and risk assessment of patients with suspected acute coronary syndromes, including myocardial infarction (MI). According to the World Health Organization, in settings without resource constraints, observing pathological changes in cardiac serum biomarkers is an essential diagnostic criteria in cases of MI (1). Cardiac troponins are currently a widely used marker of choice, due to their high sensitivity in indicating damage to the myocardium.However, new and potential biomarkers are constantly being investigated, in the quest to accurately diagnose heart problems and identify those at risk – B-type natriuretic peptide and C-reactive protein are two examples of markers currently under investigation for future use in assessing cardiac pathologies.To provide insight into the past and predictions for the future of the field, a series of metrics were applied to the last five years of the published literature.

PubMed was searched for "myocardial infarction" and "biomarkers" with results limited to the last five years. The data were analyzed in Microsoft Excel 2013.

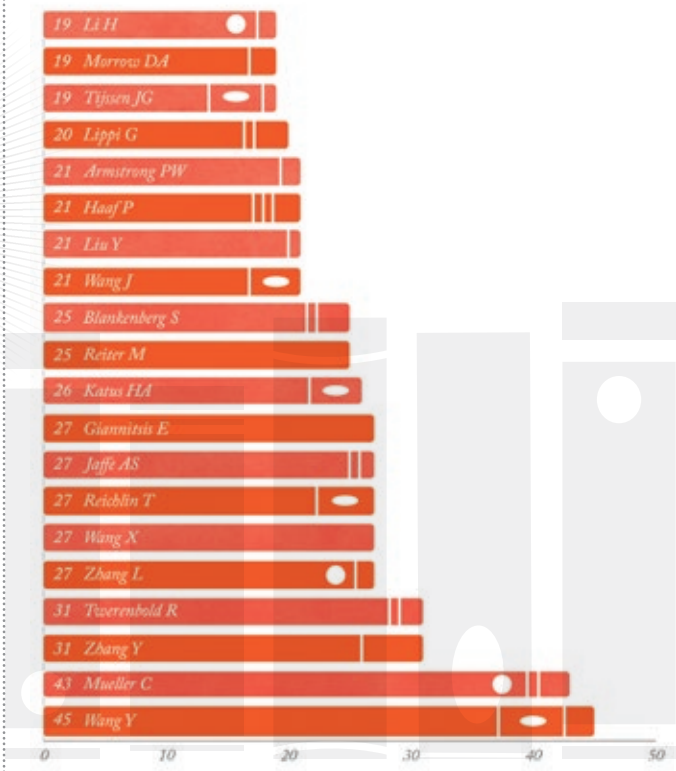


Publications by Country



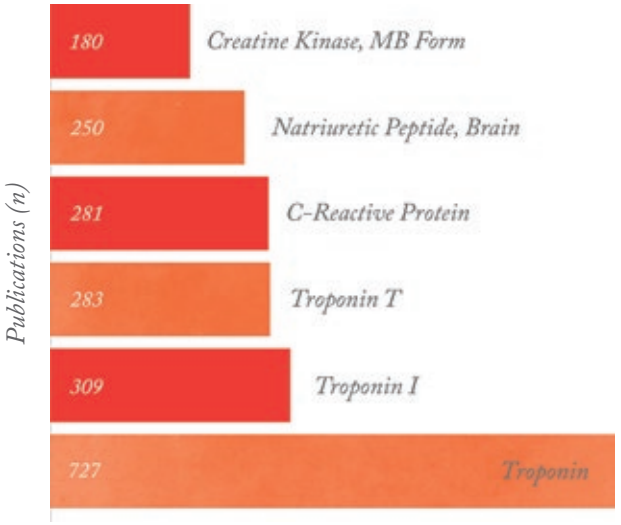
Fee or Free

Top 20 Authors

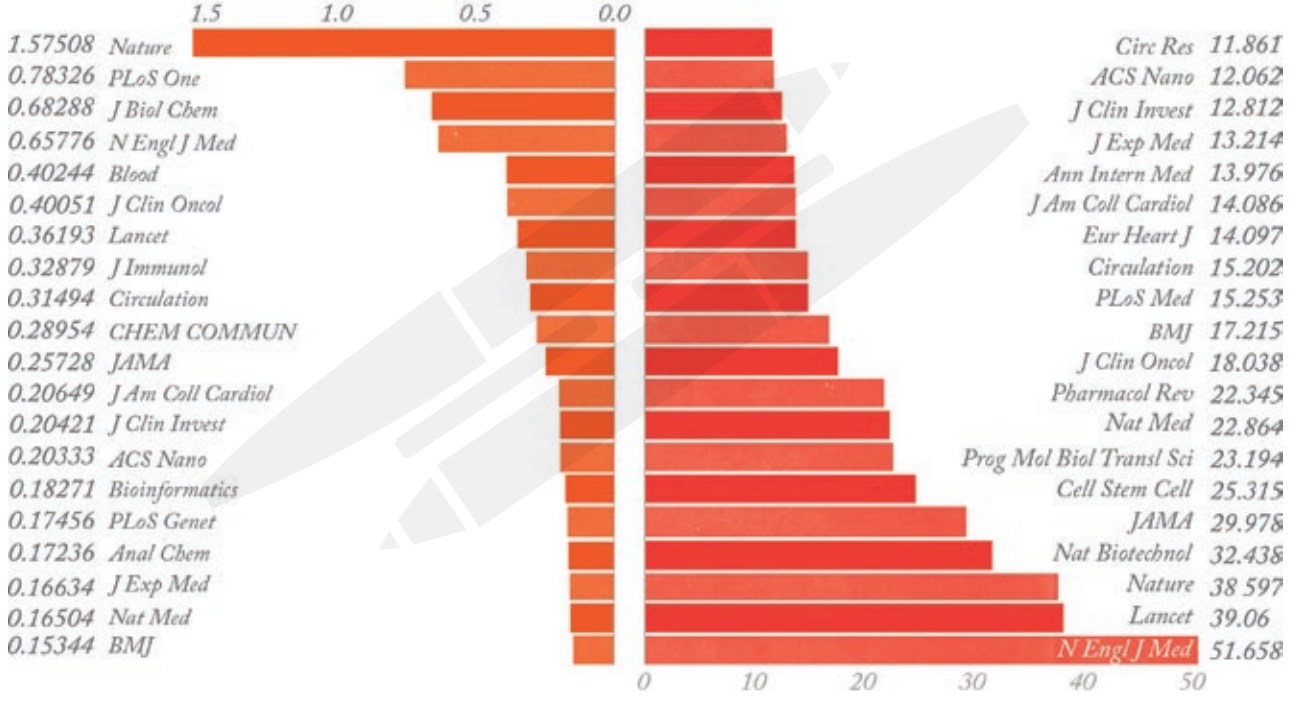


Publications per Year

Most Researched Biomarkers



Articles in MEDLINE are indexed by Medical Subject Headings (MeSH) topics, that describe the articles' main topics. Here are the top 6 most frequently mentioned biomarkers over the last five years of the myocardial infarction biomarker literature.



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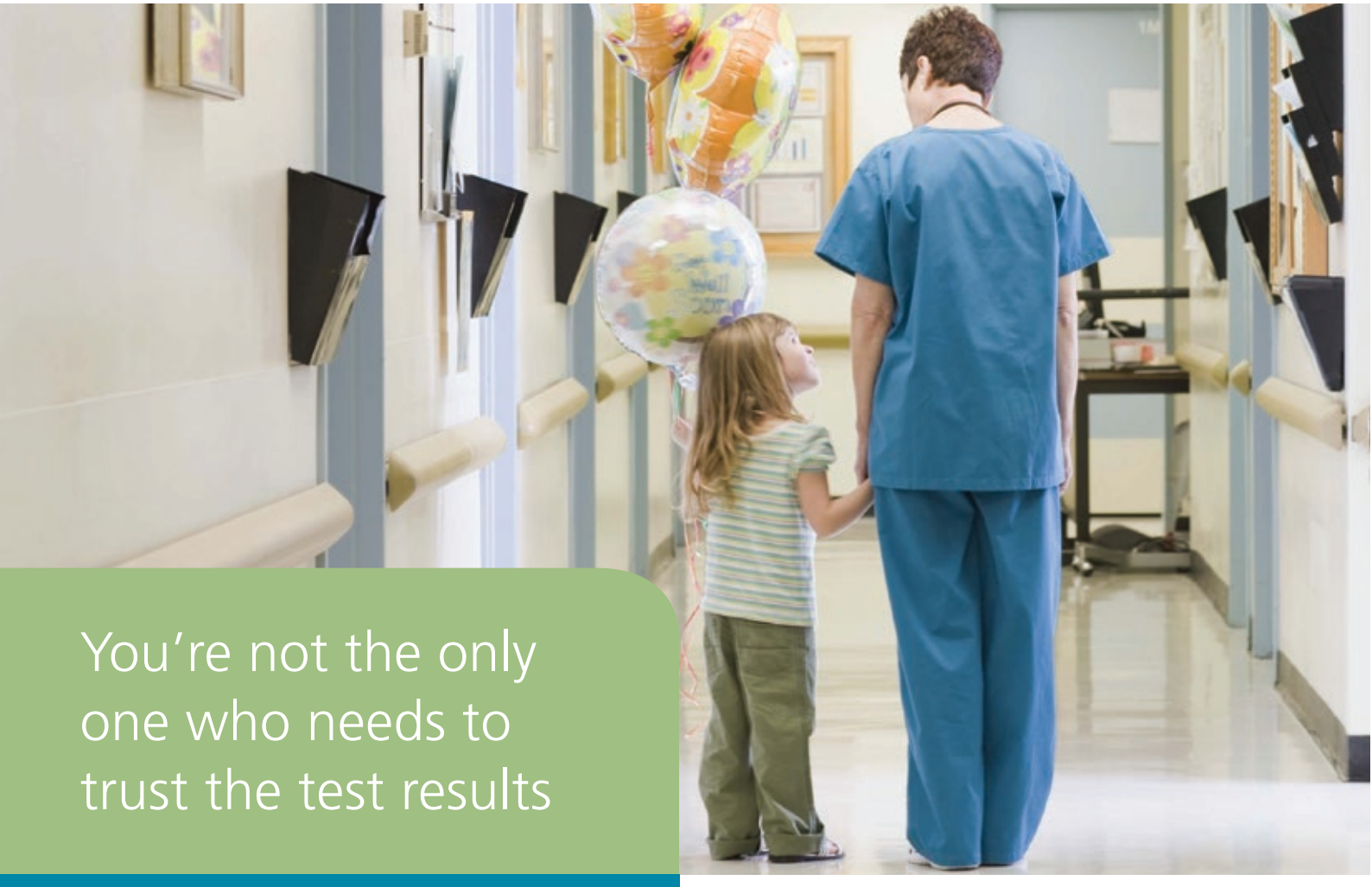

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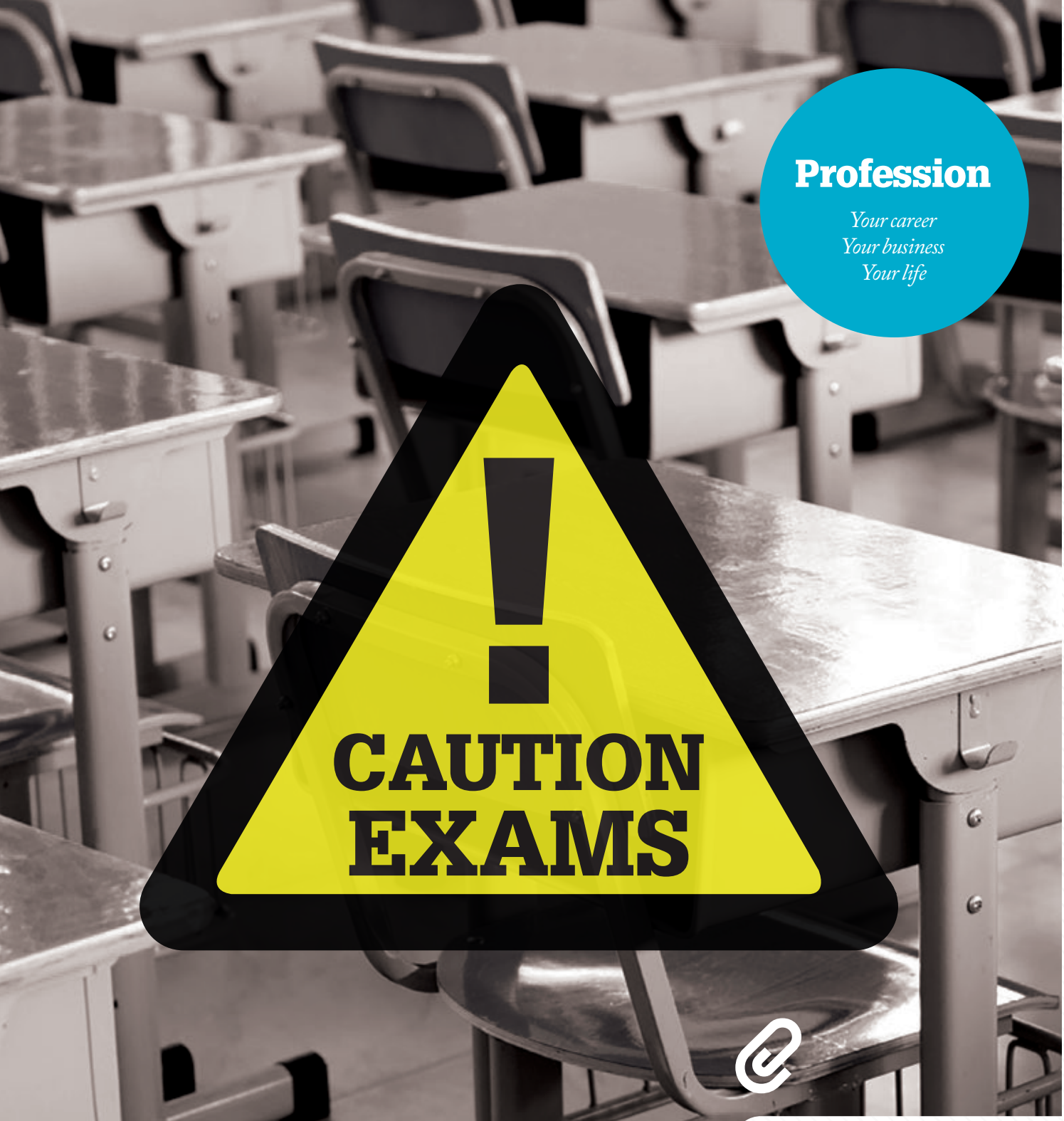

46–49
Examining the Entrance to Elysium
Some young pathologists in the UK view the FRCPath Part 2 exam as a hurdle that's just too difficult to overcome. But are their concerns justified?

Examining the Entrance to Elysium

The UK's FRCPath Part 2 examination is viewed as a problematic stumbling block by many young pathologists waiting to start their careers – but why, and is change needed?

By Michael Schubert

In order to enter the Greek underworld, the souls of the dead must first pass through its gates, which are guarded by the multi-headed hellhound Cerberus. The discipline of pathology in the United Kingdom is much the same – only in this case, Cerberus takes the form of the Fellowship Examination of the Royal College of Pathologists (FRCPath) Part 2.

Many young pathologists would agree that the hound, with his serpent's tail, mane of snakes and lion's claws, is an appropriate representation of the FRCPath Part 2. The exam consists of surgical pathology, diagnostic cytology and autopsy in various formats over the course of two days (1). It's designed to test the limits of your ability – the Royal College of Pathologists (RCPath) states that "the overall aim of the examination for medical trainees is to provide external quality assurance that a trainee is on course to […] practice as an unsupervised specialist in the specialty." But some feel that the exam isn't a fair test of trainees' abilities, and others are concerned that it may be adding to a shortage of pathologists that is already impacting patient care (2). One senior pathologist says, "The numbers that are coming through are not high enough. There have also recently been problems with the exam; they were getting 20-odd percent pass rates, which was making a big backlog of trainees that weren't coming through the other side." In fact, RCPath is aware of the issues, acknowledging in a statement that "in December 2013, a survey was commissioned by the Histopathology College Specialty Training Committee (CSTC) following concerns about the declining pass rate in the FRCPath Part 2 examination in histopathology. Over 400 College members replied to the survey, including over 100 trainees."

Unfortunately, both trainee and consultant pathologists continue to express concerns about the test – its structure, its contents and its administration. One trainee, Christine Evans, spoke for many, saying, "I can't hope to figure out how many hours we've all spent complaining, crying and stressing over this exam. The worst part is realizing that it does not test us as pathologists. It tests whether we can pass an exam; whether we know the tactics for passing." They described the effect the test and its poor pass rates – historically as low as about one-fifth of test-takers in some cases – have, not only on the pool of new consultants, but on the expectations of the trainees themselves. "It means absolute heartbreak," Evans says. "Realizing that one could function perfectly well as a practicing pathologist, but the exam is not representative of real life, where you don't sign out in a vacuum. In real life, you talk to colleagues, clinicians; you don't rush things. With the exam, we're expected to come to a definitive diagnosis in most cases. And in 10 minutes. Based on one representative slide."

Investigating infrastructure

One major problem these young pathologists have is with the testing infrastructure itself. Trainees face not only the costs of sitting the examination, but also the expense of travel and accommodation on short notice when they learn to which testing site they will be assigned. A trainee from outside the UK points out that "for those who have to travel from outside the country, this is inconvenient, at best, and prohibitively expensive at worst." According to RCPath, the intent is to provide candidates with at least six weeks' notice of examination dates and venues, but they include the caveat that this is not always practical. "Where an examination is offered across multiple centers, a number of logistical factors need to be taken into consideration to avoid conflicts of interest between candidates and examiners." Because there are limitations on where candidates are permitted to sit their exams, and on where the exams can be held – for instance, in smaller specialties where exams can't be organized until there are enough candidates, or in larger ones where candidate numbers must be finalized in advance in order to find a large enough venue – it may not always be possible to provide candidates with six weeks' notice of their exam location.

It's not just the travel expenses that frustrate candidates, though; tales of unfortunate testing circumstances

At a Glance

- *In the UK, pathologists at all stages of their careers have observed a backlog of talented trainees making it into practice*
- *Many have cited difficulty in passing the FRCPath Part 2 examination as the primary cause*
- *Trainees have identified problems with the structure, content and marking of the examination, or with the conditions under which the test is taken*
- *Though RCPath has taken in feedback from their examinees and seen an increase in pass rates, for many issues, no clear way forward has yet been agreed*

abound. Many trainees have complained about the quality of the microscopes provided at exam sittings, or about the difficulty of bringing their own, especially if traveling from overseas to some of the more remote locations within the UK. One trainee reports, "There was one autopsy exam that started an hour late because they lost some of the exam cases and were still setting up the furniture." Another had a horror story of "the time when it was in a hotel, next to a busy room in which there was – I kid you not – some kind of bell-ringing demonstration. While the door kept opening and closing." Situations like these haven't escaped the attention of the College though. "Whilst every effort is made to ensure the suitability of external examination venues," they explained, "we realize that there are occasionally events which occur on the day which create less than ideal examination conditions for the candidates and are out of the control of the examination organizers." This may be of little help to candidates sitting those examinations, but at least they can be reassured that, if enough of them make RCPath aware of the issue, they can avoid future problems with those testing locations. "Depending on the level of concern raised by this," the College says, "it may be that that venue will not be used as a center again." If pathology trainees are truly concerned by the conditions under which they sit the FRCPath Part 2 exam, it seems that the best course of action is to present a united front when raising those concerns with the College – the more candidates speak out, the better their voices can be heard.

Geographic discrepancies?

There are also differences in the ways various countries train their pathologists, which can have a knock-on effect on those candidates' chances of success in the FRCPath Part 2. Jemima Renner, a pathologist from Ireland, reports, "There are significant differences in training between the UK and Ireland, and I believe a lot of this has to do with the difficulty of the exam. UK trainees are encouraged to sit the exam after four years, while Irish trainees are sitting it after five years or more." She further comments, "UK training seems almost entirely exam-focused. They perform some limited service-work, but the consultants perform most of the day-to-day work, following up cases and going to multidisciplinary meetings. I was very taken aback to learn that you can successfully complete your training without ever attending a multidisciplinary meeting." This raises the concern that simply passing the exam does not, in and of itself, prepare trainees for the reality of working as a consultant. Renner says, "Irish training is almost entirely service-focused. Irish trainees are essential to the day-to-day running of a lab. In most labs they perform all cut-up, all postmortems, have all cases screened with a provisional report composed before consultant review, and follow up all additional investigations to completion. They prepare and present multidisciplinary meetings. Unfortunately this is at the expense of exam preparation. No exam courses are provided. Centers routinely refuse study leave in order to prioritize service provision. So an Irish trainee struggles to learn the exam techniques needed to pass the FRCPath, even if they are competent and confident with the lab's daily workload. Make no mistake, passing the FRCPath involves exam techniques that cannot be learned during routine reporting. The exam should only represent one aspect of becoming a well-rounded, competent consultant. I think the difficulties in passing have skewed training priorities, particularly in the UK."This sentiment is not unique to trainees from Ireland; Evans says, "A friend of mine who continued her training in the US said that she's relieved she never had to sit the FRCPath." When asked whether American training is easier, she replied, "Easier is maybe not the word, but fairer, perhaps."

"A friend of mine who continued her training in the US said that she's relieved she never had to sit the FRCPath."

Questioning content

Many trainees see problems with the way the FRCPath Part 2 exam is structured – but that doesn't mean that the content is flawless. Cytology was a popular target for complaints; Evans observes that "the cases in recent years have been incredibly difficult and cytology is not practiced by all pathology consultants. The emphasis on passing cytology seems disproportionate, especially when the case number is so small. I don't think that's a fair test of anyone's cytology skills." Another trainee disagrees with the choice of cases, commenting, "They say that it's not supposed to be esoteric stuff and yet an examiner once commented that he hadn't seen an example of a particular case for over twenty years." Though cytology received the bulk of the attention, one pathologist raised concerns about the autopsy component of the test, and about students' preparation for that section. "In Ireland you cannot practice as a consultant histopathologist without the autopsy part," Roberta Downey says. "In the UK it is not necessary now because of the shortage of pathologists in general,

and the thinking that a lot of pathologists dislike autopsy. There is a huge emphasis on the surgical and cytology components of the exam as it is. I believe the autopsy component is often overlooked. Because it is now an option, the exam is becoming more difficult to pass as only people who 'like' autopsy will sit it in the UK. We all have to sit it in Ireland, and training needs to be provided with this in mind."

"The survey found that there was support, although not universal, for a degree of modularization of the exam."

There's some doubt as to whether this criticism is fair, though. In response to these and other statements, RCPath states that "the selection of the cases to be used in the Part 2 examination is the responsibility of a panel of experienced examiners, including specialist and general diagnostic pathologists. Cases are not accepted unless there is consensus that they provide an appropriate basis on which to determine whether or not a candidate is able to demonstrate a safe approach to diagnosis and management." Additionally, there was extensive discussion of a potential modularization scheme that would allow candidates to sit, or to pass, different sections of the test at different times. Referring to the survey commissioned by the Histopathology CSTC, the College says, "The survey found that there was support, although not universal, for a degree of modularization of the exam. In particular, many respondents wanted histopathology and cytopathology to be separated for examination purposes. A number of options were discussed including complete separation of diagnostic cytology from histopathology with independent examinations. However, it was felt that this would be inappropriate and that competence should be demonstrated in histopathology and cytology contemporaneously." The suggestion that a pass in one section could be carried forward to the next sitting was raised, but will require consideration of many factors (including part-time trainees, overseas candidates, and administrative and logistical arrangements) before any plans for this kind of modularization can be made – especially as, in order to ensure parity between examinations, the College must then consider modularizing all 19 of the specialties in which the FRCPath tests are offered.

Mastering marking

"I would suggest," says Downey, "that modularization is a step forward, but the marking system needs to be overhauled to facilitate a real improvement." This sentiment was met with great accord by trainees and consultant pathologists alike. Though the original intent of the closed marking system was to allow marks ranging from 1.0 to 4.0 for a single surgical short case (3), Renner doesn't feel that this truly applies. "In practice," she says, "the examiners decide whether they feel a case is 'easy' or not. If they think the case is simple, they move the maximum mark obtainable to 2.5, a bare pass, or 3.0. However, if you get the answer wrong, the lowest possible minimum mark remains at 1.0. Essentially, a closed marking system within a closed marking system has been introduced, which is obviously unfair and ridiculous. Why have these cases at all unless they are all subject to the same marking system?" Her words are strong, but supported by others – one trainee, for instance, says, "I understand, intellectually, the reason for closed marking; it's critical to get pathology diagnoses right out in the real world – but there is something deeply demoralizing when you realize that merely getting a correct diagnosis will give you a bare pass and, in some cases, it is impossible to get more than 2.5 out of 5." Renner adds yet another concern in that candidates aren't informed of which cases are capped at a maximum mark of 2.5, so they are unable to allocate their testing time accordingly.

It's important to note, though, that RCPath doesn't make a monolithic decision as to how each case will be marked – rather, the panel responsible for selecting the cases prospectively decides the model answers and marking schemes. Two examiners mark each paper independently against the agreed marking scheme, and the papers are then independently moderated by a third and possibly even fourth examiner if there's a significant discrepancy between the original two marks, or in the case of a borderline fail. Where candidates are very close to a pass, the College assures them that every effort is made to scrutinize the marks to ensure that the correct result is given. Though the FRCPath Part 2 has suffered from historically low pass rates (3), things in that respect may be looking up – the pass rate for the most recent set of exams was 68.6 percent.

In examinations set by RCPath, candidates are not provided with detailed information about their results. Nor are they permitted to make appeals that challenge the academic judgement of the examiners, an unpopular policy but one in line with those of other royal medical colleges. (More information on RCPath's complaints (4) and appeals (5) procedures can be found online.) But the complaint and appeal systems, too, are a source of unhappiness for

trainees anticipating the exam, with one commenting, "Even secondary school exams have the right to appeal. The lack of transparency is just one of many worrying things about the setup." Candidates worried about the impact of this policy on borderline marks – one, having failed the surgical section by a single mark, was unsatisfied with the lack of information provided to explain the result. "If you fail, you're told which components you've failed – which is only a recent development. You get a comment on whether it was a narrow fail or a big fail. And now, through your trainer, you can get a breakdown of your marks. But it's numbers, not helpful comments. The advice I was given in my generic failure letters: needs more experience in x, where x is dermatopathology or cytology or something along those lines." Clearly, pathologists who take the test are concerned about the level of transparency provided by the College – and perhaps, with more detailed information about exam results both good and bad, trainees might sit fewer times and be more satisfied with the procedure as a whole. "They say that repeating the exam makes for better pathologists," says Evans, "but I disagree. It's made me angrier, sadder and poorer, but I don't think it has made me better."

Facing the future

It's clear that pathologists – both those who have found their way to Elysium and those who have yet to cross the river and gain entrance – have strong feelings about the FRCPath Part 2 examination and would like to see it change in the future. Their ideas are fairly solid, too. Many would like to see the exam modularized, the cases more reflective of everyday lab work, and the marking system reformed. They'd like to have better opportunities to appeal unfair results. And they'd like to be able to get a firmer grip on the test procedure itself – where they'll be going to sit their exam and what they can expect to find on their arrival. At the moment, though, progress isn't without its stumbling blocks. RCPath has discussed the outcomes of the Histopathology CSTC survey at length, but has stated that "any changes to an examination system of this nature must be approved by the General Medical Council, who have specific time frames for these submissions. At present, no clear way forward has been agreed, and until we are confident that a fair, feasible and workable solution can be submitted for consideration, the examination will continue in its current format."

Hopefully, the changes will come soon enough for today's pathology trainees, whose frustrations are beginning to build. "If someone told me tomorrow that I could give up pathology and medicine and still be financially secure," says one young pathologist, "I'd do it without a second thought."

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** Please note that those interviewed wish to remain anonymous, hence their names have been changed for the purpose of this article.*

Inspiring the Next Generation

Sitting Down With… Michael Prystowsky, Professor and University Chairman of Pathology at Montefiore Medical Center and Albert Einstein College of Medicine, New York, USA.

Why pathology?

Both of my parents were physicians in community practice. Their strong commitment to helping people, ability to do good, and patients' respect and appreciation made medicine an appealing career. Three of my four brothers are physicians!

My studies provided research and teaching opportunities – I enjoyed both. While I tried to believe that there were more than 24 hours in a day, the only way to satisfy my needs in a career, including my intense research interests, desire to help people through clinical medicine, longstanding interest in teaching, and any hope of spending quality time with my family, was to become a pathologist. It suited me perfectly.

I graduated from medical school in 1981 and started my pathology residency at the University of Chicago.

And the rest is history?

Not quite. My career path that led me to Montefiore was quite unconventional. I had the opportunity during my residency in Chicago to start a clinical flow cytometry service, which I continued in my first faculty appointment at the University of Pennsylvania. There I worked tirelessly to build a grant-funded research program and publish papers, and I became tenured, at the expense of board certification.

In 1993, I accepted the role of vice chair of pathology for the newly unified pathology department between Albert Einstein College of Medicine and Montefiore Medical Center and, in a quirk of fate, I became interim chair two years later. I could not be considered for the permanent chair unless I was board certified. Because I had a good relationship with the faculty, they supported me to become the permanent chair, which I did in 1997. I've been leading the unified department of pathology since then.

Can you explain the service line model at Montefiore?

We support all programs and work with all levels of administration – hospital to president – taking active responsibility for delivering optimal service. The pathologists and laboratory directors run the service line, not just individual laboratories. It's a true partnership with the hospital. By managing all pathology services we can be responsive to the medical center's clinical and programmatic needs. It took years to build that trust within the whole medical system, but we've done it.

From when I started at Montefiore, it's grown from a system of two hospitals to eight hospitals plus more than 150 ambulatory care sites in the Bronx and Westchester County, New York.

You head up one of the busiest pathology services in the US and serve as a board member for the College of American Pathologists (CAP) and councilor for the Association of Pathology Chairs (APC); how do you do it?

Effective delegation is of course important. But in each of my roles, education is a key focus area for me. Delivering the right kind of training to residents is absolutely essential to the delivery of an excellent pathology service and to the future of our field. And we have many ways of doing this.

At Montefiore, we use Clinical Looking Glass, a program developed by Eran Bellin at Montefiore to enable longitudinal analysis of patient cohorts. Beyond looking at reams of patient data, temporal analysis of patient populations enables the development of effective and efficient care models for specific diseases. We're teaching our residents to use Looking Glass to ask the right questions: "Why is a particular test being done?", "Is it helpful in managing patients?", and so on. In so doing, our pathologists are actively supporting the delivery of effective healthcare and test utilization. Under-utilization actually costs the healthcare system more money than over-utilization. We need to manage the care of patients efficiently and effectively. If we look at diabetes, for example, a simple test to make sure someone's in control of their glucose will minimize the risk of future complications, poor health, and higher costs.

That's been the Montefiore system – looking to care for patients in a way that manages care and keeps people healthy – I think it's going to keep our patients healthier and save us a lot of money.

How can pathologists demonstrate their value?

Programs that train effective communication will help pathologists get the message out. But every healthcare provider needs to know what pathologists do and they need to recognize our value – with changing curricula in medical schools, pathologists are losing teaching hours. This is something we're looking to address by using our contact time with students more effectively.

Common themes, such as test utilization, communication, and CME are all key educational focuses for both the APC and the CAP. Training pathologists to partner with physicians; communicating effectively and succinctly patient data (including an understanding of all new and emerging fields such as genomics and informatics); and supporting effective test utilization and patient management – these are all crucial educational initiatives. All of these services demonstrate our value.

Would you change anything?

I have no regrets looking back; this career has been absolutely terrific and it's allowed me to do everything that I have wanted to do. My most important achievement is in the nurturing of people to develop their careers. The preservation of any discipline depends on the next generation – we are simply guides to help them see and develop the means to manage their reality.

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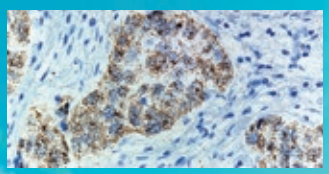

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