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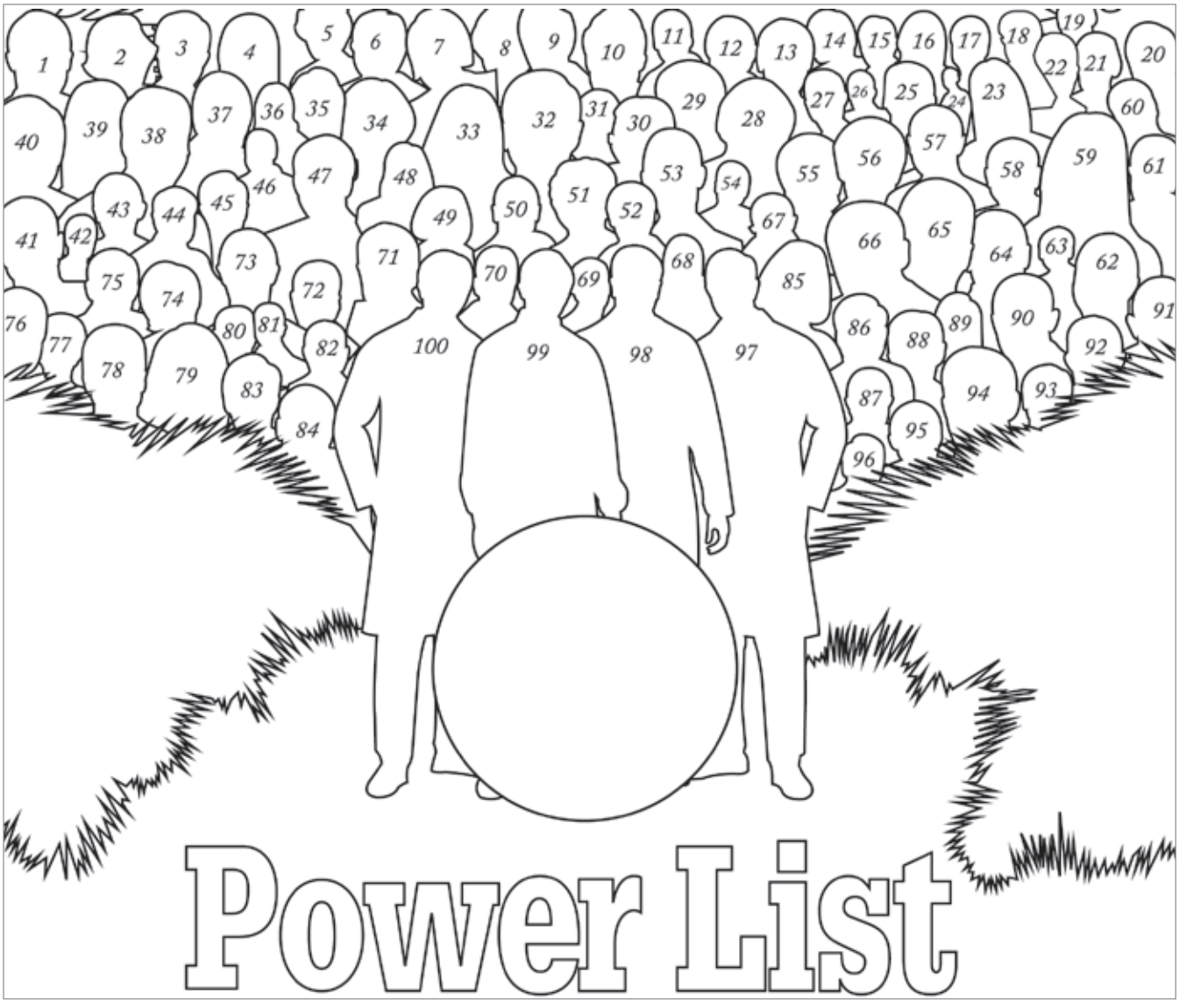

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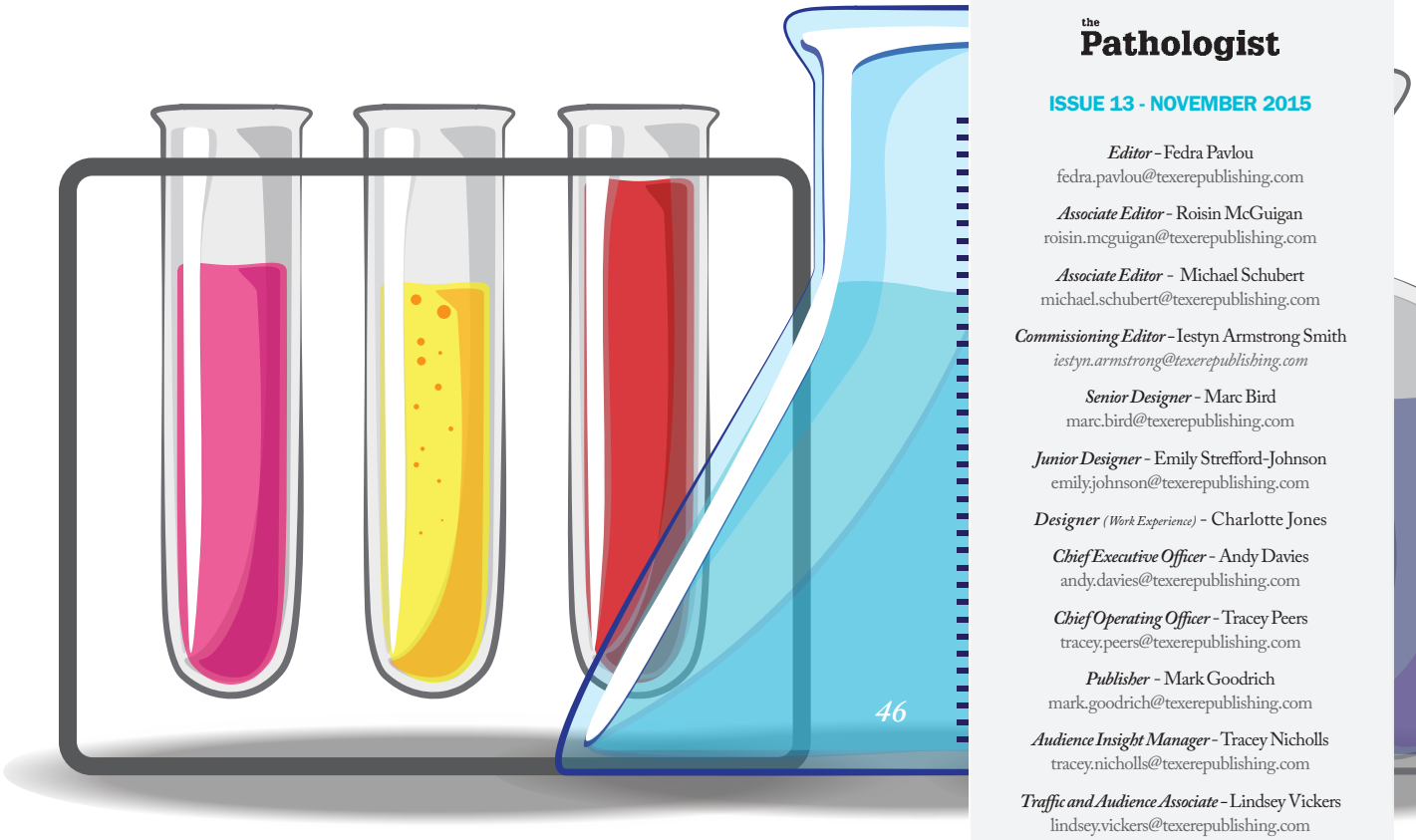

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The Power of the List

The long-awaited Power List is unveiled. Now let's shout about it!

The nominations have been counted, the judges have deliberated, and now it's time to share The Pathologist's inaugural Top 100 Power List. First, a word of thanks – to quote a track from Sgt. Pepper's Lonely Hearts Club Band, The Power List could only be put together "with a little help from my friends" – you, our readers.

For a profession that is often viewed as unpretentious and shy of the spotlight, you may wonder why we thought the Power List was a remotely good idea. There were two main reasons: first, to celebrate the exceptional achievements of those who have really had an impact on the field; and second, to highlight the truly groundbreaking work of laboratory medicine and its intrinsic role in patient care and the molecular revolution. In a nutshell, we wanted to give the profession the boost in publicity it so desperately needs and absolutely deserves.

How did we go about it? We began by asking you to cast nomination(s) for those who you consider to be deserving of recognition for their valuable contribution to laboratory medicine – both the trailblazers and the unsung heroes. We collated the nominations and recruited an independent judging panel of eminent laboratory professionals, spanning numerous specialties and geographies, to select their top 100 and rank the 20 that were particularly deserving of attention. We compiled all of the judge's results to create our final top 100 Power List.

Admittedly, we weren't sure how you would respond to our nomination request. Of course, not everybody got involved – but many of you did, providing heartfelt and inspiring reasons for your choices. And though we would never claim that our list is definitive, it does echo our objective for each and every issue of The Pathologist – to be the voice of our readers. You may be surprised that someone influential is missing from the list – that is, until you recall that you didn't nominate him or her either... Why not get involved next time to ensure that your lab champion's contribution to our vital field of medicine is recognized?

What particularly struck me during the process was the high number of US-based nominees, which resulted in Americans accounting for almost 50 percent of the 2015 Power List. I found myself wondering if the results were reflective of reality; is the US the true center of innovation and evolution in the field of pathology? Or is it more reflective of a greater willingness to embrace our bold and celebratory endeavor? I would value your thoughts.

Regardless of the geographic split, I feel sure you will agree that everyone who made it onto the final list is deserving of praise. And so, without further ado, we invite you to explore and enjoy the 2015 Power List (see page 19).

Fedra Pavlou
Editor

Upfront

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

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

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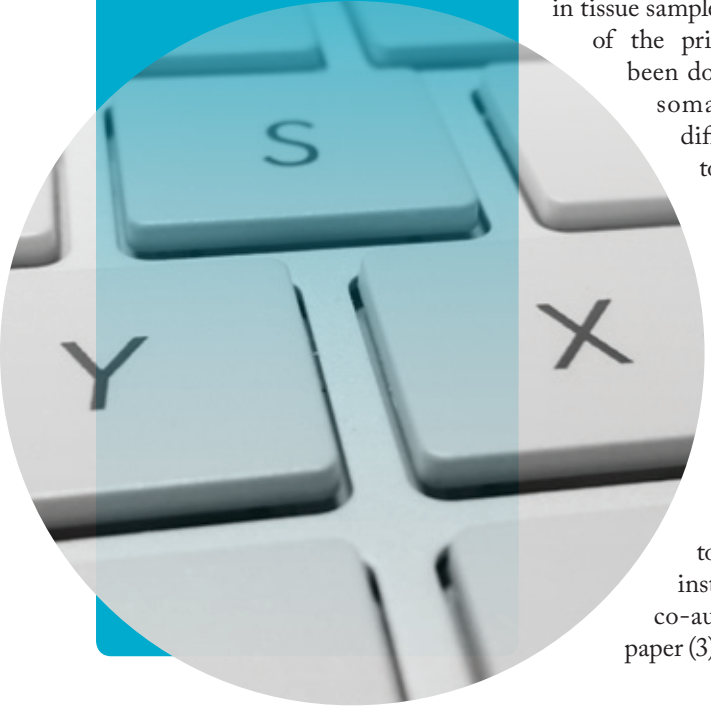

Origin Unknown? Not For Long...

A computer algorithm could help shed light on the origins of metastatic cancers

Although most cancer patients present with a primary tumor, up to 15 percent first come to the oncologist's attention with metastatic disease without a clear origin (1). Pathological study of cancers of unknown primary site (CUP) is challenging, and in roughly two to five percent of cases, no primary site is found (2) – resulting in a lengthy diagnostic process, and potentially delaying treatment. But what if a computer program could help identify the source?

Uniting genetics and computer science, an international team of researchers have created a potential solution – a program, known as TumorTracer, which analyzes DNA mutations and mutation patterns in tissue samples to identify the location of the primary tumor. "We had been doing research comparing somatic mutations across different types of cancer, to determine which ones might respond to specific chemotherapies. And various groups had published pan-cancer analyses of the somatic mutations found in various cancers. One day, it occurred to us that we could turn the problem sideways – using somatic mutations to identify the cancer type instead," says Aron Eklund, co-author of the associated paper (3).

The team analyzed three aspects of somatic mutations – point mutations in cancer driver genes, copy number variations, and base substitution frequencies – and discovered that all three contributed independently to cancer identification, explains Eklund. They used this information to build and validate their algorithm. The initial results show promise: the algorithm classified some initial tumors with known primary sites with 85 percent accuracy. Analysis currently takes around 48 hours, but as sequencing becomes faster, this could be reduced.

The next steps will be to extend the range of cancers the algorithm can identify, and further optimize it. "One obvious application is to help diagnose metastatic tumors whose primary site hasn't been identified. We don't yet know whether or not our method will be more accurate than existing methods based on histopathology, various scans and examinations, gene expression signatures, and so on. But we imagine that it won't be long before every tumor biopsy gets sequenced to identify targetable mutations — and then applying TumorTracer would require only negligible incremental time and cost. So even if TumorTracer is only marginally useful in aiding diagnosis, we think it could find widespread use," says Eklund. *RM*

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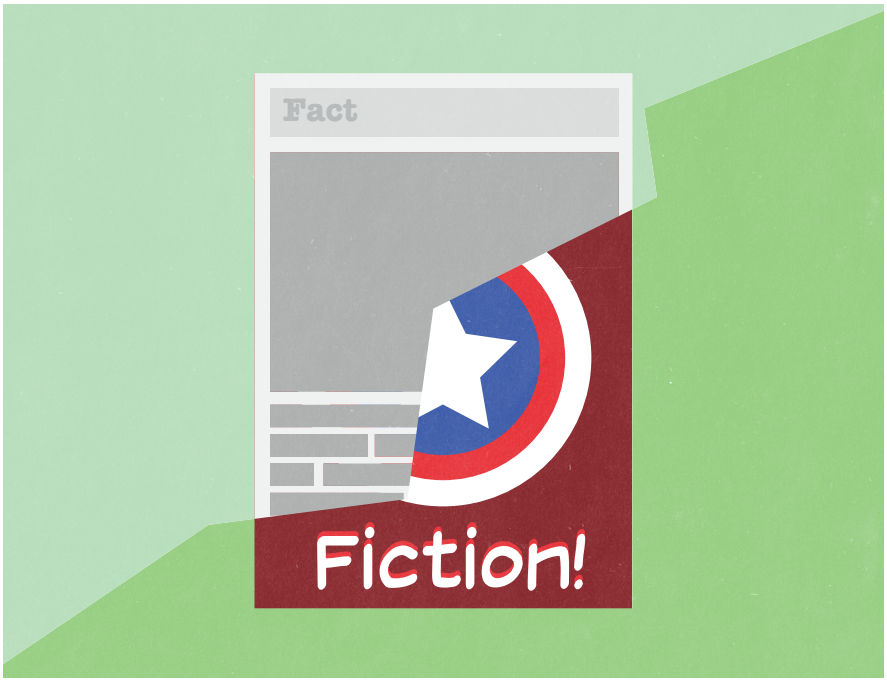
Theranos: Science Fact or Science Fiction?

The secretive diagnostic startup has been making headlines – but not always for the right reasons…



There's been a lot of buzz around the enigmatic health startup Theranos. The company's disruptive diagnostic technology is designed with the aim of completely changing the way patients access sampling and testing, with plans to create a system whereby one fingerprick can be cheaply used for dozens of tests. And, as we've reported previously (1), the company has been cleared by the FDA to market its herpes simplex test in the US, and received a waiver which means the test can be used outside of traditional lab settings. Despite the fact that the company is still to release any details of their testing equipment, or to publish any peer-reviewed data (2), Theranos has garnered a huge amount of attention.

But a scathing article recently published in the Wall Street Journal (WSJ) (3), has levelled several accusations against the company, claiming its revolutionary testing methods are inaccurate, and its success overhyped. A recent FDA inspection of Theranos also made the news when the resulting report contained mentions of the company's "nanotainer" tube technology being listed incorrectly (4), with the report stating, "You are currently shipping this uncleared medical device in interstate commerce, between California, Arizona, and Pennsylvania."

An official statement released by the company (5) addressed and refuted all of the claims made by the WSJ – but without producing any data or other details on the accuracy of their testing systems. The statement also criticized the reporter responsible for the story, claiming that, "From his very first interactions with Theranos, the reporter made abundantly clear that he considered Theranos to be a target to be taken down, and not simply the subject of an objective news story."

Since releasing the statement, the company has announced its intentions to release data comparing its technology to reference testing methods, although when and where this will happen remains unclear (6). CEO Elizabeth Holmes, hailed by some as a diagnostic wunderkind (7), has also hit back at critics, saying "This is what happens when you work to change things. First they think you're crazy, and then they fight you, and then all of a sudden you change the world" (8).

So is Theranos set to transform diagnostics, or have the tales of its technology been greatly exaggerated? The debate rages on. *RM*

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Virtually Detecting Early Alzheimer's

It could be possible to predict Alzheimer's risk using virtual reality navigational testing, decades before symptoms develop

Figure 1. The virtual arena used to perform the object-location memory task.

With no cure available, a better understanding of the early pathological mechanisms in Alzheimer's disease (AD) could be a huge step forward in the quest to treat the disease effectively, and to detect it earlier. Although many recent studies focus on biochemical tests, or neuroimaging techniques, some new research explores a very different angle – identifying those at increased genetic risk of AD by analyzing the way they navigate a virtual landscape.

What inspired such an interesting approach? According to co-author of the associated paper (1), Nikolai Axmacher, the focus is on grid cells, found in the entorhinal cortex. In 2014, a team won the Nobel Prize in Physiology or Medicine, partly for demonstrating that grid cells are a crucial constituent of the brain's positioning system, allowing for navigation (2). Earlier research also showed that functional magnetic resonance imaging (fMRI) could indirectly measure the function of the grid cell system (3). Finally, spatial disorientation is one of the first symptoms of AD, and altered activation of the medial temporal lobe has been found in previous fMRI studies of AD genetic risk carriers.

Nikolai and his team set out to discover if they could detect entorhinal dysfunction in subjects under 30 years old, who are APOE-ε4 carriers (and therefore at a higher genetic risk of developing AD), using fMRI and an object-location memory task which involved navigating in a virtual environment (see Figure 1). "We found that genetic risk carriers had strongly reduced 'grid-cell-like representations' (GCLRs) on fMRI – they were not impaired in spatial memory, but we found that participants with impaired GCLR activated their hippocampus (an adjacent brain region) to a larger degree. This had a direct behavioral consequence: genetic risk carriers navigated more often at the boundary (rather than in the center) of the virtual arena. Even though increased levels of hippocampal activation may be used to compensate for behavioral deficits, in the long-run they may facilitate the development of Alzheimer's disease," says Nikolai.

Although the impaired grid cell function was expected by the researchers, the altered navigational preference was completely unanticipated – now, the team aims to further investigate the link between GCLR and early neuropathology. They also plan to test if GCLRs are impaired and navigational preference is altered, in older participants at a high genetic risk for AD, and in patients with early-stage disease. "It will be important to find out if fMRI and navigational behavior can be used as an early biomarker of Alzheimer's disease. In the future, this may allow for a very early treatment of high-risk individuals," adds Nikolai. *RM*

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On the Scent of a Parkinson's Test

A UK woman who noticed a change in her husband's smell, years before his diagnosis of Parkinson's disease, could hold the key to a noninvasive and accurate test

Accurately diagnosing Parkinson's disease (PD), especially early-stage or presymptomatic disease, isn't easy. No validated diagnostic test exists, and instead, clinicians must rely mainly on physical symptoms and neurological examination. But recently, a small study demonstrated the skills of a woman who diagnosed PD with 92 percent accuracy, without observing any of the study subjects. How? Surprisingly, she simply followed her nose…

Joy Milne, from Perth, UK, first noticed a difference in smell six years before her husband was diagnosed with PD at age 45. "His smell changed and it seemed difficult to describe. It wasn't all of a sudden. It was very subtle – a musky smell," she says (1).

After joining a UK charity and meeting more people with PD, Joy linked the scent she was detecting to the disease, and

mentioned this to Tilo Kunath, a Parkinson's UK senior research fellow. "I was giving a public outreach seminar on my stem cell work during Parkinson's Awareness Week," says Kunath, "and during question time, Joy Milne asked me if people with Parkinson's smell different. It was completely unrelated to what I just spoke about, and I didn't take the question seriously. Later, a colleague convinced me I should find her and test her. I didn't know her name at the time, but I eventually tracked her down."

Kunath and his colleagues decided to see if Joy really could sniff out Parkinson's. She was given the t-shirts of 14 subjects (eight with PD, and six controls) to test, and she identified the shirts belonging to PD patients with 92 percent accuracy – an incredibly accurate result, says Kunath. A key finding was also the source of the scent, adds Kunath. Originally, the researchers suspected that the odor was found in sweat, but the smell Joy was identifying was found on the collars of the shirts – indicating the metabolites she is detecting are likely coming from the sebaceous glands.

About eight months after the study, the researchers got the biggest surprise of all: "The one mistake Joy made was to identify a control volunteer as having the 'PD odor'. However, this individual went on to be diagnosed with PD," recalls Kunath, "so her accuracy was even better than we thought!"

But what does this mean for diagnostics? The charity Parkinson's UK is now funding studies in Manchester, Edinburgh and London to further investigate the source of the smell Joy is detecting, with the hope of developing a simple, non-invasive test for early PD detection. "Preliminary gas phase and liquid phase chromatography mass spectrometry were used to analyze a small number of samples. But, the sample size is too small to conclude anything. The grant recently awarded by Parkinson's UK will allow collection and analysis of 100 PD samples and 100 control samples for a statistically significant analysis, in order to identify the metabolic signature of the odor," says Kunath. *RM*

Reference

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Avoid Mass Spec-ulation: Use References

The introduction of a global reference method for measuring beta-amyloid biomarkers in cerebrospinal fluid could harmonize Alzheimer's diagnostic results

Analysis of beta-amyloid in the cerebrospinal fluid (CSF) is an increasingly common method for early diagnosis of Alzheimer's disease (AD), and is seeing use in both clinical and research settings. But just how accurate are these tests? A reference method for harmonizing beta-amyloid measurement, developed by the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) Scientific Division Working Group on CSF proteins, has now been formally classified as the international standard, in order to address current issues with diagnostic testing.

Although several assays exist for measuring beta-amyloid in CSF, problems like matrix effects, different testing platforms, and a lack of defined standards, means these tests may not be directly comparable – affecting general cutoff measurements, and hampering interlaboratory comparisons of tests. The IFCC working group set out to solve the problem by developing a validated reference measurement procedure to reduce the variability in AD biomarker results.

"The primary use of this test will not be in general laboratories. It will be used in specialized laboratories to measure the absolute concentration of beta-amyloid 1-42 in certified reference materials that will be used by commercial kit producers to calibrate their assays," says Henrik Zetterberg, a member of the working group, and co-author of the associated paper (1). "The main benefit is that the method is not dependent on antibodies – it is a mass spec-based assay in which the CSF sample is denatured, liberating all beta-amyloid 1-42 and

making it accessible to measurement. The denaturing step prior to analysis makes us certain that no beta-amyloid 1-42 escapes our detection," he adds.

The reference materials based on the method will be made available to the producers of AD testing kits at a not-for-profit cost, via the Institute of Reference Materials and Measurements in Belgium. *RM*

Reference

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Urgent Call for New Diagnostics

UK report demands serious changes to diagnostic development to slow the pace of antimicrobial resistance

A report commissioned by the UK government, the Review on AMR (antimicrobial resistance), has called for fundamental change in order to curb the misuse of antibiotics, and the development of antibiotic resistance. So what's their solution? To put it simply, better diagnostics. "To avoid the tragedy of 10 million people dying every year by 2050, the world needs rapid diagnostics to improve our use of antibiotics. They are essential to get patients the right treatment, cut down on the huge amount of unnecessary use, and make our drugs last for longer," says AMR Chairman, Lord Jim O'Neill.

The Review's authors have pointed the finger at healthcare companies as being part of the problem, saying that, "Many drug companies, meanwhile, including those producing affordable generic antibiotics, have no commercial interest in the advent of rapid diagnostics, which would act to limit the number of antibiotics prescribed." This has stifled development and resulted in a dearth of diagnostic innovation, they conclude. The proposed solution is to ensure better incentives for test developers, in order to stimulate the market (1).

But what might these new diagnostics look like? The review contains both a breakdown on what information a test might contain (see Figure 1) and a preliminary diagnostic "wish list" suggested by a group of healthcare professionals (see Figure 2).

The next steps for the ARM Review team will be to take a look at issues other than human misuse of antibiotics that are contributing to the problem – such as agricultural consumption of antibiotics, antibiotic alternatives, and ways to limit and prevent the spread of infection, before intervention becomes necessary. *RM*

Reference

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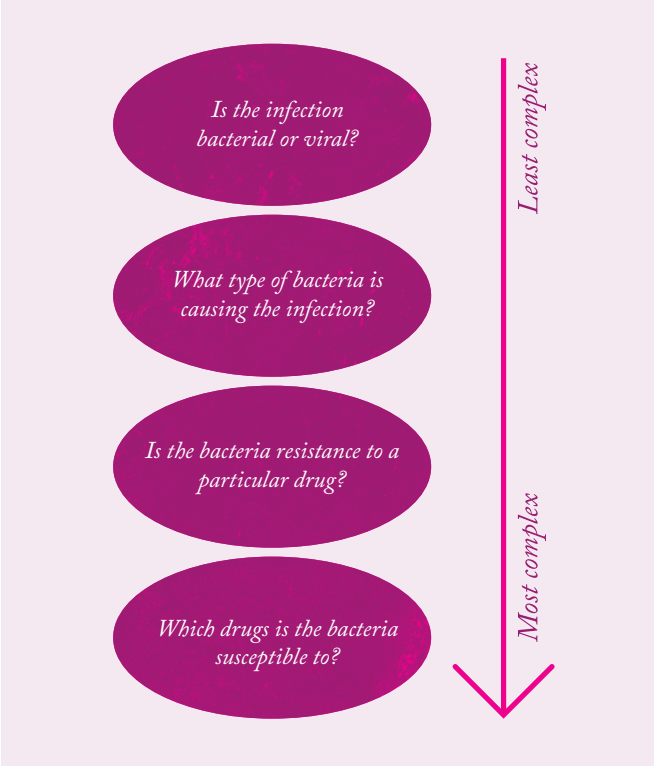

Figure 1. The different types of results a new bacterial diagnostic could provide.

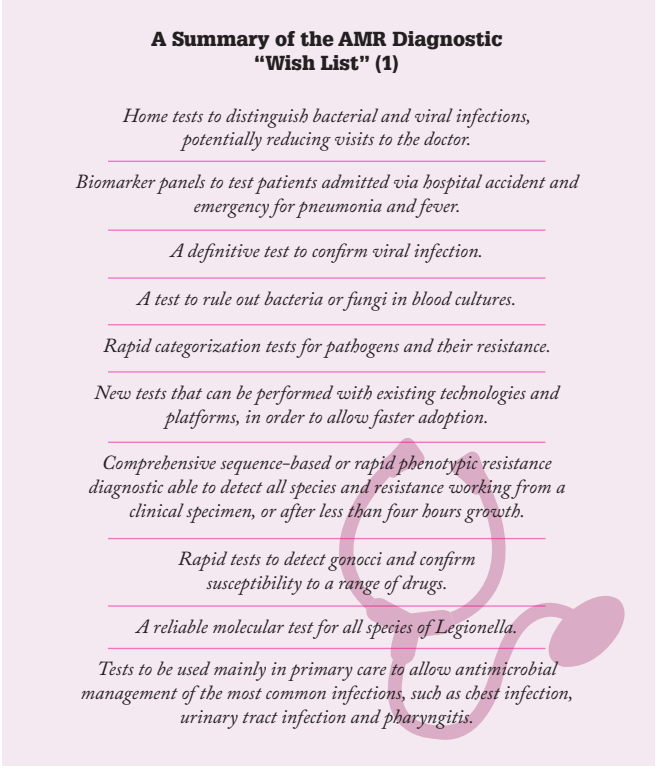

Figure 2. Some of the diagnostic game-changers suggested by healthcare professionals to the AMR Review.

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In My View

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

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

Contact the editor at fedra.pavlou@texerepublishing.com

The Isotopic Doctor

High-precision isotopic analysis of essential metals is beginning to show real promise for medical diagnoses. Here, I share some of the progress in this exciting application area.

By Frank Vanhaecke, professor, Department of Analytical Chemistry, Ghent University, Belgium.

The lightest elements vary in their isotopic composition due to isotope fractionation; this is something we've known for quite a while. It occurs when the isotopes of an element do not take part with exactly the same efficiency in a physical process or (bio)chemical reaction. Differences in reaction rates (kinetics) and in equilibrium (thermodynamics), therefore, occur – for example, the lighter of two isotopes will react more quickly, while the heavier will prefer the strongest bonding environment.

In 'traditional' isotope systems (hydrogen, nitrogen, carbon, oxygen and sulfur), variations can be studied using gas source isotope ratio mass spectrometry (IRMS). But for heavier elements, the relative difference in mass between the isotopes was initially thought to be too small to result in a measurable variation in the isotopic composition. However, with the advent of improved instrumentation – especially that of multi-collector inductively coupled plasma-mass spectrometry (MC-ICP-MS) in the early 1990s – it is now generally accepted that all elements with two or more isotopes show natural variation in their isotopic composition because of isotope fractionation effects.

Before the introduction of MC-ICP-MS, only thermal ionization mass spectrometry (TIMS) provided sufficient precision for studying natural variation in the isotopic composition of heavier elements. However, its widespread use was hampered because of low sample throughput capability and the limited ionization power of its source (only elements with an ionization energy up to 7 eV are efficiently converted into M^+ ions). With the ICP providing a much more powerful ionization source at atmospheric pressure, MC-ICP-MS can analyze a broader range of target elements. Indeed, geochemists welcomed MC-ICP-MS with open arms for studying non-traditional isotope systems in various application areas.

Today, a few institutions around the world are using MC-ICP-MS for high-precision isotopic analysis of metals in body fluids as a potential new tool for medical diagnosis. In a NASA-funded study, a research group at Arizona State University, USA, discovered that natural changes in the isotopic composition of calcium in urine indicate bone loss in bed rest patients (1). In follow-up work, they demonstrated that the approach could also signal multiple myeloma disease activity (2). In a pilot study, researchers at the École Normale Supérieure de Lyon, France, showed that the isotopic composition of serum copper in breast and colorectal cancer patients reflected response to chemotherapeutic treatment more quickly than traditional biomarkers (3).

Ghent University, Belgium, is among these pioneering institutions. In the

work performed so far, we have shown that Wilson's disease, a hereditary illness that interferes with the excretion of excess copper into the bile, leads to a significantly lighter isotopic composition of serum copper (4). In liver cirrhosis sufferers, we have revealed that the isotopic composition of serum copper reflects the severity of the disease (5). This breakthrough is potentially useful for prioritizing liver transplant patients.

Another promising application is isotopic analysis of whole blood/serum iron, as pioneered by researchers at ETH-Zürich, Switzerland (6). The serum concentration of ferritin is the clinically most useful measure of iron storage. Low serum ferritin levels indicate depleted iron, whereas increased levels may indicate overload. Inflammatory conditions (or infections, cancer and liver disorders) will also influence ferritin concentration; as a result, a large number of patients remain at risk from iron depletion or overload. We have seen a link between iron status and the isotopic composition of whole blood iron (7). This is a potentially better marker for iron status and it has the benefit of offering access to both short-term (via serum iron) and longer term (via red blood cells or whole blood iron) information.

Despite the relatively high cost of an MC-ICP-MS analysis, the medical world is interested in the approach for earlier and non-invasive diagnosis and prognosis of diseases. Are we there yet? Not exactly. Several issues, such as the specificity and reproducibility of the shift in the isotopic signature of the target element(s), need assessing, and we need a more thorough understanding of the underlying causes of the changes we observe in isotopic composition. However, we are working on this, experimenting *in vitro* and *in vivo* to gain greater insights.

In a biomedical context, the isotopic analysis of non-traditional isotope systems is, therefore, intriguing, particularly as it shows real potential for clinical practice. I am glad that my research group and I – and our colleagues from the Ghent University Hospital – can contribute to progress in this exciting area.

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This Sporting Life

Physical activity is an important preanalytical variable in blood analysis and here's why.

By Giuseppe Banfi, associate professor of clinical biochemistry and clinical molecular biology at the Vita-Salute San Raffaele University in Milan, Italy.

Clinical pathology data play an important role in advancing sports medicine. Biochemical and hematological parameters help assess the health of recreational and professional athletes, prevent infectious diseases and injuries, measure performance, and, detect the use of illicit and unethical substances or methods (1) (something that is becoming ever more important given the recent negative media attention that doping in athletes has gained). As a result, the preanalytical phase is crucial for evaluating and interpreting clinical data, especially when laboratory results may have legal consequences for the athlete.

Specific knowledge in this area has burgeoned in recent years resulting in much more awareness about the correct drawing, transport and storage of biological material. In fact, both The European College of Sport Science and the American College of Sports Medicine have warned of the influence of preanalytical factors – time of blood drawing, food intake, time of analysis after the end of exercise, gender, age, etc. – on laboratory data (2).

Given the rising number of controversies in athletic sports regarding illicit drug use, anti-doping programs strongly promote and support the measurement of biochemical and

hematological parameters in athletes; but, there are some challenges to following the guidelines. For example, fasting is crucial for most laboratory parameters, but in sports medicine it is not easy – and sometimes impossible – to define, perform, organize, and (or) control it.

"To assure accuracy, all preanalytical variables should be documented and referenced when evaluating laboratory results in sports medicine."

During a three-week-stage cycle race, for instance, athletes will follow a 6,000 kcal a day diet, consuming 1,500 kcal each morning before the start of each stage. Because food intake may influence many laboratory parameters, this makes correct blood drawing difficult. Also, clinically significant variations in neutrophils, eosinophils, erythrocytes, hematocrit volume (packed cell volume) and mean corpuscular hemoglobin levels occur up to four hours after eating. There are also increases in alkaline phosphate (ALP), triglycerides, albumin, calcium, sodium, magnesium, potassium, C-reactive protein (CRP), uric acid, bilirubin, alanine transaminase (ALT) and aspartate aminotransferase (AST). And, in endurance sports, athletes must eat continuously to restore glycogen. You see the challenge…

So, when evaluating biochemical and hematological parameters, blood dilution or concentration needs accurate definition. The Dill & Costill equation, which is based on the concentration of hemoglobin and on the percentage of hematocrit before and after exercise, is accepted in scientific literature for correcting the alteration in erythrocyte concentration in plasma due to physical activity. The equation requires the immediate analysis of hematological specimens and it's been recently proposed that it can be used for calcium too, which is helpful for monitoring a range of conditions relating to bones, heart, nerves and kidneys (3). Recent research has also demonstrated that, with a modification, it could also be used at different environmental temperatures (4).

Such is the emphasis that is placed on blood monitoring of athletes, the "Athlete Biological Passport" has been designed to store data on athletes' hemoglobin concentration and the percentage of reticulocytes over time. While the preanalytical factors that can influence hemoglobin are known, those that affect reticulocytes, especially during physical exercise, required in-depth study and evaluation before they could be included in the athletes' biological passports (5,6).

Reticulocytes have higher intraindividual variability in athletes than in nonathletes. They also have high interindividual variability, even in homogeneous athlete populations. Only by monitoring reticulocyte values in a single subject over time can this variability be accounted for and an accurate interpretation made.

Interestingly, it's difficult to compare scientific studies on reticulocytes. They are less stable than hemoglobin, and their stability depends on the method used for counting; storage at cold temperatures (ideally 4°C) is required to guarantee stable values. Acute exercise does not modify reticulocytes, but training and competitions during a season does influence their values. Also, the differences between consecutive seasons are greater than those within a season in the same group of athletes. It is especially remarkable that reticulocyte modifications noted during the season do not always follow those seen in hemoglobin.

In my view, the preanalytical phase is fundamental for assuring correct interpretation of laboratory data. To assure accuracy, all preanalytical variables should be documented and referenced when evaluating laboratory results in sports medicine. After all, an inaccurate laboratory result has the potential to change an athlete's life – for better or for worse.

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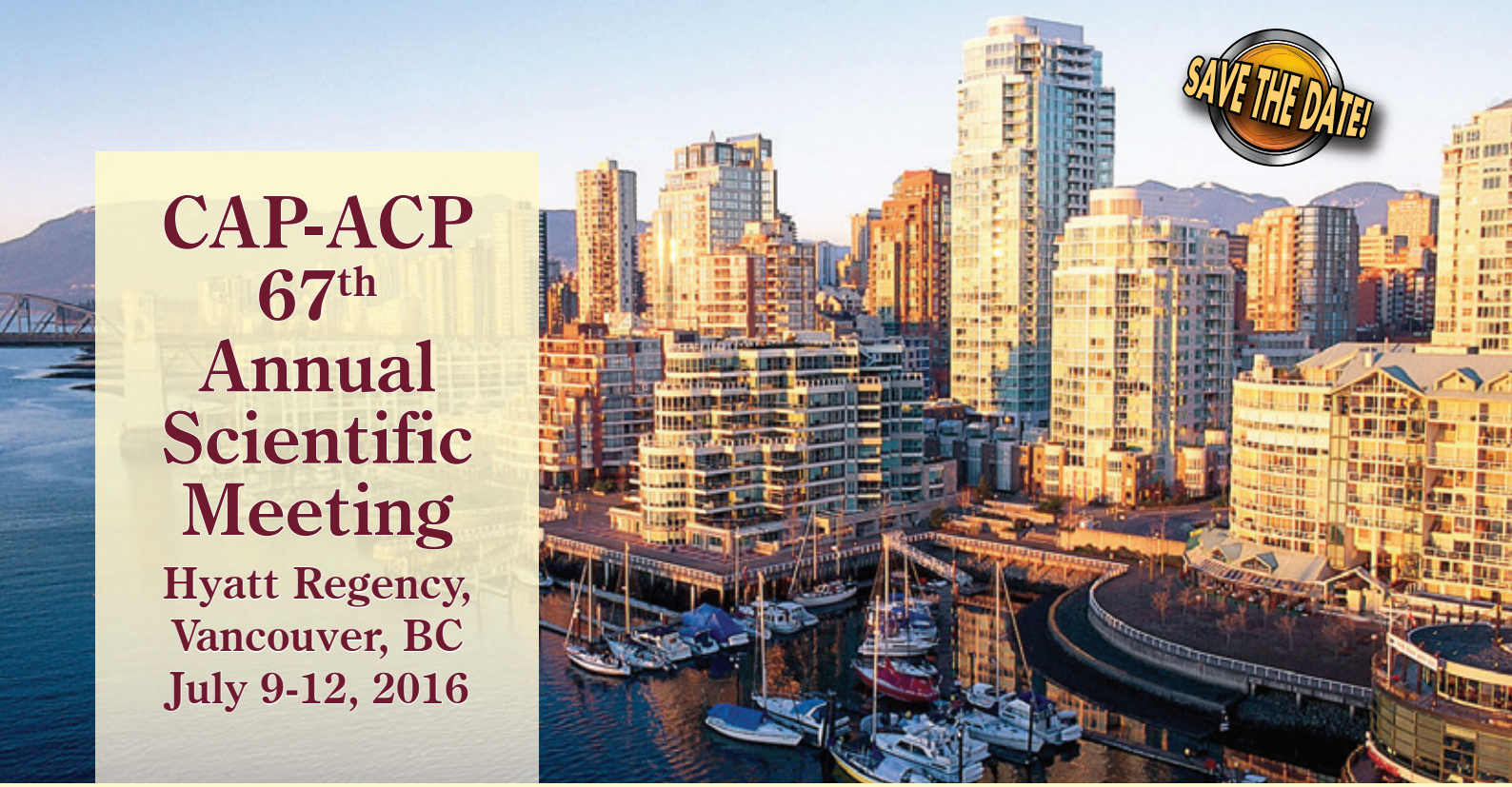

CAP-ACP 67th Annual Scientific Meeting

Hyatt Regency, Vancouver, BC July 9-12, 2016

The CAP-ACP Annual Meeting consists of two days of workshops (Saturday and Sunday) followed by two days of symposia. There is a half day with proffered paper/posters and a half day of CAP-ACP specific awards lectures. There are two evenings of special interest group and specialty network meetings. The overall meeting is under the supervision of the Annual Meetings Committee with subcommittees including the LOC, CPD Committee, CAP-ACP Sections and the CAP-ACP Awards Committee.

The Local Organizing Committee, under the direction of Chair, Dr. Martin Trotter have confirmed that the President's Reception will be held at the Museum of Anthropology, UBC (transportation is provided) and that they will be assisting with the PA program to include a wet-lab on Sunday morning at St. Paul's Hospital.

Confirmed speakers to date:

Dr. Mary Bronner is our invited Cam Coady Slide Seminar speaker and will be giving a talk titled: "*GI Tract Mucosal Biopsy*" on Tuesday, July 12, 1400-1700.

The Forensic Pathology section has invited **Dr. C. Paul Johnson**, a Forensic Pathologist from the UK (Liverpool). He has a research interest in, and will be presenting on "*Traumatic Subarachnoid Haemorrhage and the Mechanisms of Vertebral Artery Trauma*".

The Humanities/International Health Symposium speakers will be **Dr. Maadh Aldouri**, from the Royal College of Pathologists, UK, sharing a talk on his "*Experience with Labskills Africa Project*", and **Dr. Phil Clement**, who will be giving a talk on "*The History of Endometrial Carcinoma*".

Program to include:

- Pathologist Assistants Program
- Junior Scientist Award Lecture
- Cam Coady Slide Seminar
- William Boyd Lecture
- Awards Banquet
- Special Interest Groups
- President's Reception
- Workshops
- Poster Presentations
- Satellite Symposia
- Networking
- Industry Partners

This event is an Accredited Group Learning Activity (Section 1) as defined by the Maintenance of Certification program of the Royal College of Physicians and Surgeons of Canada. This activity was approved by the Canadian Association of Pathologists.
Through an agreement between the Royal College of Physicians and Surgeons of Canada and the American Medical Association, physicians may convert Royal College MOC credits to AMA PRA Category 1 Credits™.
Through an agreement between the Royal College of Physicians and Surgeons of Canada and the European Union of Medical Specialists (UEMS) physicians may convert Royal College MOC credits to ECMEC®.

See www.cap-acp.org/2016meeting.php for more information

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Who are the most influential laboratory medicine professionals? That's the question we posed to ourselves – and then to you – over two months ago, ahead of open nominations and a painstaking judging process. Here, without further ado, we celebrate the answer.

Brian Smith

An internationally recognized leader in laboratory medicine education, Brian is professor and chair of the Department of Laboratory Medicine at Yale University, as well as a professor of biomedical engineering of medicine (hematology) and of pediatrics. He is well-known for his contributions to immunohematology, a field in which he investigates the inflammation-coagulation interface. In addition to his involvement in clinically oriented research, Brian has published in bioethics and is engaged in educational methodology research to improve medical student education.

Mario Plebani

"I strongly believe that laboratory information plays an increasing relevant role in assuring early diagnoses, better prognoses and effective monitoring," says Mario, who is chief of the Department of Laboratory Medicine and professor of clinical biochemistry and clinical molecular biology at the University-Hospital of Padova. Currently chief of the Center of Biomedical Research, a specialized regional center for quality in laboratory medicine, Mario has held numerous national and international representative roles and has published over 900 publications.

Danielle Freedman

Danielle is consultant chemical pathologist and associate physician in clinical endocrinology, director of pathology, and chief medical advisor at Luton & Dunstable University Hospital. Despite many professional appointments, including as chair of LabTestsOnline.org, she says, "The most unexpected event that has happened in my career was being voted in as vice-president of the Royal College of Pathologists (2008–2011)." She believes the real importance of pathology and laboratory medicine lies in bridging the knowledge gap at the clinician/laboratory interface.

Marcial García Rojo

Marcial is the principal investigator in the EURO-telepath EU project, which aims to develop a technological framework for the consolidation and management of healthcare records via the Internet. He authored the first Spanish-language telepathology book, among other books on the subject of medical informatics. Apart from informatics, his research interests are human papillomavirus in cervical cancer and biomarkers in colon cancer, and he is currently head of pathology at the University General Hospital of Ciudad Real in Spain.

Ruth Katz

Ruth is a well-known lecturer in cytopathology, has authored nearly 200 peer-reviewed articles, and is on the executive committee of the American Society of Cytopathology. Involved in cervical cytology quality assurance for over 20 years, her contributions toward improvement include facilitating the institution of new regulations as required by the Clinical Laboratory Improvement Amendments Act of 1988. As a professor in the Department of Pathology/Cytopathology, University of Texas MD Anderson Cancer Center, she studies genetic susceptibility to lung cancer.

David Bailey

David, a consultant histopathologist and lead trainer in Buckinghamshire Healthcare NHS Trust, has previously been training program director, head of pathology school, and associate postgraduate dean in Oxford. He's held several positions in the Royal College of Pathologists, including chair of the national histopathology training committee, director of training and assessment, and vice president for communications. He says, "If the colleagues around you are supportive, the team communicate well and they work for each other, you can cope with anything."

Jorge Reis-Filho

A surgical pathologist with Memorial Sloan Kettering Cancer Center, Jorge's expertise lies in breast cancer gene expression profiling and genomics, and in combining traditional pathology with data generated by high-throughput molecular techniques.
The youngest-ever Fellow of the Royal College of Pathologists to have become a member via published works, Jorge received the 2010 Cancer Research UK Future Leaders prize. His main research focus is on rare breast cancer types and the development of diagnostic, prognostic and predictive biomarkers.

Suzanne Powell

Suzanne is a professor of pathology and genomic medicine at Houston Methodist's Institute for Academic Medicine, program director of residencies in Anatomic and Clinical Pathology and Neuropathology, and an associate professor of pathology and laboratory medicine at Cornell University's Weill Medical College. She is the Houston Methodist Hospital site director for the Baylor College of Medicine Neuropathology Fellowship Program and she co-directs the Houston Methodist/MD Anderson Neuropathology Fellowship Program. Her own research is in dementia and neurodegenerative diseases.

Jonathan Edgeworth

Jonathan is the Medical Director of Viapath at Guy's and St Thomas' Trust in London. Joining the trust as an academic consultant microbiologist, he initially pursued research into antimicrobial resistance and infections in critical care. He now divides his time between his duties as Viapath's medical director, leading the infection service for critical care at Guy's and St Thomas' Hospital, and directing research at the King's College London/Guy's And St Thomas' Hospital Centre for Clinical Infection and Diagnostics Research.

Paola Domizio

Paola's passion for education has made her a professor of pathology education and deputy director for Teaching at the Blizard Institute. She has also been the first chairman of the Education subcommittee of the Pathological Society of Great Britain and Ireland, coordinating the development of a national undergraduate curriculum in pathology. She is now director of Public Engagement at the Royal College of Pathologists, striving to improve the public image of the discipline, and regularly appears on radio and television.

Barbarajean Magnani

The pathologist-in-chief at Tufts University School of Medicine, Barbarajean is an expert in clinical chemistry and toxicology. She has received a Recognition Award for Significant Service from the Massachusetts Poison Control Systems in Boston and has authored several books on toxicology, as well as a toxicological novel, *Lily Robinson and the Art of Secret Poisoning*. Barbarajean serves as chair of the College of American Pathologists' Toxicology Resource Committee and has received awards for her seminars and workshops on the subject.

Greg Miller

As current president of the US Clinical and Laboratory Standards Institute (CLSI), Greg has been active in the CLSI consensus process, serving as chairholder of the Consensus Committee on Clinical Chemistry and Toxicology. Greg is also past president of the American Association for Clinical Chemistry (AACC) and a recipient of the 2007 AACC Outstanding Lifetime Achievement Award in Clinical Chemistry and Laboratory Medicine. Outside the CLSI, he is a professor in the Department of Pathology at Virginia Commonwealth University Medical Center.

Bruce Smoller

After serving as executive vice president of the United States and Canadian Academy of Pathology for three years, Bruce accepted a position as chair of the Department of Pathology and Laboratory Medicine at the University of Rochester Medical Center. With over 235 original articles, 39 book chapters and 13 textbooks on the subject of dermatopathology, one of his proudest achievements is receiving the American Society of Dermatopathology's Walter R. Nickel Award in 2004, recognizing a lifetime of excellence in teaching.

James Faix

With research interests including markers of sepsis, myeloma, autoimmune disease and allergy, and recipient of Lifetime Achievement Awards from Harvard Medical School and the College of American Pathologists (CAP) among his multiple achievements, James is a significant figure in clinical chemistry and immunology. He's currently a member of the CAP Council for Scientific Affairs and Chemistry Resource Committee, as well as the chair of the American Association for Clinical Chemistry's Division Management Group and a member of the LabTestsOnLine.org editorial board.

Raouf Nakhleh

Raouf is a dedicated advocate of quality improvement in pathology – he chairs the College of American Pathologists' (CAP) Quality Practices Committee and has contributed to organization-wide efforts to improve pathology practice. This includes involvement in the CAP Standards Committee and the Pathology Performance Measures Development Working Group. After chairing the first panel on Consensus Statement for Effective Communication of Urgent Diagnoses and Significant Unexpected Diagnoses in Surgical Pathology and Cytopathology, Raouf is working to develop guidelines to reduce interpretive diagnostic errors.

Roy Herbst

Roy's positions at the Yale Cancer Center include Ensign Professor of Medicine (Medical Oncology), professor of pharmacology, associate director for translational research, and translational working group leader in the Thoracic Oncology Program. His best-known work is in developmental therapeutics in personalized therapies for non-small cell lung cancer. He chairs the Tobacco Task Force of the American Association for Cancer Research and the communications committee for the International Association for the Study of Lung Cancer, and holds numerous professional memberships.

Iris Schrijver

Iris, a professor in the Department of Pathology, directs the Molecular Pathology Laboratory and the Molecular Genetic Pathology fellowship program at Stanford University. A past president of the Association for Molecular Pathology whose research involves molecular diagnostics, inheritance and genotype-phenotype correlations, Iris says, "We are actively practicing precision medicine, and I look forward to continued advances." She and her husband recently co-authored a book, *Living With the Stars*, based on the fascinating connections between the universe and the human body.

Andrew St. John

"Andrew is driving the health economic value of pathology initiatives in Australia," writes a nominator. The result of his work, a call for a value-based approach to laboratory medicine funding, has involved collaboration across global networks, particularly in the United Kingdom and Canada. Andrew is chair of the Australasian Association of Clinical Biochemists' Health Economic Working Group, publishes regularly on issues affecting lab medicine professionals, and is frequently invited to present his work as an expert in health economics.

Paul Bachner

Paul is currently professor and past chairman of the Department of Pathology and Laboratory Medicine at the University of Kentucky in Lexington. He additionally serves as medical director of the Commonwealth of Kentucky's Division of Laboratory Services, Department for Public Health, as past president of the College of American Pathologists (CAP), and as an inspector in CAP's Laboratory Accreditation program; he also currently chairs CAP'S Accreditation Committee.

Eric Kilpatrick

Eric is a consultant in chemical pathology in the Department of Clinical Biochemistry of Hull Royal Infirmary, as well as an honorary professor in clinical biochemistry at Hull York Medical School. A former president of the Association for Clinical Biochemistry and Laboratory Medicine, Eric has been involved with numerous national and international groups, including the National Institute for Health and Care Excellence, the Global Task Force for Glycemic Control, and the Speciality Advisory Committee of the Royal College of Pathologists.

Ian Tomlinson

A professor of molecular and population genetics, consultant physician, and leader of a laboratory group at the Wellcome Trust Centre for Human Genetics at the University of Oxford, Ian has over 400 published papers and book chapters in the field of cancer genetics. His research interests include the identification of genes that predispose to colorectal and other cancers, a field in which his work saw him named a European Voice EV50 Achiever of the Year in 2005.

David Leslie

Diabetes research is the framework of David's career – he's a consultant physician at St. Bartholomew's Hospital, London, professor of diabetes and autoimmunity at the Blizard Institute, reviews editor of Diabetic Medicine, director of the British Diabetic Twin Trust and a member of the National Institutes of Health Advisory Board on the Prevention of Diabetes. He was recently elected president of The Association of Physicians of Great Britain and Ireland and currently investigates the causes of autoimmune diabetes.

Richard Friedberg

Richard's election as president of the College of American Pathologists is his latest step in a long history of service to the organization. In addition to advocating for his field, Richard is chairman of the Department of Pathology at Baystate Health, medical director for Baystate Reference Laboratories, and professor and deputy chairman in the Department of Anatomic and Clinical Pathology at Tufts University School of Medicine. He's passionate about the technological revolution that underpins pathology's future as a diagnostic specialty.

Ian Grierson

"An ocular pathologist who has done more than most to help us understand the disease processes of the aging eye," Ian specializes in dry eye disease, glaucoma, and age-related macular degeneration. He is emeritus professor of ophthalmology in the Department of Eye and Vision Sciences at the University of Liverpool. He also runs a consultancy firm advising on vision and nutrition, has written four recipe books for vision loss charities, and works to promote patient health and safety in care homes.

Wolf Fridman

Few pathologists have as unique a claim to fame as Wolf, who, with a colleague, published the first description of a patient's immune response to acute leukemia. Since then, he has focused his research on the role of the immune system in controlling human tumors, an interest that led to many more discoveries in cancer immunology. Having created his own laboratories and research organizations over the years, he's now professor emeritus of immunology at the Paris Descartes University Medical School.

Hermann Einsele

A professor of internal medicine and director of the Medizinische Klinik und Poliklinik II of the Julius-Maximilians-University in Würzburg, Hermann is also a visiting professor at the Fred Hutchinson Cancer Research Center in Seattle and the City of Hope Hospital in Duarte. He's chairman of the German Study Group on Multiple Myeloma and on the board of the German Society of Blood and Marrow Stem Cell Transplantation, as well as an active member of numerous organizations related to his field.

Bernard Gouget

Bernard is Counsellor for Public Health at the Fédération Hospitalière de France and an assistant professor at the University Hospital in Paris Descartes. In the laboratory, he studies organ physiology in intensive care, chronic diseases, nosocomial infections, pandemics, and illnesses related to lifestyle; in his public health capacity, he's interested in biomedicine and ethics, bioterrorism, patient safety, and adapting health care services for better patient care. He's a strong advocate and advisor in many aspects of healthcare and health research.

Margaret Goodell

A professor and director of the Stem Cells and Regenerative Medicine Center at Baylor College of Medicine, Peggy's chief research interest is in the regulation of hematopoietic stem cells. She studies adult stem cells' stress, aging, and self-renewal and activation to better understand how these mechanisms may cease to function correctly. Peggy has also held leadership roles in the International Society for Experimental Hematology, in the International Society for Stem Cell Research and the American Society of Hematology.

Peter Kelly

Peter is a member of Council and the Dean of the Faculty of Pathology at the Royal College of Physicians of Ireland. He's also a consultant histopathologist in the Department of Pathology at Mater Misericordiae University Hospital in Dublin, and a consultant pathologist and director of laboratories at the Mater Private Hospital. He has previously been involved with the Joint Working Group on Medical Laboratory Accreditation, the National Taskforce on Hospital Medical Staffing, and the European Union of Medical Specialists.

Mauro Panteghini

Mauro is president of the European Federation of Clinical Chemistry and Laboratory Medicine and professor and chair of Clinical Biochemistry and Clinical Molecular Biology at the University of Milan Medical School. He also directs the Department of Laboratory Medicine and the Clinical Pathology Unit of the "Luigi Sacco" University Hospital and the Center for Metrological Traceability in Laboratory Medicine of the University of Milan. He has published over 470 manuscripts and 440 abstracts and given over 290 presentations.

Patrick Fitzgibbons

Patrick was nominated for "his contributions to patient care and safety," in particular in chairing the development of the College of American Pathologists (CAP) guideline, "Principles of Analytic Validation of Immunohistochemical Assays." A pathologist at St. Jude Medical Center and a clinical assistant professor of pathology at the University of Southern California School of Medicine, Patrick has a long history of service to CAP and other professional organizations, and was a 2009 winner of CAP's Distinguished Patient Care Award.

Peter Schirmacher

Peter is acting chairman of the German Society of Pathology, director of the Institute of Pathology at Heidelberg University Hospital, and president of the German Association for the Study of the Liver. His research interests include molecular and morphological digestive system carcinogenesis, especially of the liver and pancreas, tumor banking, and virtual microscopy. He has published over 80 peer-reviewed publications and thinks that "pathology has a bright future, with great challenges in molecular diagnostics, biobanking, and innovative imaging approaches."

Gerrit Meijer

As head of VU University Medical Center's Department of Pathology in Amsterdam and a leader in numerous international scientific societies, it's no wonder that Gerrit – whose current research focuses on DNA- and RNA-based genomic tumor profiling in gastrointestinal cancers – is optimistic about what lies ahead for pathology. He has successfully implemented comparative genomic hybridization and helped introduce DNA microarray technology in his department. He says, "The pathologist of the future has the chance to be a diagnostic guide in clinical decision making."

David Weedon

An internationally acclaimed pathologist at Sullivan Nicolaides Pathology and professor of pathology at Bond University in Australia, David's claim to fame is *Skin Pathology*, the definitive textbook on dermatopathology (now in its fourth edition). A past president of the Royal College of Pathologists of Australasia and the Australian Medical Association, he was appointed an Officer of the Order of Australia in 1997 for his services to medicine, particularly in education, pathology and dermatopathology.

Fatima Carneiro

Fatima is described by nominators as "an excellent scientist involved in multiple breakthrough discoveries in the field of gastric cancer." A past president of the European Society of Pathology and current holder of numerous professional appointments, she is a professor of anatomic pathology at the Medical Faculty of Porto, head of the Department of Anatomic Pathology at Hospital Sao João, and senior investigator at the Institute of Molecular Pathology and Immunology at the University of Porto (IPATIMUP).

Alan Wells

"Pathology was the obvious choice to merge clinical impact with investigative research in molecular cell biological mechanisms of disease processes," says Alan of his decision to pursue a career in the field. Currently medical director for the University of Pittsburgh Medical Center clinical laboratories, executive vice-chairman of the Section of Laboratory Medicine, and Thomas Gill III Professor of Pathology, he says, "What success I have had is due to my large and changing group of friends and colleagues."

Mark Caulfield

As chief scientist for Genomics England, Mark leads the 100,000 Genomes Project, which has the opportunity to not only contribute massively to genomic discovery in cancer, but also transform tissue handling, molecular pathology and cancer diagnostic methods in the National Health Service. He is a consultant in the Barts Blood Pressure Clinic in London. His research is frequently rated amongst the top scientific discoveries in his field and he is one of the 200 most cited researchers in the world.

Barbara Crothers

A colonel in the US Army Medical Corps, Barbara is program director of the National Capital Consortium's anatomic and clinical pathology residency program, internship and clerkship, and medical director of cytopathology at Walter Reed National Military Medical Center. She has been recognized for her military service with five Meritorious Service medals and two Army Commendation medals, and for clinical contributions with the Roy M. Pitkin award for outstanding research and the College of American Pathologists' Public Service Award.

Dora Dias-Santagata

A specialist in the molecular characterization of lung, thyroid, and rare malignant tumors, Dora developed and implemented the first high-throughput clinical multiplexed cancer genotyping assay. The test is able to identify 120 mutations in 13 different cancer genes. Dora is still involved in both innovative assay development and patient care, working as assistant professor of pathology at Harvard Medical School and as assistant molecular pathologist and co-director of the Translational Research Laboratory at Massachusetts General Hospital.

Anita Borges

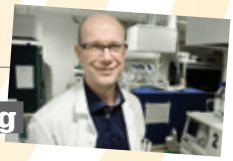
Anita currently serves as president of the SRL Diagnostics center of excellence for histopathology and as vice president (Asia) of the International Academy of Pathology. She also chairs the clinical laboratory accreditation committee of the National Accreditation Board for Testing Laboratories and acts as dean of the Indian College of Pathologists. Educated in London, New York and India, she has spent 25 years as a cancer pathologist, most recently at the Tata Memorial Cancer Hospital in Mumbai.

Philip Cagle

Philip is a professor of pathology and genomic medicine at Houston Methodist's Institute for Academic Medicine, as well as the director of pulmonary pathology, a full clinical member of Houston Methodist Research Institute and a professor at Weill Cornell Medical College. He has been named Pathologist of the Year (2013) by the College of American Pathologists (CAP) and is a previous winner of CAP's Distinguished Patient Care Award and the Texas Society of Pathologists' John J. Andujar Citation of Merit.

Louise Jones

A lecturer in the University of York's Department of Biology, Louise has made a massive contribution to research in breast cancer pathology – studying the factors involved in the progression of *in situ* to invasive disease – and has been a trailblazer in innovative approaches to tissue banking. She is clinical lead for pathology for the 100,000 Genomes Project and is using that role to introduce innovate practices for vacuum-packing and tissue handling into the UK's NHS.



Jens Petter Berg

Jens Petter's professional interests are in biochemical and hormonal changes in endocrine diseases, a research focus he pursues as professor in the University of Oslo's Department of Medical Biochemistry. He also acts as head of research for the Division of Diagnostics and Intervention at Oslo University Hospital. He has authored over 100 papers and review articles and has held the position of editor-in-chief of the Scandinavian Journal of Clinical and Laboratory Investigation.

Didier Raoult

France's most-published researcher, with over 2,000 indexed publications to date, Didier is a specialist in infectious and tropical diseases. A professor at Marseille School of Medicine and director of the clinical microbiology laboratory for the university hospitals, Didier founded the Rickettsia Unit at his home university, which later became the National Rickettsia Reference Center and a World Health Organization collaborative center. He also co-founded ESCCAR, the European Study Group on *Chlamydiales, Coxiella, Anaplasma, Rickettsia* and other intracellular bacteria.

Kim Collins

Kim is recognized for her "innovative and engaging teaching techniques" as faculty for the College of American Pathologists (CAP)'s annual meeting, the Engaged Leadership Academy and the Multidisciplinary Breast Pathology Advanced Practical Pathology Program. She is medical director of LifePoint, South Carolina's organ and tissue donation procurement service. A forensic pathologist, Kim is a director of the National Association of Medical Examiners, past chair of CAP's Autopsy Committee and winner of the organization's 2008 Distinguished Patient Care Award.

Enrique de Álava Casado

Enrique is director of the Anatomical Pathology Clinical Management Unit at Virgen del Rocio University Hospital and Osuna health area. He studies the molecular pathology of sarcomas as principal investigator of the Sarcoma Molecular Pathology Laboratory and director of the Diagnostic Molecular Pathology Laboratory-Tumor Bank in the Cancer Research Center at the University of Salamanca-CSIC. Enrique also holds leadership positions at the National DNA Bank, the Superior Council for Scientific Research, and as president of the Spanish Society of Pathology.

Philippe Gillery

Philippe, who leads the department of biology at the University Hospital Center of Reims, is also head of the Regional Conference of Health and Autonomy in Champagne-Ardenne. His chief research focus is on the relationship between extracellular matrix proteins and inflammatory cells, a field in which he examines the pathological effects of protein post-translational modifications in a wide variety of disorders. Philippe has spent over 25 years developing and standardizing glycated protein assays and he has published over 110 peer-reviewed articles.

Ab Osterhaus

Considered one of the most important virologists in the world, especially for his work on SARS and avian influenza, Ab is a professor at Erasmus University Medical Center in Rotterdam and State University Utrecht. His professional leadership roles include director of the National Influenza Center and of the World Health Organization Collaborating Center for Arboviruses and Haemorrhagic Fever Reference and Research, chairman of the European Scientific Working Group on Influenza, and chief scientific officer of Viroclinics BV and ViroNative BV.

Jonathan Kay

Jonathan, who is clinical informatics director at NHS England, holds the positions of honorary consultant chemical pathologist at Oxford University Hospitals and senior clinical lecturer at the University of Oxford. His interests involve persuading computers to communicate in ways that offer clinical benefits – including work on automated laboratory report transmission to GPs, hypertext advisory systems, and handheld wireless computers. At the moment, he is working on improving blood transfusion with positive patient identification and process re-engineering.

Ian Cree

Ian is a molecular pathologist at University Hospitals Coventry and Warwickshire, visiting professor at Coventry University, and honorary professor of pathology at University College London's Institute of Ophthalmology. His research investigates disease mechanisms to improve diagnosis and treatment, particularly for cancer, and he currently leads the Royal College of Pathologists' Research Committee and the Early Cancer Detection Consortium. In the future, he expects to see more technological involvement in pathology, augmented by new sequencing, mass spectrometry and Big Data.

Bill Carman

A clinical virologist, Bill founded Fast-track Diagnostics and later became its full-time CEO. He has long recognized the importance of accurate diagnosis of infectious diseases and, according to nominators, has "driven the development and clinical introduction of molecular diagnostics for infectious disease, both within the National Health Service and his company. His seminal contribution was to recognize that clinicians need results for most, if not all, pathogens that may cause the clinical presentation, all in one sample at one time."

Samir Amr

Samir is well known for his dedication to laboratory quality and safety. He has previously served as the College of American Pathologists' deputy commissioner in the Middle East region, handling all duties there in times when inspectors from the United States could not enter. He has also been the president of the Arab Division of the International Academy of Pathology (IAP), as well as vice-president for Asia, and is noted by the IAP for his dedication to teaching and mentorship.

Teresa Darragh

A world expert in anal cytology and pathology, Teresa has been president of the American Society for Colposcopy and Cervical Pathology (ASCCP), chaired ASCCP's Pathology Committee, and co-chaired the LAST Project on standardizing terminology for HPV-associated squamous lesions of the lower anogenital tract. A pathologist in UCSF's Departments of Pathology and Obstetrics, Gynecology and Reproductive Sciences, she says her career "has been blessed with a wealth of opportunities coupled with being in the right place at the right time."

Jerad Gardner

"We as pathologists have to speak on behalf of pathology," declares Jerad, one of pathology's best-known social media users. "No one else will do it for us!" An assistant professor at the University of Arkansas for Medical Sciences, he also runs the school's dermatopathology fellowship program and is clinical co-director of the musculoskeletal/skin block for its College of Medicine. He chairs the social media subcommittees for the United States and Canadian Academy of Pathology and the American Society of Dermatopathology.

Gwyn McCreanor

Gwyn started as an academic research scientist; discovering that she enjoyed the diagnostic side of the role led her to pathology. It's been a fruitful endeavor – she's now consultant clinical biochemist, clinical director for pathology, business unit director for clinical services, and clinical lead for research at Kettering General Hospital. She says, "The most surprising moment of my career was being asked to become president of the Association for Clinical Biochemistry and Laboratory Medicine – such an honor and so unexpected."

Markku Miettinen

Currently senior clinician and head of general surgical pathology in the National Cancer Institute's Center for Cancer Research, Markku has also worked as distinguished scientist, chairman and registrar in the Armed Forces Institute of Pathology and as an attending pathologist at Jefferson Medical College and Thomas Jefferson University Hospital. With research interests in soft tissue and gastrointestinal stromal tumors (GISTs), Markku's work involves prognostic, molecular, and biomarker analysis of GISTs and evaluation of new diagnostic markers for soft tissue tumors.

Marta Cohen

"Pediatric pathology is a vast field of medicine, where the cutoff is not organ- but age-related," says Marta. "A pediatric and perinatal pathologist specializes in all organs and conditions." This diversity attracted her to her field, where she is now consultant pediatric and perinatal pathologist at Sheffield Children's Hospital as well as president of the International Pediatric Pathology Association and director of the organization's Post-Graduate Advanced Course. Her research focuses mainly on sudden death in infancy and childhood.

Elizabeth Montgomery

"In 1992, an oncologist asked why I went into surgical pathology when I would be obsolete in 10 years. Now it is 2015 and I'm busier than ever," says Elizabeth. Currently professor of pathology, oncology and orthopedic surgery and director of clinical gastrointestinal pathology at Johns Hopkins University, she's also involved in numerous editorial boards and professional societies. The most important lesson she's learnt over her career is "to learn from rather than be crushed by my errors."

François Blanchecotte

A man of many responsibilities, François is the president of the Syndicat des biologistes, France's national biologists' union – as well as director of the Valbiolab medical laboratory and leader of the UNAPL (national professional union) Committee on European and International Affairs. He was awarded the Legion of Honor in 2014 and is currently involved in three projects: better workplace access for people with disabilities, youth employment, and government funding for clinical laboratories.

Stanley Robboy

Stanley's research career began as an undergraduate when he expressed his envy of a fellow student's summer research. He was overheard and, to his surprise, soon received a research offer of his own from the associate dean of the medical school. The early exposure paid off – Stanley, now vice chair of pathology and a professor of obstetrics and gynecology at Duke University, advises young pathologists to work hard, identify opportunities, take advantage of them, and "blaze new trails."

David Roth

"I was looking for a specialty that would lend itself to biomedical research with a focus on pathogenesis of human disease," says David of his choice to enter pathology. Though he started as a musician, David rose quickly through the ranks after discovering a love of molecular biology. Currently the Simon Flexner Professor and chair of the Department of Pathology and Laboratory Medicine at the University of Pennsylvania, he was recently also named director of the institute's Precision Medicine Program.

Richard Ablin

Discoverer of prostate-specific antigen and a pioneer of cryosurgery and cryoimmunotherapy, Dick is no stranger to leadership in pathology. He is a book author, a professor in the Department of Pathology, University of Arizona College of Medicine, Arizona Cancer Center and BIO5 Institute, and president of the Robert Benjamin Ablin Foundation for Cancer Research, founded in memory of his father. He advises young pathologists, "If you are uncertain of what you have done, never be fearful to ask for assistance."

Marc Ladanyi

Marc is currently attending pathologist and chief of the Molecular Diagnostics Service in the Department of Pathology at Memorial Sloan-Kettering Cancer Center, where he is also William Ruane Chair in Molecular Oncology. His research focuses on the genetics, genomics and molecular pathogenesis of cancers. He thinks the future of pathology holds "a shift away from histopathology, towards molecular analysis, leading to broad redefining of pathology as the specialty dedicated to extracting information from human tissues to direct clinical care."

Neal Lindeman

As a current member of the College of American Pathologists' Molecular Oncology Committee, Neal has contributed significantly to efforts to standardize molecular testing. He co-chaired the Pathology and Laboratory Quality Center expert panel that created evidence-based recommendations for lung cancer biomarkers. As an associate professor of pathology at Harvard Medical School and an associate pathologist at Brigham and Women's Hospital, Neal studies genetic alterations in solid tumors, particularly involving growth factor signaling pathways in adenocarcinomas of the lung.

Leslie Biesecker

Leslie works in genetics and genomics; his lab has shed light on many diseases, including Proteus and McKusick-Kaufman syndromes. In addition to his work as chief and senior investigator of the Medical Genomics and Metabolic Genetics Branch at the National Human Genome Research Institute of the National Institutes of Health, Leslie previously served on the board of American Society of Human Genetics, and on advisory panels for victim identification efforts following the events of 9/11 and Hurricane Katrina.

Miguel Reyes-Múgica

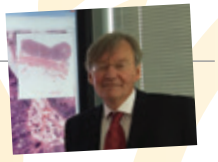
Miguel feels that "the study of life under abnormal conditions" helps him to understand disease – providing his patients with the best possible diagnoses and delving into the mechanisms behind their diseases. He is chief of the Department of Pathology at Children's Hospital of Pittsburgh and holds the Marjory K. Harmer Endowed Chair in Pediatric Pathology. He says, "The most important lesson learnt in my career is that thinking of the patient will always keep me on the right track."

Christopher Fletcher

Chris is a man of many motivations – "the challenge of rendering accurate and clinically useful diagnoses, the wish to guide patient care and share knowledge, the excitement of continual discovery and the pleasure of interacting with trainees." Trained in the United Kingdom, he says a career highlight was moving to Boston, where he is professor of pathology at Harvard Medical School, vice chair for anatomic pathology at Brigham and Women's Hospital, and chief of onco-pathology at the Dana-Farber Cancer Institute.

James Nichols

Jim, who is a professor and medical director of clinical chemistry at Vanderbilt University Medical Center, says, "Knowing that our laboratory test results are directly impacting patient care and their health management motivates me each day. Seeing the faces of the children and other patients being discharged reinforces the importance of the laboratory and need for quality test results." The highlight of his career so far has been "getting to collaborate with the greatest experts each day."



Phil Quirke

Phil, whose research focuses on bowel cancer, is section head of pathology and tumor biology and leader of the colorectal cancer group at the Leeds Institute of Cancer and Pathology. Though he is president of the Pathological Society of Great Britain and Ireland and a fellow of many professional associations, he says the highlight of his career is "seeing the impact of the work of our team and our collaborators on the management and outcomes of bowel cancer."

Marilyn Bui

"I feel passionate about contributing to cancer diagnosis and education, creating new knowledge through research, and advancing our profession to ultimately benefit patient care in a significant way," says Marilyn, a practicing pathologist, academic researcher, program leader and section head at Moffitt Cancer Center. In addition to her many scientific publications and awards, Marilyn holds several patents in digital pathology and is the editor of a forthcoming art book, *Healing Art of Pathology*, focusing on "the people behind the microscope."

Stephen Peiper

Stephen was motivated to enter pathology because of his commitment to a career in academic medicine and because it offered the opportunity to be a consultant for other physicians. "I was taught in my fourth year of medical school that the pathologist is the ultimate patient advocate," he says. He's now the chair and Peter A. Herbut Professor of Pathology, Anatomy and Cell Biology at Jefferson Medical College and has over 140 peer-reviewed publications and 30 book chapters and symposia.

Carolyn Compton

"I was looking for a career that would allow me to sit at the interface between biomedical science and medicine, learning from one to inform the other," says Carolyn of her decision to pursue pathology. As a gastrointestinal disease specialist with interests in colorectal cancer, medical prediction, biospecimen and biobanking science and biomarker development, she has authored over 500 scientific publications, holds professorships at multiple institutions, and has leadership roles in numerous projects for the advancement of precision medicine.

Rachael Liebmann

A specialist breast and skin pathologist, Rachael is registrar of the Royal College of Pathologists and deputy medical director at the Queen Victoria Hospital NHS Foundation Trust. A holder of numerous leadership roles, including as a General Medical Council performance assessment team leader, she also helped to establish RCPath Consulting, which provides independent authoritative advice on pathology service provision, reconfiguration and commissioning issues. Her advice to young pathologists? "Do what you enjoy. The chances are you are good at it."

Michael Misialek

"Patients are healthier because of pathologists," says Michael, whose tips for being an effective pathologist include making sure you're part of the care team, actively searching out opportunities to demonstrate value, and being your own advocate by sharing your story with colleagues, administrators, legislators, patients and the public. He practices in all areas of pathology at a busy community hospital while holding several academic and clinical appointments and serving on several committees with the College of American Pathologists.

Ana-Maria Šimundić

Ana-Maria is head of the Department for Medical Laboratory Diagnostics at the Sveti Duh Clinical Hospital in Zagreb. She's also president of the Croatian Society of Medical Biochemistry and Laboratory Medicine and chair of the European Federation of Clinical Chemistry and Laboratory Medicine preanalytical phase working group. Ana-Maria is motivated by her passion for her profession and the people that she has met along the way."I believe that laboratory medicine is a very exciting field. It offers us the possibility to influence the quality of patient care. To make a difference. To improve things. To save lives. It feels good to know that what we do matters to others."

Liron Pantanowitz

A professor of pathology and biomedical informatics, Liron says informatics is at the forefront of advancement in lab medicine. He is director of pathology informatics and the Pathology Informatics Fellowship Program at the University of Pittsburgh Medical Center, past president of the Association of Pathology Informatics, and a leader in the College of American Pathology and Digital Pathology Association. "Innovating in informatics pushes the limits of our discipline," he says. "As a result, I have come to expect the unexpected."

John Goldblum

John's introduction to pathology came young, thanks to an uncle in the field. That, combined with a knack for interpreting slides, prompted him to enter gastrointestinal and soft tissue pathology, where he's had an extremely successful career. He's now chairman of the Cleveland Clinic's Department of Pathology and president of the United States and Canadian Academy of Pathology. But despite his illustrious career path, he says, "it's always wise to remain humble – and soft tissue pathology humbles me every day."

Han van Krieken

A pathologist with special expertise in gastrointestinal and hematopathology, Han is immediate past President of the European Society of Pathology, the chair and department head of pathology at Radboud University Medical Center in Nijmegen, as well as co-chair of the Radboudumc Center for Oncology. He chose to enter pathology because of the intellectual challenge and the huge impact pathologists have on patients' wellbeing, and says that the highlight of his career was "the discovery that mantle cell lymphoma is a distinct entity that can be easily diagnosed using cyclin D1 staining."

Carl Wittwer

Described as "a pioneer in nucleic acid analysis," Carl invented a number of key polymerase chain reaction technologies that are now used worldwide. He is a professor of pathology at the University of Utah Medical School, technical vice president and medical director of the Immunologic Flow Cytometry and Advanced Technology laboratories at Associated Regional and University Pathologists, a co-founder at BioFire, and a recent winner of the Utah Genius Lifetime Achievement Award for his contributions to molecular diagnostics.

Sharon Weiss

A surgical pathologist with expertise in diagnosing bone and soft tissue neoplasms, Sharon directs Emory University's Expert Consultation Service in Anatomic Pathology. She is a professor of pathology and laboratory medicine and assistant dean for faculty development at Emory's School of Medicine. She oversees a diagnostic service that provides second opinions both within and outside the Emory system and directs a year-long soft tissue fellowship at her institution. Her research deals with clinicopathologic features and biomarkers of soft tissue neoplasms.

18 Andrea Rita Horvath

Rita is clinical director at South Eastern Area Laboratory Services Department of Clinical Chemistry at the Prince of Wales Hospital in Sydney. As well as this position, which she's held since 2009, she is an honorary professor at the University of Sydney and a conjoint professor in the University of New South Wales' School of Medical Sciences. A specialist in evidence-based laboratory medicine, Rita is no stranger to international pathology – she spent eight years as a scientist and lecturer in the UK and 11 leading the Department of Laboratory Medicine at Hungary's University of Szeged before her arrival in Australia. She was president of the Hungarian Society of Laboratory Medicine from 2005 to 2008, and of the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) from 2009 to 2011. She has also served on the EFLM's Committee on Evidence-based Laboratory Medicine and as secretary of the European Communities Confederation of Clinical Chemistry and Laboratory Medicine.

20 James Musser

James, a researcher in bacterial pathogenesis and pathogen-host interactions, is Fondren Presidential Distinguished Chair of the Department of Pathology and Genomic Medicine at Houston Methodist Research Institute. He also directs the Center for Molecular and Translational Human Infectious Diseases Research at Houston Methodist Hospital and has previously served as chief of the Laboratory of Human Bacterial Pathogenesis at the National Institute of Allergy and Infectious Diseases. His laboratory seeks new information on the molecular basis of infections caused by group A *Streptococcus* and *Mycobacterium tuberculosis* pathogens. He's currently involved in a project to identify key vaccine candidates against group A *Streptococcus* using molecular dissection, *in vivo* disease models, and analysis of clinical material. Other projects in his laboratory include collaborating internationally to elucidate the molecular genetic events that contribute to group A *Streptococcus* epidemics, and taking advantage of modern genetic analysis techniques to define human genetic factors determining susceptibility to tuberculosis.

19 David Harrison

A professor and John Reid Chair of Pathology at the University of St. Andrews, David is also an honorary chair at the University of Edinburgh. His clinical expertise is in medical liver, kidney and transplant pathology and, as such, he serves as the designated individual for tissue governance for National Health Service (NHS) Lothian and contributes to the diagnostic service of the Scottish National Liver Transplant Program. He's also director of laboratory medicine for NHS Lothian and of the Edinburgh Breakthrough Breast Cancer Research Unit. Though David's research interests are varied, they all revolve around understanding the ways in which cells and tissues respond to injury through molecular pathology and genetic regulation. He is chair of Medical Research Scotland and deputy chair of the Food Standards Agency Committee on Toxicity, as well as a member of a wide variety of professional organizations. He holds an honorary professorship in medicinal chemistry at the University of Florida.

17 Simon Herrington

A professor of cancer pathology at the University of Dundee's Medical School, Simon is also clinical lead for the Tayside Tissue Bank, co-director of the Division of Cancer Research in the Medical Research Institute, and lead for the Dundee Cancer Center. He's held leadership roles in organizations including the International Society of Gynecological Pathology (of which he's been both president and vice-president), the Pathological Society of Great Britain and Ireland, and the Association for International Cancer Research. His research deals with the pathogenesis of anogenital epithelial neoplasia, hoping to increase understanding of the mechanisms involved and improve disease diagnosis. To accomplish this, he studies the role of human papillomavirus (HPV) infection in epithelial neoplasia and the non-HPV-dependent pathway to vulvar intraepithelial neoplasia development. In addition to his work on pathogenesis, he collaborates with the School of Physics and Astronomy at the University of St. Andrews to develop imaging technology that can discriminate between normal and neoplastic tissues.

16 David Bruns

"I chose laboratory medicine because it provides great opportunities to do both research and clinical service," says David. He's currently a professor of pathology, director of clinical chemistry, associate director of molecular diagnostics, and founding co-director of the Fellowship in Clinical Chemistry and Laboratory Medicine at the University of Virginia School of Medicine. His research centers on quality requirements and harmonization for medical tests, fields in which he's authored over 170 peer-reviewed papers, given more than 130 invited talks, and won numerous awards. A past president of the Academy of Clinical Laboratory Physicians and Scientists and of the Association of Clinical Scientists, he has also served on the board of directors of the American Association for Clinical Chemistry and as chair of the ethics task force of the International Federation of Clinical Chemistry. He says, "Laboratory medicine provides satisfaction in proportion to personal effort and dedication, but each success reflects the input of many people."

15 Emanuel Rubin

Emanuel, currently Gonzalo E. Aponte distinguished Professor of Pathology, Anatomy and Cell Biology at Thomas Jefferson University, is also chairman emeritus of his department and an attending pathologist and senior autopsy consultant at Thomas Jefferson University Hospital. He's a well-recognized and much-honored pathologist, having won the F.K. Mostofi Distinguished Service Award of the United States and Canadian Academy of Pathology, the Tom Kent Award for Excellence in Pathology Education, a Lifetime Scientific Achievement Award from the Sbarro Health Research Organization, a Distinguished Service Award from the Association of Pathology Chairs, a Gold Medal Award from the International Academy of Pathology, and a Gold-Headed Cane Award from the American Society of Investigative Pathology. But he's also recognized for other achievements – in 1989, he won the American Medical Writer's Association Award for best medical textbook of the year and now serves on the editorial boards of a wide range of medical journals.

14 Maurizio Ferrari

As president of the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC), Maurizio is dedicated to molecular techniques. Over his career, he's developed new methods for DNA analysis that take advantage of multiplex PCR, capillary electrophoresis, ligase chain reaction and gradient technologies. His own research interests involve nucleic acids circulating in maternal plasma, molecular diagnostics, and molecular studies of genetic pathologies; he hopes that detecting fetal DNA in maternal plasma will allow noninvasive prenatal diagnosis, as well as having applications in genetics and oncology. At the moment, as a professor of clinical pathology at the Università Vita-Salute San Raffaele, he is using next-generation sequencing to develop new diagnostic tests. In addition to his role in the IFCC, Maurizio is also president of the European Society of Predictive Medicine and leader of the Clinical Molecular Laboratory and the Genomic Unit for the Diagnosis of Human Pathologies in the Division of Genetics and Cell Biology at IRCCS San Raffaele Pisana.

13 Peter Ward

A pathologist for over 50 years, Peter's focus of study is the acute inflammatory response – how it's initiated, how it progresses, and its outcomes. This interest began in his early years as a pathologist, when he discovered during a postdoctoral fellowship that a fragment of complement component 5 is chemotactic for neutrophils, and has continued to this day as he attempts to identify tissue-damaging inflammatory products. According to a nominator, "his work in the field of sepsis and innate immunity has transformed scientists' understanding of the disorder and the working of the immune system." Peter spent two years serving as chief of the Immunology Branch of the Armed Forces Institute of Pathology before chairing the Department of Pathology at the University of Connecticut Health Center for nine years and at the University of Michigan for 25. He is now Godfrey D. Stobbe Professor of Pathology at the University of Michigan School of Medicine.

12 Harald Stein

Harald's career is marked by an impressive series of findings, including three new types of lymphoma (anaplastic large cell lymphoma, plasmablastic lymphoma, and nodular B cell-rich classical Hodgkin lymphoma), the cellular proliferation marker protein Ki-67, the derivation of histiocytic lymphomas from B cells, and the identification of CD30 as the most characteristic cytokine receptor of Hodgkin lymphoma. He also contributed to the discovery that the dysplastic cells of Hodgkin disease are monoclonal expansions of B cells. Harald's prizes and honors include the Carlo Erber Award in 1982, the German Cancer Prize in 1998, the Johann Georg Zimmermann Medal in 2005, and the German Cancer Aid Award in 2009. He also co-founded the International Lymphoma Study Group, which generated the World Health Organization lymphoma classification. An emeritus professor of the Charité University Medicine Berlin, Harald is chairman of the Berlin Reference Center for Lymphoma and Hematopathology and director of the Institute for Pathodiagnostik Berlin.

11 Juan Rosai

A pathologist who wears many hats, Juan is currently director of the International Center for Oncologic Pathology Consultations at the Centro Diagnostico Italiano in Milan, visiting professor at Harvard University and Massachusetts General Hospital, adjunct professor at Cornell University's Weill Medical College, and senior consulting pathologist at LabCorp. His motivation comes from "the opportunity to ask important mechanistic questions on the basis of microscopic imaging, and the attempt to answer them in collaboration with colleagues by using the new wave of sophisticated molecular, genetic and computational tools." His well-respected career in pathology spans over 50 years, during which time he has characterized novel medical conditions including Rosai-Dorfman disease, a type of histiocytosis, and the rare cancer desmoplastic small-round-cell tumor. Juan feels that ahead of pathologies lies "the most exciting phase of its brilliant evolution, progressing from humoral to anatomic, and from there to microscopic, ultrastructural, immunohistochemical, genetic, epigenetic, molecular, computational, and who knows what else?".

10 Graham Beastall

Graham is immediate past president of the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) and has recently served as professional advisor to Health Education England and the Academy of Healthcare Science in implementing higher specialist scientific training in pathology and laboratory medicine. He's also held numerous representative roles, including chair of the UK NEQAS Steering Committee for Clinical Chemistry, chair and president of the Association for Clinical Biochemistry, vice chair of Medical Research Scotland, vice president of the Royal College of Pathologists, secretary of the European Communities Confederation of Clinical Chemistry and Laboratory Medicine, and board member of Clinical Pathology Accreditation (UK) Ltd. He says his overriding motivation is "to work with others to improve the quality and appropriate use of pathology and laboratory medicine in order to achieve better clinical outcomes for patients," and thinks pathology's bright future relies on "those in the profession showing leadership at local, national and international level."

9 Andrew Hattersley

Lauded for his medical, research and educational contributions to clinical science, Andrew is a consultant physician and professor of molecular medicine at the University of Exeter Medical School in the UK. It was Andrew's work as a training fellow at Oxford that identified glucokinase as the first known genetic cause of diabetes and piqued his interest. In his 20 years at Exeter, he has taken the university from one without a genetics lab to one hosting the premier international research center for monogenic diabetes – where he now leads a 29-person team that integrates research, diagnostics and patient care. Just over 10 years ago, he discovered that many patients formerly diagnosed with diabetes were not incapable of producing insulin, but rather possessed a potassium channel gene defect that prevented their pancreatic beta cells from responding to increases in blood sugar. Shortly thereafter, he demonstrated that sulfonylurea drugs produce excellent glycemic control in these patients – who, thanks to his work, no longer require insulin treatment.

8 Ian Ellis

Having spent 35 years practicing pathology, Ian Ellis is internationally renowned for his work in clinical and translational research in breast disease – particularly in its classification, molecular pathology, and prognostic factors. He has over 500 peer-reviewed publications and has served as president of the Pathological Society of Great Britain and Ireland and chairman of the UK National Coordinating Committee for Breast Pathology. He's also been a specialty advisor to the Royal College of Pathologists, the World Health Organization, the UK Department of Health, the Union for International Cancer Control, and the International Agency for Research on Cancer. In addition, he has founded a specialist laboratory service, PathLore, and serves as medical director of Source Bioscience plc. "I hope that histopathology embraces the emerging areas of molecular pathology and patient focused precision medicine going forward," he says. "Histopathologists are best placed to handle the range of emerging assays required for therapeutic management of patients in a single coordinated, integrated report."

7 Suzy Lishman

Suzy is a histopathologist and president of the UK's Royal College of Pathologists. In Peterborough, she leads the cellular pathology department and has a particular interest in colorectal pathology and cancer screening. As president of the College, she provides leadership for pathologists and scientists internationally. She passionately represents the views of members, working closely with other specialist societies, and forging links with parliamentarians and other policy makers to ensure that pathology is considered in health-related discussions. She can still be found performing virtual autopsies and talking to school groups in between presidential duties. Her public engagement work has led to some amusing situations, including "being filmed for television demonstrating the effect of wearing a tight corset on a male model at Griff Rhys Jones' London home, performing a virtual brain autopsy at Latitude Festival (complete with blancmange brain), and being interviewed by actor Larry Lamb about the pathology faced by soldiers in WWI trenches."

6 Fred Bosman

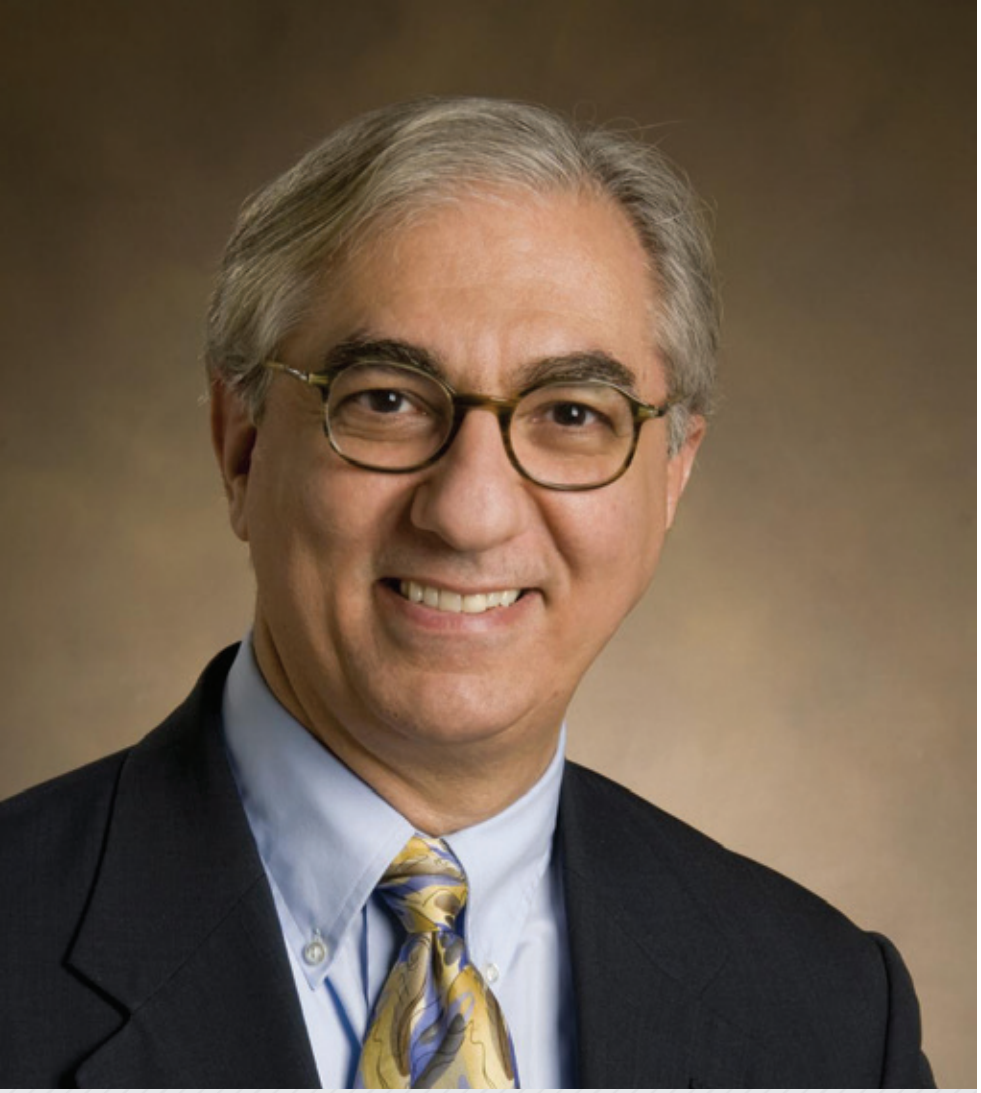
Asked for his advice to young pathologists, Fred – whose career in gastrointestinal pathology spans 40 years – says, "Be happy that you chose a very dynamic discipline in modern medicine. Realize that pathology is 'understanding disease,' and only through this understanding can optimal diagnostic support be provided and tomorrow's medicine developed." Now emeritus, his most recent position was as professor and director of the University Institute of Pathology at the University Medical Center of Lausanne. He's also been the president of the Society for Histochemistry, the Dutch Society for Pathology and the European Society of Pathology, and is honorary fellow of the Royal College of Pathologists and foreign correspondent of the Royal Netherlands Academy of Sciences. After publishing over 350 papers and 50 book chapters, Fred continues to sit on the editorial boards of numerous international journals in his field, edit textbooks, and advocate for more integration of the various disciplines that make up laboratory medicine.

5 George Kontogeorgos

After nearly 40 years in pathology, George says that the most important lesson he's learned is "to keep in mind that behind every glass slide is a human being I have to treat with respect." George has headed the Department of Pathology at "G. Gennimatas" General Hospital of Athens for more than 20 years, as well as acting as a research associate in the Laboratory of Histology and Department of Pathophysiology at the University of Athens, and as a visiting professor at the University of Toronto. He's also president-elect of the International Academy of Pathology, recipient of the George Papanicolaou Prize in 1992, and recipient of the George Papanicolaou Award in 2008. During his career, he has published 160 papers, 300 abstracts, and 14 book chapters. His research interests are in endocrine, molecular and neuropathology, and his motivation comes from a desire to "prove the pathos-/logos- (reason of suffering) by making the correct diagnosis and contributing to the appropriate therapy."

4 James Westgard

Described as "one of the most recognized experts in laboratory quality assurance and quality control in the world," Jim is professor emeritus in the Department of Pathology and Laboratory Medicine at the University of Wisconsin School of Medicine and Public Health. He is co-founder and principal at Westgard QC, Inc., which provides laboratories with technology and training for quality management. Initially interested in method evaluation protocols, he served as the first chairman of the Evaluation Protocols Area Committee of the Clinical and Laboratory Standards Institute. During a sabbatical at Uppsala University, Jim grew interested in quality control and began development work on the multi-rule control procedure now known as "Westgard Rules." He continues to work with the University of Wisconsin as a teacher in the Clinical Laboratory Science Program and co-director of an online graduate certificate program in laboratory quality management. He also conducts research into quantitative techniques for analytical quality management.



3 Michael Laposata

Michael is the current chairman of the Department of Pathology at the University of Texas Medical Branch at Galveston. His clinical focus is on blood coagulation, with a particular expertise in the diagnosis of bleeding disorders and hypercoagulable states. Between this and his research into fatty acid metabolism, he has authored over 170 publications and continues to lead research grants. In order to improve the diagnosis of disordered coagulation, Michael developed an innovative method of systematically interpreting clinical laboratory data. This method, which requires a physician with specific expertise to interpret the data and write a patient-specific narrative paragraph, is intended to allow clinicians to better synthesize and understand the results of complex diagnostic testing and has also led to Michael's recognition in 2005 by the Institute of Quality in Laboratory Medicine of the Centers for Disease Control and Prevention. A dedicated advocate for pathology education, Michael's goal is "to create better pathologists" – a task he accomplishes not only through his own mentoring of research students and postdoctoral fellows, many of whom are now leaders in their own fields, but also by establishing and maintaining programs like the American Society for Clinical Pathology (ASCP)'s Resident Review Course. For his contributions, he has received many teaching awards, including an Award for Outstanding Contributions in Education from the American Association for Clinical Chemistry in 2009 and the American Society for Clinical Pathology's H.P. Smith Award for Distinguished Pathology Educator in 2012.

2 Michael Wells

"I am motivated to strive for excellence in my specialty, gynecological pathology, for the benefit of the patients we serve," says Mike. Now an emeritus professor, he recently retired as professor of gynecological pathology at the University of Sheffield in the UK and honorary consultant histopathologist at Sheffield Teaching Hospitals NHS Foundation Trust. He holds a Platinum National Health Service Clinical Excellence Award and maintains a part-time histopathology consultancy at Leeds Teaching Hospitals NHS Trust. He has written and contributed to numerous textbooks, acts as the editor of the journal Histopathology and is on the editorial boards of Virchows Archiv, Gynecologic Oncology and the International Journal of Gynecological Pathology. Mike also holds numerous positions in professional associations – including as a director of the International Collaboration on Cancer Reporting and as a member of the European Society of Pathology, the Gynecological Visiting Society of Great Britain and Ireland, and the Education Committee of the International Academy of Pathology. His former positions include presidencies in the British Division of the International Academy of Pathology, the British Gynecological Cancer Society, the International Society of Gynecological Pathologists, and the European Society of Pathology, among many other leadership roles. But despite his many titles, Mike says, "The highlight of my career was being made a Fellow of the Royal College of Obstetricians and Gynecologists. The professional recognition of my clinical colleagues means a lot to me."

1 Manuel Sobrinho-Simões

Manuel has been a pathologist for over 40 years – and has not once in those years suffered from idle hands. After completing a medical degree (and simultaneously becoming ping-pong champion) at the University of Porto, he continued on to a doctoral degree with a focus on cancer of the thyroid. After traveling for postdoctoral research, he returned to the University of Porto in 1980. Less than 10 years later, he founded IPATIMUP, the Institute of Molecular Pathology and Immunology of the University of Porto. The institute, which he still leads, is dedicated not only to research and diagnosis, but also to training pathologists and educating the general public on scientific subjects. Nominators referred to him as an "educator par excellence" and "an enthusiastic teacher who is always ready to share what he knows." In the course of his career, Manuel has won many national and international awards, including the 1996 Bordalo Prize, the 2002 Seiva Prize, and the 2002 Pessoa Prize. In 2004, he was awarded the Grand Cross of the Order of Prince Henry for services to Portugal, and in 2009, he became a Commander of the Royal Norwegian Order of Merit for outstanding service in the interests of Norway. He's also held leadership positions in professional organizations including the European Society of Pathology and the European School of Pathology, authored hundreds of publications including peer-reviewed journal articles, chapters and books, and enjoys spending free time with his family.

Nominators said:

"He has contributed more than anybody else to the visibility of pathology in Europe."

"A supporter of young pathologists from all over Europe."

"He represents the perfect combination of scientific intelligence and nobility."

"He is not only a great scientist but also a kind, caring, generous and charismatic person."

"His contributions to the clinical diagnosis of thyroid cancer have been outstanding: hospital pathologists worldwide follow his rules in their day-to-day routines."

"A prominent scientist from a small country with few resources, founding a prominent institution that makes a difference, without leaving his country of origin."

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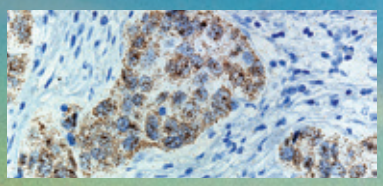

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Piloting Progress

Early cancer diagnosis could save 11,000 lives in the UK every year – and a new digital pathology pilot program is exploring ways to turn that potential into reality

By Chris Scarisbrick

The UK's Independent Cancer Taskforce has a radical new goal: to allow an additional 30,000 patients every year to become 10-year survivors of cancer by 2020 (1). That's no small number – it's nearly 10 percent of all cancers diagnosed in the UK, or nearly one-fifth of all UK cancer deaths (2). But it's not an impossible goal; in fact, we could achieve more than one-third of it – 11,000 patients – by simply diagnosing them sooner. It seems clear that early diagnosis is an area worthy of more attention, and new plans to take action against cancer have sparked a national ambition to spot and stop the disease as early as possible.

At a Glance

- *The UK aims to increase 10-year cancer survival by 30,000 patients a year – and digital pathology has a large part to play*
- *A pilot program at Salford Royal NHS Foundation Trust is exploring the intricacies of transitioning from traditional to digital pathology*
- *So far, pathologists in the program are enthusiastic about the increased efficiency, convenience and potential for communication and consultation*
- *Organizational and financial challenges are preventing widespread implementation of digital systems, but there are ways that these can, and should, be overcome*

Backed by National Health Service (NHS) England chief Simon Stevens, the taskforce's plans call for significantly increased diagnostic capacity in the NHS. The aim is for 95 percent of patients to receive their results within four weeks, and to provide general practitioners with direct access to key investigative tests. But numbers alone will not be enough to deliver the increased diagnostic capability needed to make these ambitions reality. And when it comes to pathology – a key player in cancer diagnosis – many of the processes and practices in the NHS remain largely unchanged since the birth of modern pathology in the 19th century. The discipline has also been facing diminishing capacity and now battles with the serious challenge of attracting younger people, many of whom don't relish the idea of decades at a microscope. So how can the NHS deliver the diagnostics needed to make it a reality?

A move toward modernization

The first step into modernizing pathology is a big one – we need significant and immediate action to provide pathology departments with the technology that more and more pathologists want. The attraction of sharing expertise and findings with clinical colleagues, no longer needing to handle (or fear losing) hundreds of slides, and rapid reporting is clear. And all of this is achievable with digitization, a move that's already having an impact on improved diagnoses and timely cancer care in other parts of the world. Put simply, the microscope can no longer be a pathologist's only tool if a health service wants to increase its lifesaving abilities by tens of thousands of lives every year.

The good news is that pioneering parts of the NHS are already changing the status quo. Salford Royal NHS Foundation Trust has become a pioneer in the north of England by piloting a digital pathology system that has shown immediate benefits for speedy and connected pathology reporting. In this pilot program, the trust chose neuropathology for digitization due to the pathologists' familiarity with digital images – and it seems to have paid off. Despite initial hesitations, the pathologists became very enthusiastic very quickly, declaring the system intuitive and easy to use. Though they still had microscopes, they rapidly moved to a primarily digital method of reporting and now insist that they don't want to go back to their old systems. They're pleased to be able to compare multiple slides at once on the same screen, with extremely high standards of image quality. They're noticing the ability to report much more quickly and effectively, no longer having to keep manually changing slides. And, crucially, reception in multidisciplinary team meetings has been very strong; images and specific areas of samples can be shown quickly on screen, eliminating the time-consuming processes of preparing and loading slides to share with clinical colleagues. Thanks to these simplified processes, turnaround times have decreased considerably with the introduction of digital imaging.

Salford Royal's pathologists have noticed less tangible benefits, too. "You feel more in command of the case," explained Daniel du Plessis, a consultant neuropathologist and clinical lead in the department. He highlights the ability of an efficient system to help him maintain focus and momentum, and adds that the system's ease of use offered an incentive to tackle even non-urgent cases quickly. He and his colleagues all report different benefits of their new methods – comparing multiple stains on a single screen, rapid access to archived images, easier communication with other specialists, better teaching and training – and they're not the only ones interested. The results of the digital pilot have intrigued pathologists and clinical staff both within the trust and at other hospitals

throughout the region and beyond. A conference held at Salford Royal this year showed a huge appetite for digitization from pathologists who turned a question-and-answer session into a passionate open discussion on regional collaboration, the potential for "super-labs," and ways to make digitization into a reality.

Lessons from radiology

As a former NHS radiographer, I have seen the clinical benefits of digitization firsthand. Radiology embarked on the digital journey 15 years ago to eliminate the loss of X-rays in the backs of people's cars and from the drawers of their desks. At the time, 10 to 15 percent of all images were being mislaid – and you can imagine the impact it had on timely care. Digitizing radiology solved that problem, but the transformation was much broader than that. Hopefully, as a closely related diagnostic discipline, pathology will fare even better as it builds on the technologies already deployed in many hospital radiology departments and learns from what was done in its fellow diagnostic discipline only a decade or two ago.

But when transitioning to digital imaging, radiology had one luxury pathology lacks – central funding. Now, each hospital must find its own way to fund digitization. It isn't be easy at a time when NHS purse strings are held more tightly than ever, but there are options: large trusts with control over their own budgets can procure pathology solutions and sell them to other hospitals to generate revenue, while hospitals in smaller trusts can collaborate to buy a shared system.

Whether large or small, the challenges of moving to a digital workflow aren't coming from pathologists, many of whom would like to make the transition sooner, rather than later. There's a real hunger to shift to digital, which we've seen with the Salford Royal pilot program. Clinicians and radiologists in the north of England are eagerly watching what Salford is doing. The only dissatisfaction seems to be impatience: the pathologists who are already using digital systems want to see them everywhere. "If we had this system pan-Manchester, it would revolutionize pathology," said Anne Yates, the cellular pathology services manager at Salford Royal. It would prevent having to package and send slides from one hospital to another when a patient needs specialized care only available in certain locations. In discussing the potential for a digital neuropathology network, du Plessis echoes Yates' sentiments. "It would be wonderful to have this system, which has much better quality images, which is much easier to navigate, to provide intraoperative smear cover or to share cases immediately," he said. "This would allow us to do what we do far more efficiently."

So what's holding up digital implementation across the board? The challenges are at the organizational level, not in the clinic. But with an opportunity for cancer outcomes on the NHS to match those of the countries with the highest survival rates, organizational differences simply aren't a good enough reason not to proceed. In my opinion, the NHS should now prioritize enabling its hospitals to move away from analog approaches to pathology. Only by digitizing can we match growing demand, increase access to specialist expertise, and improve the speed and accuracy of reporting. And when we do those things, we achieve the kind of timely intervention that can save lives.

Chris Scarisbrick is National Sales Manager at Sectra.

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Making the Move to 100 Percent Digital

LabPON is the first laboratory in the world to fully digitize its histopathology services – but how did they approach it? And has it paid off?

By Alexi Baidoshvili

Digital pathology has been grabbing headlines lately as more and more labs explore its possibilities. It's shown its merits for long-distance work, teaching and training, and expanding the capacity of overworked labs in need of time-saving techniques. But how far does the digital revolution go? At the Laboratory for Pathology East Netherlands (LabPON), we have taken a bold step into a computer-driven future – transitioning all of our manual diagnoses to digital.

As the largest pathology laboratory in our country, LabPON consults on more than 55,000 histological cases each year – over 300,000 slides of human tissue. We currently employ 17 pathologists and a total of 115 staff, but even that isn't enough. There's likely to be a steep increase in future demand for our services, driven by the aging population and new screening programs, so we concluded that we needed a further increase in efficiency that still allowed us to maintain quality. It was our laboratory's participation in a digital network project in 2009 that yielded the answer – after trialing it, we decided to transition all of our manual diagnoses to digital. We are now the first laboratory in the world to completely digitize its histopathology diagnostic processes.

At a Glance

- *LabPON was prompted to move away from manual histopathology after participating in a digital network project in 2009*
- *Digital pathology has four key benefits: efficient workflows, connected teams, increased safety and new insights from analyzing large datasets*
- *The move required a lot of planning, considering everything from adjustment periods to ergonomics, but the results have paid off*
- *The lab hopes to set an example of improved networking and patient care with its new processes, and assist others in making the same move*

Taking the first step

Our initial vision was that digitization would improve the logistics of remote consultations and case revisions, but we began to realize even more benefits the more we used it. The impetus to move away from manual was strong for us; traditional pathology workflows have innate delays built into their processes. For example, transferring glass slides runs the risk of loss, and when collaborating with others – whether with specialists for second opinions, or with other sites – takes time, which delays how quickly a diagnosis can be made and a patient's treatment can begin. Digitizing images that are normally viewed through a microscope can minimize these delays and improve the operational efficiency of a lab. Pathologists can then directly access image files and view the same case at the same time irrespective of whether it is an internal and external consult – making diagnosis simpler, safer and more efficient.

In my opinion, digital pathology has some key benefits:

- Digitized workflows increase organization, streamline processes and reduce turnaround time;
- Connected teams enable remote communication and collaboration across sites and specialties;
- Increased safety results from a reduction in diagnostic errors caused by mistakes in material handling; and
- New insights come from analyzing large sets of clinical data.

It's clear that digital analysis can improve a lab's performance – but how does a major transition like that begin? Before our team at LabPON began the process of implementing digital technology solutions, we first had to formulate a business vision. We needed to establish a long-term strategy, create a staged timeline that would allow measurable results and validation of the transition, and justify such a significant investment. Most of all, we had to consider just how different our new way of working would be. We weren't just replacing our existing equipment to make the shift – we had to adopt a completely new workflow throughout the lab, which meant that we had to make sure every member of our team was on board.

The journey to 100 percent

Approaching the transition in phases allowed us to make adjustments to workflows and processes "on the fly." For example, in 2012, we gave our pathologists the option of working digitally as well as with their microscopes. Knowing that we would eventually be fully digitized, this let each person incorporate it into their daily routines at their own pace. At LabPON, adoption generally took between three and eight months. For our pathologists, the most difficult part of the transition was learning to trust the digital image. Once they realized that the image on the screen was still just as valuable – if not more so – than what they could see through the microscope, acceptance was quick.

Of course, they also took some time to adapt their logistics and work processes. Each pathologist has a different organizational and workplace style, and some were easier to adapt than others. For other labs seeking to follow in our footsteps, it's important to understand that – although there was some delay in performing diagnoses during the transition – once our pathologists got used to the new system, throughput time of diagnosis actually accelerated. There are always a few bumps in the road to any new way of working, but the benefits of digitization have far outweighed those hiccups.

Speeding up services

Before we implemented digital pathology throughout our laboratory, we had to study its impact on workflow and turnaround time. It's not always obvious, and microscopy is a good example of this. Although an experienced pathologist was able to establish a diagnosis just as quickly using either manual or digital methods, digital diagnostics are faster overall when the entire logistical process is taken into consideration. The instant accessibility of previous cases, the ability to view slides side-by-side with different stains, measurements, counting, annotations and the simplification of internal and external consults all contribute to increased speed and quality. And that's only the beginning; we expect that introduction of image analysis software in the future could help our pathologists work even more quickly.

Our laboratory also uses multidisciplinary discussions – where members from diverse teams discuss difficult cases – to improve diagnosis. Our study of digital pathology showed that, at these discussions, switching to digital saved 28 hours of administrative work for the support staff, a financial gain of nearly three-quarters of a full-time administrator's salary. These initial gains have been promising, and we're currently setting up a new flow analysis so that workflow optimization is more readily transparent. Overall, our experiences so far indicate that using digital diagnostics has significantly improved internal logistics, consultations, efficiency and accuracy at LabPON – that ultimately will lead to savings in cost and time.

An education in ergonomics

One factor you might not immediately think about when considering a digital move is the ergonomics of the increased computer usage for pathologists. We found that using keyboard shortcuts and touchpads reduced the risks of repetitive strain injuries from frequent mouse usage. Monitors are another concern – and I would advise that anyone transitioning to a computer-based lab consider a few things:

- Using at least two monitors of the same size prevents eye strain

arising from variation in the size of images, letters, and other visuals.
- In terms of settings (color, brightness and resolution), the monitors should be equivalent and of good quality. This prevents discrepancies in color, contrast and other details that can't be corrected through calibration.
- The necessary monitor size depends on its quality and the viewing distance of the pathologist. Regardless, though, I recommend keeping the monitor size under 24–30 inches, as larger screens can cause excessive neck strain.

Our pathologists were much happier to transition – and benefited much sooner – when they knew that we were careful to ensure their health and wellbeing.

Goal-setting, goal-getting

As our goal was always to go 100 percent digital in terms of histopathology diagnoses, it was important to focus strategically on our expected outcomes. So that everything ran smoothly, we established a clear list of what we'd like to see:

- Full digitization of the work process: we clearly established the areas of transition so that we could step smoothly from analog to digital, rather than being caught in years of combined service – letting us see results sooner.
- All-digital images: the full digitization of our images allowed us to realize the benefits of speedier retrieval, case comparison, specialist consultation and second-opinion acquisition.
- The integration of diagnostics into the oncological treatment chain: this reinforces the position of the pathologist in multidisciplinary discussions and

allows pathologist participation in other clinical discussions.
- Image recognition systems: full digitization in pathology creates the possibility of linking data in the future by means of image recognition, resulting in better diagnostics. Combining this information intelligently with pathology data from past treatments could potentially create better care.

These were only our biggest goals. We also had a list of smaller ones – increased access (even allowing pathologists to work remotely), specialization (allowing cases to be assigned by workload and specialty), improved frozen section services (no longer requiring a pathologist and technician to travel to a particular site or wait during surgery), the potential for regional networks and external services, and the birth of the Pathology Image Exchange (PIE) project. The last item is a collaboration between The Netherlands Society for Pathology, the PALGA Foundation, the national database where all pathological results are stored and the network for data exchange with all pathological anatomical laboratories in the Netherlands. Their goal is to set up a working group to develop a national platform for image sharing, and we hope to be a significant part of that.

Admittedly, transitioning an entire workflow to a digital process is a complex endeavor. At LabPON, we had no roadmap for an ideal implementation of digital pathology, and there's been a lot of learning and development. As we overcame teething problems and discovered new challenges, it sometimes felt like we were taking two steps forward and one back. But in the end, making digital pathology a reality at LabPON was inspired by vision, rather than short-term ROI factors – so we kept going, and ultimately, we made it. Our digital laboratory is a source of great pride to us, because it strengthens our commitment to ensuring that our patients and clinical colleagues receive the fastest, most effective and best-informed diagnoses possible.

Alexi Baidoshvili is a pathologist and project director of the digital pathology team at LabPON, The Netherlands.

Improving Workflow with Thermo Gemini AS Autostainer & ClearVue Coverslipper

Cheltenham General Hospital is part of one of the largest NHS Foundation Trusts in the UK. The pathology laboratory faces constant pressure to meet turnaround times while reducing costs, and central to that is their need for reliable staining and coverslipping.

In 2014 they dealt with over 42,000 new cases, and almost 143,000 H&E stains. When they needed additional capacity, Cheltenham looked at the available options for their staining and coverslipping. Initially, they had a combined unit at the top of their "ideal" list. However a trial of such a system gave disappointing results, and they found that they just didn't get on with it at all. A number of instruments were trialled and after performing favourably and being on the NHS preferred supplier framework, Thermo Scientific's Gemini AS autostainer and Clearvue coverslipper were selected. The Gemini features five heaters, 26 reagent pots and intelligent software to maximize throughput even with multiple racks and protocols. The ClearVue coverslipper can manage up to 11 slide racks simultaneously, and can automatically handle both histology and cytology slides.

After installing these instruments, the Cheltenham staff soon found that their workflow was optimized far better than they thought possible. As the Deputy Lab Manager explains, "the bottleneck is now at the end of the workflow, needing staff to sort and label the slides. With Gemini you can have 12 racks on the go and you know every single rack is going to take the same amount of time."

While laboratory throughput typically remains at a consistent level, issues such as staffing shortages can often lead to backlogs building up. In January this year, the Gemini and ClearVue certainly proved their worth. As the Deputy Lab Manager again explains, "We had nine people cutting all day, every day for 2 weeks to clear the backlog, and it all went through the Gemini. We were processing over 2,000 slides per day with no problem at all. We were running out of racks because it was going through so fast! Having the Gemini and ClearVue now, I wouldn't specify a combined unit."

In line with all NHS trusts, the Cheltenham General Hospital is under pressure to meet targets for sample turnaround and optimized patient care. In fact they now meet the required throughput time for 100 percent of biopsies. The Gemini enables them to rush any urgent samples through quickly, and automatically prioritizes such samples for fastest turnaround. The Deputy Manager again explains, "Before, there would be another day's delay queuing for the staining machine. Families and lives are on the end of it, and we certainly couldn't have achieved that before having the Gemini."

With future plans including bringing vital HER2 testing in-house, Cheltenham's workload is only going to increase. After the success of Gemini, the Deputy Lab Manager concluded, "We'd have no problem in just going for another Gemini. We'd really struggle without it now."

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The (True) Value of Laboratory Medicine

Laboratory medicine is often misquoted as having a role in 70 percent of clinical decisions – but how can we measure the true value, and more importantly, how can we improve it?

By Mike Hallworth

As lab medicine professionals, we are fully aware of the unquestionable importance of our profession. In the UK alone, every citizen has an average of 14 tests per year performed by a laboratory medicine specialist (1). Department heads increasingly rate quality care and value-for-money as key priorities, so a recognition of the value of lab medicine is of crucial importance, especially when it comes to ensuring appropriate allocation of resources. But is laboratory medicine falling at the last hurdle when it comes to providing improved benefits for patients? The International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) task force on the impact of laboratory medicine on clinical management and outcomes was set up in 2012 to settle this very problem, to evaluate the evidence supporting the impact of laboratory medicine, and to promote contributions from the field (2).

At a Glance

- *The common claim that laboratory medicine has a role in 70 percent of clinical decisions may not be as accurate as many believe*
- *The IFCC task force, which evaluates the evidence supporting laboratory medicine's role in healthcare, has devised principles for establishing the value of individual tests*
- *Inaccurate results are cause for concern, but factors like not receiving test results on time can cause even more harm*
- *Outcome studies are needed to better evaluate the benefits of new and existing tests*

The misleading 70 percent claim

No doubt you will have heard the frequently cited claim that laboratory medicine plays a role in 70 percent of clinical decisions. That assertion sounds plausible, but the data on which the claim is based represent unpublished studies and anecdotal observations, and cannot be objectively verified at this stage (3). So where did it come from?

The earliest reference to the claim can be found in a 1996 paper from the Mayo Clinic in the US, where the author stated, "We know that, although the laboratory represents a small percentage of medical center costs, it leverages 60–70 percent of all critical decisions, e.g. admission, discharge and therapy " (4). But even that paper failed to provide evidence for its statement. In the 19 years since the paper was published, in true Chinese whispers style, the statement has been taken and extrapolated upon, from 70 percent of critical medical decisions to 70 percent of all medical decisions (3).

A similar claim that 70 percent of all electronic medical records consist of laboratory data is also a likely contributor to the confusion (3). But this figure is completely separate from the medical decisions claim, and – unlike that claim – is backed by published papers, although the precise percentage varies between articles. It's important not to confuse the two statements, because the amount of data in the record is a poor proxy for the importance of that data in the care of an individual. Rather than paying attention to the volume of information we gather, we should be focusing on what that information means to the life and health of our patients. This is consistent with the global shift from volume to value in healthcare provision.

A number of major organizations have seemingly fallen into the "70 percent" trap, including the UK Department of Health. A report from the House of Commons Select Committee on Health in 2002 stated "up to 70 percent of all diagnoses in NHS patients depend on laboratory tests, hence NHS pathology services are critical for the day-to-day evidence-based care of patients." Although the idea behind that statement is certainly true, the 70 percent claim was unsupported by evidence in that report, and appears increasingly unlikely when you consider mental health and all the minor diagnoses made in primary healthcare. I would hazard a guess that, even from such a reliable source, the claim probably represents an unintentional misquotation of the Mayo Clinic study.

Measuring and improving the value

Use of the various "70 percent claims" should be resisted in favor of more specific and evidence-based indices of added value that require a better understanding of the mechanisms by which value is added or reduced. But how do we measure these values, and more importantly, how do we improve them?

Outcomes, which are defined as the results of medical interventions in terms of health or costs, provide the only real measure of clinical impact but are often overlooked in favor of prognostic accuracy studies. These accuracy studies ask simple questions centered on the diagnostic sensitivity and specificity of a test: "Does this test predict an outcome of interest?" Outcome studies go the extra step, accepting that a test might predict an outcome, but going on to

question whether or not the application of the test in practice will make a real difference to patients.

The model proposed by the IFCC task force for measuring the net clinical value of a test involves balancing the benefits that a test delivers against any harm it may cause. For the model to work and to increase the value of a test, it's important to first accept that testing can sometimes cause harm. In general, that harm stems from one of five possible sources, originally described by Epner et al. (5):

- An inappropriate test may be ordered
- The appropriate test may not be ordered
- The appropriate test result may not be used properly
- The appropriate test result may be delayed or missed
- The appropriate test result may be wrong or inaccurate.

An incorrect result, the area that receives most of our attention, is also the area with the lowest cause of diagnostic error – primarily because we in the lab have spent so much time focusing on this aspect (2). Now's the time we need to get serious about some of the other factors.

	UK	FR	AUS	US	CA	NOR
Overall rank	1	9	4	11	10	7
Safe care rank	1	2	3	7	10	11
Delayed abnormal results	4%	3%	7%	10%	11%	10%
Incorrect diagnostic tests	2%	3%	4%	5%	5%	4%

Table 1. The healthcare quality rankings of six countries as determined by the Commonwealth Fund (7). The incidence (as a percentage) of problems caused by delayed and incorrect results are shown, along with "safe care" rankings for each country.

Clinicians need our help

It's clear to everyone who works in laboratories that, unless we help them, clinicians use lab tests badly. No matter how good a lab test is, if it isn't used properly, it will never contribute to improved outcomes. One study questioning family physicians in the United States found that physicians order tests in 30 percent of all patient encounters. In almost 15 percent of these cases, physicians admitted to not completely understanding what tests they were ordering. An additional 8 percent admitted to being confused by the results that came back (6). The sheer volume of tests available and the rapid rate of increase means that physicians cannot be expected to understand optimal testing strategies for all conditions. They need help out there.

The next area that we need to tackle is the fact that, when doctors get appropriate test results, they don't always use them correctly. This could occur for a number of reasons; for instance, the recipient may simply not understand the significance of the test, or the results may be misleading, either generally or in specific circumstances. Falsely labeling normal results as abnormal can confuse physicians and lead to severe effects on patients. Such errors can result from something as simple as variation reference ranges between laboratories, and urgent action is required to improve reference range harmonization.

Perhaps the most avoidable, yet one of the least talked-about issues affecting the value of laboratory medicine is that of correct test results not reaching the right place at the right time. The Commonwealth Fund, an organization dealing with healthcare and healthcare inequality in the United States, examined a range of outcome indicators based on surveys of patients and physicians, and ranked individual countries according to quality of care. Safe care rankings were produced by a range of metrics, including both the frequency of inaccurate test results and issues with getting test results back on time. In every case except France, producing the right result but not delivering it to the right place on time caused twice as much reported harm as an incorrect result (Table 1) (7). It is relevant that, in France, patients are often custodians of their own results.

Lab personnel can work really hard to optimize a method and obtain a completely accurate result, but all of that work can be a complete waste of time if we can't do the simple task of getting the result to where it is needed, when it is needed. How much effort do we put into getting the result right, and how much effort do we put into making sure that someone actually sees it in time and does something about it?

Asking the right questions

Until now, outcome studies for lab medicine have been infrequent because of the challenges involved in linking a diagnostic test to a clinical decision and its possible downstream effects. We're very good at asking whether or not we can trust a test, and at asking whether or not it tells us something we want to know – but we need to go on to ask, "Does this test help?" When developing new tests, we can significantly improve the value of laboratory medicine just by looking beyond how accurate the results are and asking whether the test helps us to make better or quicker diagnostic decisions, or to increase the overall effectiveness of the treatment.

To improve our evaluations of new lab tests, we need to put more emphasis on outcome studies. A good recent example is a paper from the European Group on Tumor Markers (8), wherein they outline tumor biomarker monitoring trials and how they are defined. The panel proposes a four-phase model for biomarker monitoring trials, similar to the one used for new drug investigations. The first and second phases involve characterizing a marker and evaluating its ability to provide a readout on disease status. The third phase looks at the effectiveness of the biomarker by monitoring patient outcomes in randomized trials, whereas the final and most important phase involves post-marketing surveillance to assess the validity of the new marker's benefits. I think a model like that is excellent – but I don't think that it should just apply to tumor markers. I think it could, and should, potentially be applied to any biomarker.

"How much effort do we put into getting the result right, and how much effort do we put into making sure that someone actually sees it in time and does something about it?"

Progress in improving the five factors negatively affecting laboratory medicine is essential if we want to demonstrate and enhance the value of our specialty. To make that progress, we'll need investment from governments and commissioning agencies, and we (and they) will need to place more emphasis on outcome studies. The long-awaited Institute of Medicine report on Improving Diagnosis in Health Care (released September 2015) (9) emphasizes that healthcare organizations should facilitate and support collaboration among pathologists, radiologists, other diagnosticians and treating healthcare professionals to improve diagnostic testing processes (Recommendation 1A of the report). That collaboration will require strong partners in the lab medicine community. That's why, in the future, I hope that laboratory medicine professionals who choose to work in relevant areas will take a leading role in improving patient care – so that together, we can ensure that laboratory medicine is a true clinical specialty, rather than simply a number-generating service. The rewards are better patient care and more job satisfaction for those who work in laboratories – a real win-win situation!

Mike Hallworth is chair of the IFCC Task Force on the Impact of Laboratory Medicine on Clinical Management and Outcomes (TF-ICO). He has recently retired from the post of consultant clinical scientist to the Shrewsbury and Telford Hospital NHS Trust in the United Kingdom.

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Leica Biosystems CEREBRO Automated Sample Tracking

Excerpt from an article by Paul Williams MSc CSc FIBMS, Head Biomedical Scientist Cellular Pathology, East Kent Hospitals University NHS Foundation Trust, UK.

Full article originally published in Hospital Healthcare Europe 2015

East Kent Hospitals University NHS Foundation Trust is one of the UK's largest NHS Hospital Trusts, serving a population of 759,000 comprising five hospital sites. The Cellular Pathology department provides a centralised service for the population of East Kent in the UK, located at the William Harvey Hospital, Ashford.

Prior to CEREBRO specimen tracking technology introduction, we were reliant upon a combination of laboratory information system (LIS)-generated and manual data collection throughout the workflow, which was often incomplete or missing and of unreliable quality, making workflow analysis difficult and often of limited value.

After an initial six-month pilot in 2013 with the Leica Biosystems CEREBRO specimen tracking solution, we fully implemented CEREBRO in the summer of 2014. The CEREBRO pilot had proven it was able to significantly improve patient safety and facilitate the management of the workflow with effective monitoring of each part of the process.

Our experience pre-CEREBRO had found that the majority of errors occur in the preanalytical phase, such as accessioning, grossing, embedding, microtomy and case assembly. Such errors occurred in approximately 0.25 percent of cases. CEREBRO provides a robust system that tracks and verifies the identity of every specimen at every point of the workflow. Six months into the full implementation, the preanalytical mislabelling errors have already reduced to 0.12 percent.

CEREBRO specimen tracking has clear patient safety advantages. The ability to scan a barcode and feel confident that identifiers are being compared and matched throughout the process significantly reducing the need for 'eyeball' checking and the subsequent impact on ensuring the correct specimen is for the correct patient.

In addition to patient safety, CEREBRO offers the ability to monitor quality by attaching a note to an individual specimen, cassette or slide at any step of the process. In East Kent we are developing key quality indicators to monitor processes within the laboratory using the audit trail of notes posted. Using CEREBRO's ability to date and time stamp every part of the process and identify the client and individual user it is possible to record and therefore count per individual the various quality issues identified.

Efficiency is also enhanced by CEREBRO's ability to produce exception reports that can list specimens that are going to breach set turnaround times at different stages of the process.

CEREBRO specimen tracking has provided assurances of enhanced patient safety compared with previous manual systems as well as releasing some efficiency throughout the process flow. This provides a high level of confidence that the slides the pathologists are reporting and requesting extra tests on are for the correct patient.

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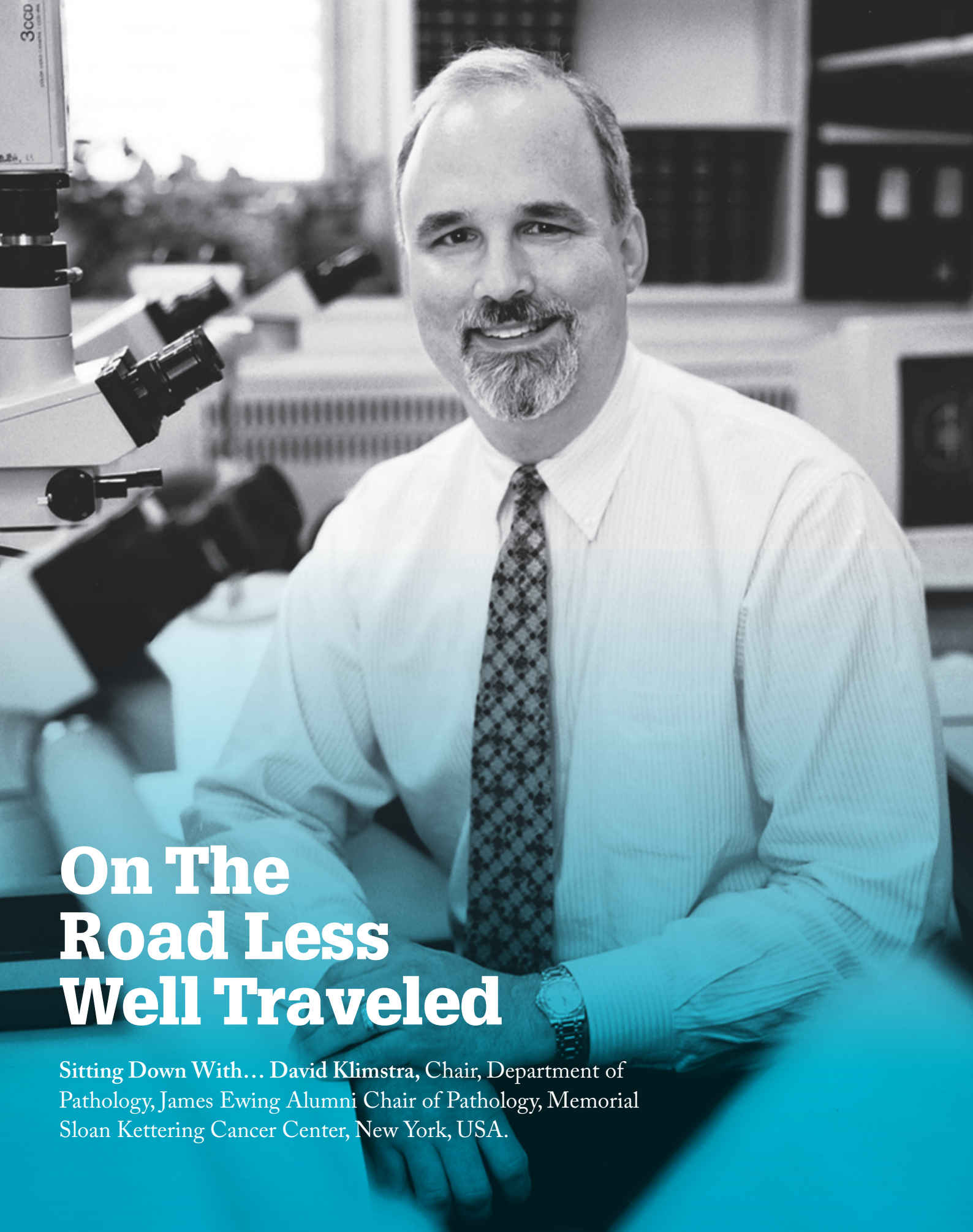

On The Road Less Well Traveled

Sitting Down With… David Klimstra, Chair, Department of Pathology, James Ewing Alumni Chair of Pathology, Memorial Sloan Kettering Cancer Center, New York, USA.

Why did you choose to specialize in GI tract and hepatobiliary (HPB) cancer?

As a resident I encountered a rare case of pancreatic acinar cell carcinoma. It was a challenging diagnosis, and my mentor, Juan Rosai, told me that there were no comprehensive studies on this tumor type, and no immunohistochemical markers available. He suggested that I assemble a series of cases, and arranged for me to review the collection of the US Armed Forces Institute of Pathology. After I completed my study, I realized that there were very few American pathologists studying pancreatic neoplasia – and I decided to make this a focus of my research.

What have been the most groundbreaking advances during your time in the field?

Without a doubt, I would say the advances that we have witnessed in molecular pathology. In particular, in pancreatic and colorectal carcinomas (CRC) – two of the most prevalent cancers in the HPB/GI areas – we have taken a major step forward in understanding their molecular underpinnings. This new information has shown that molecularly distinct subtypes exist within these broad tumor categories, which the heterogeneity of histomorphology we encounter when studying them pathologically predicts.

Survival rates for GI and HPB tumors remain low – why?

In these highly aggressive cancers, we still need a better understanding of precursor lesions, to allow detection before invasive carcinoma develops, and this remains the best chance of a cure. Being able to identify these lesions, and knowing their risk of progression, would allow more effective screening and earlier detection. Despite technical advances though, surgery remains a significant clinical intervention, and only with a thorough understanding of a patient's risk can the best treatment decisions be made. Having said that, a lot of progress has been made in our understanding of the pathologic and molecular features of precursors in the colorectum, pancreas, gallbladder, biliary tree, and stomach, and this has already impacted CRC mortality, but, to date, there have not been similar advances in pancreatic carcinoma.

At the other end of the neoplastic process, our knowledge of how GI and HPB cancers spread and cause death is still lacking. Research has predominantly focused on relatively early stage cancers, but the later stages of these diseases are less well studied. The occurrence of genetic heterogeneity is well-known, and techniques to identify the full range of genomic alterations in advanced disease, as well as the mechanisms of metastasis, will be needed in order to develop and apply targeted therapy.

"Our knowledge of how GI and HPB cancers spread and cause death is still lacking."

Why is funding a problem in GI and HPB cancers?

Some of these cancers are relatively uncommon in the US, and few advocacy groups have been formed to sponsor and support research. I also think there is a level of nihilism about the likelihood of major progress for cancers with a particularly dismal outcome (such as pancreatic cancer). Unfortunately, many creative ideas remain unexploited, especially now that federal research funding has become particularly challenging to obtain. I believe it is important for researchers in these fields to work with advocacy groups to raise awareness, and to pursue great ideas collaboratively within the research community. We must ensure we use our existing resources in the most effective ways, to make the greatest impact possible. Having said that, progress is being made, thanks to increasing awareness, and the existence of some specific funding sources that target uncommon cancers.

What are the next potential game-changers?

The ability to detect targetable genetic alterations and tailor medical therapy would be a huge advance, and there are multiple examples of how this is already happening in GI cancers (colorectal and gastric in particular). Finding targets in HPB cancers would be a further step forward, and our improved understanding of the genomic landscapes of several major tumor types has promised to accelerate this discovery. But most therapeutic targets identified so far do not allow curative treatment, so further understanding of all of the oncogenic pathways involved in these cancers is needed to move beyond the modest survival gains we have seen so far.

How important is pathology?

Pathology is the key to understanding tumors. Proper diagnosis and subclassification is the first step to studying the biology, treatment response, and all other clinical aspects of different tumor types. Unraveling the genetic basis for cancer has helped us understand many of the pathologic findings we previously regarded as largely descriptive. Now, we can begin to appreciate the basis for the morphologic features pathologists have long recognized as characteristic of carcinomas. Increasingly, we are learning that specific microscopic findings reflect a predictable underlying genetic alteration, and informed pathologic analysis is needed to draw conclusions about the mechanisms of morphologic alterations. To define tumor characteristics, and to understand how tumor alterations translate into specific morphologies, you need pathologists!

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