OCTOBER 2014 # 01

the Pathologist

Facing the Digital Future of Pathology

Are concerns around digital pathology technology based on fear or fact?

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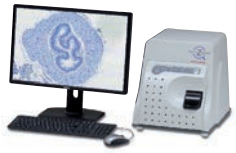

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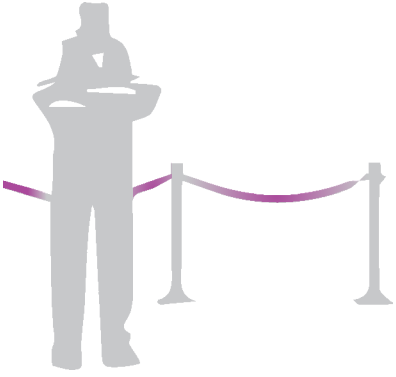

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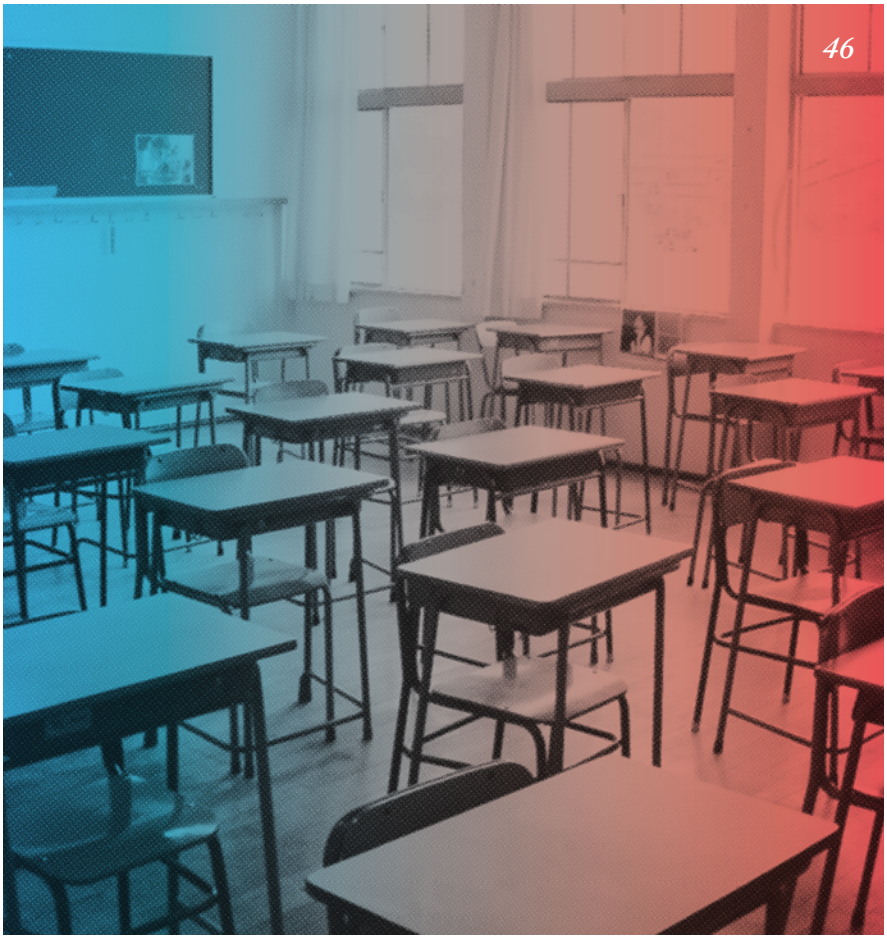

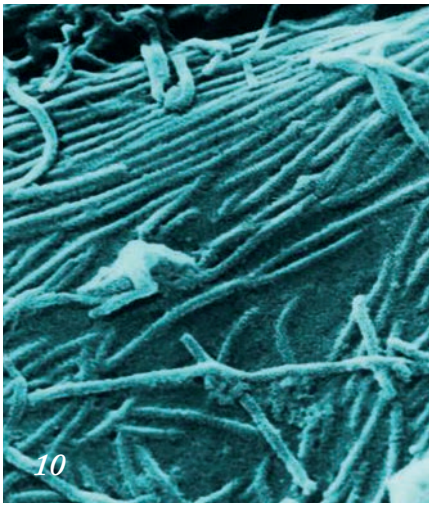

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DIGITAL PATHOLOGY CONGRESS

4-5 December 2014 London, UK London Heathrow Marriott Hotel

UNDERSTANDING AND UTILIZING DIGITAL PATHOLOGY AS A TOOL FOR ADVANCING PATHOLOGY PRACTICE AND ENABLING ENHANCED PATIENT CARE

KEYNOTE SPEAKERS

JO MARTIN,
National Clinical Director of Pathology NHS England, Professor of Pathology, Queen Mary University of London, Director of Academic Health Sciences, Barts Health NHS Trust

LIRON PANTANOWITZ,
Associate Professor of Pathology & Biomedical Informatics, Director of the Pathology Informatics Fellowship Program and Associate Director of the Pathology Informatics Division at the University of Pittsburgh Medical Center, USA

MARCIAL GARCIA ROJO,
Head of Pathology Department, Hospital de Jerez de la Frontera, Cádiz, Spain

DAY 1
Stream 1: Digital Pathology - Strategy and Technology
Stream 2: Pathology Informatics

DAY 2
Stream 1: Digital Image Analysis
Stream 2: Digital Pathology Applications and Research
Case Studies Utilizing Digital Pathology

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Welcome to The Pathologist

From academic to clinical pathology, microbiology to molecular pathology, we promise to report on the issues and innovations at the heart of your field.

Welcome to the first issue of The Pathologist. What is this new publication all about? Well, our aim is to provide you with insight into the latest research and technological breakthroughs that affect – or will affect – your work in the field of pathology.

For example, our first issue focuses on a topic that has divided the community – digital pathology (see page 16). While it's not a new phenomenon, opinions vary vastly. The general consensus: if you're not using it, you probably will be in the next few years. And though cynicism remains, the digital pathology seminar held at this year's European Congress of Pathology (ECP) was packed to the rafters and was followed by an extremely energetic discussion. Evidently, people are interested, but there are also concerns; cost, standardization, training, and privacy issues, for example, all need to be addressed.

A senior manager of a company that's actively involved in digital solutions admitted to me recently that pathologists will only adopt the technology if industry can demonstrate that there is a clear need. Despite opinions being divided, Berlin's Manfred Dietl made an interesting point in his presentation at ECP: you cannot afford to ignore it. After all, bad press surrounding false diagnoses and inaccurate reports, in particular for patients with cancer, have publicly emphasized areas that need to be addressed. Although Dietl accepted there are downsides to integrating digital technology, the upsides – increased need for quantification, reduced variability and increased objectivity – are far greater. I hope such hot topics will fully engage each and every one of you. If you want to contribute to the ongoing debate on digital pathology, please drop me an email.

In addition to offering in depth or high level coverage of topics that are destined to have a wide and great impact, we want to focus our editorial lens on other important areas that directly affect your daily work; we'll look at changes in regulations, quality and standards, training and education, and funding, to name but a few. Importantly, we will also become the forum where you can learn from and communicate with your peers.

Our vow is to use every avenue – the monthly print magazine, website (www.thepathologist.com), e-news, and social media (Twitter: @pathologistmag; Facebook: thepathologistmag) – to report on the people and subjects that are important to you. And, of course, if there's something you'd like to share, please email me at fedra.pavlou@texerepublishing.com.

Finally, I'd like to take this opportunity to offer my sincere thanks to our contributors and to the thought leaders who provided invaluable support and guidance in the run up to our launch. This is just the beginning of an exciting journey together.

Fedra Pavlou
Editor

Suzy Lishman

Specializing in gastrointestinal pathology, Suzy is a cellular pathologist in Peterborough and President Elect of the Royal College of Pathologists (RCPath). She leads the College's public engagement program, which has seen over 2,000 events run to date. She wants to promote pathology and engage with students to encourage careers in the field. "The molecular revolution will transform the development of pathology. My job is to lead the College and ensure pathologists remain at the forefront of this research. I'd like to have pathology at the center of all health policy decisions."

Read about Suzy's plans to maximize pathology's profile on page 46.

Ian Cree

Ian is Professor of Pathology at Warwick Medical School in the UK, he chairs the inter-specialty committee on Molecular Pathology for the RCPath and sits on the NICE diagnostics advisory committee. Trained as a general pathologist with a PhD in immunology, his research interests are mostly cancer-related; he has published over 200 papers and two books. Currently he's involved in developing guidelines for molecular pathology testing for cancer patients, which he discusses on page 36. "I would urge pathologists to look at the results of EQA schemes and look at the mistakes of others, and avoid them," he says.

Enrique Rodríguez-Borja

Enrique has headed the pre-analytical and LIS department at the University of Valencia Hospital Clinic, Spain since 2009. "Since I started working in pathology, I've been concerned about the lab's role in coordination and ensuring appropriate utilization. Hospitals have evolved into larger and more complex systems, and laboratory professionals need to define new roles. After implementing computer provider order entry (CPOE) in our department and getting rid of paper documents, I wondered if available laboratory requests were consulted by clinicians and if so, how fast – this was part of my improvement strategy."

Find out what Enrique's research revealed on page 40.

Marcial García-Rojo

Director of Pathology at der Jerez de la Frontera Hospital, Spain, Marcial's research interests include informatics standards in digital and molecular pathology; he's published three books and 125 scientific papers, and edits the Spanish Journal of Pathology. An advocate of digital pathology, he's keen to see it develop. "The problem is it's evolving very quickly. Pathologists want to concentrate on their work, not on technology issues, so the discussion is around how to find solutions and make them easy to deliver."

Marcial outlines his experiences with digital pathology and his thoughts on how to improve it on page 20.

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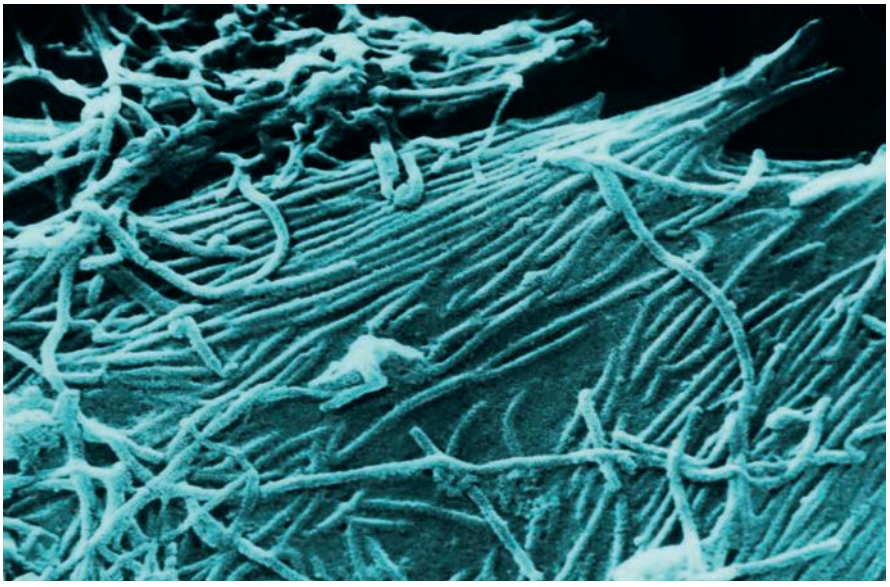

Tracing the Ebola Genome

The sequencing of 99 Ebola genomes has not only highlighted the likelihood of viral adaption, but also the high risks for researchers.

More than 50 researchers from four countries have collaborated to publish a collection of Ebola genome sequences from the current outbreak in Sierra Leone. But with five co-authors dead after contracting Ebola virus disease (EVD) before the paper was published, it also highlights the devastating human aspect of research into the disease.

The team used massively parallel viral sequencing to gain information on the spread of the virus; 99 genome sequences were obtained from 78 patients (some genomes were sequenced twice) ahead of data analysis.

Worryingly, the team uncovered a total of 395 mutations (1), which sets this outbreak apart from previous outbreaks. Arguably of equal concern was the finding that molecular testing could prove inadequate – regions of the Sierra Leonean genomes used in five separate PCR-based assays did not match the PCR probes.

With regards to transmission of the disease, no zoonotic sources were found to be involved in its spread. The genetic similarities suggested a single transmission from the natural reservoir, followed by extensive human-to-human transmission.

All of the genomic data has been made available to the research community as it is generated. The team hope that their work will aid diagnosis, the formation of public health strategies, and potentially guide research into Ebola treatments. "There's nothing you should crowdsource more than an epidemic," said co-author Pardis Sabeti.

The current outbreak of the virus in West Africa is the largest ever documented (2), with over 5,000 reported cases (3). Several authors of the genome study work at the Kenema Government Hospital (KGH), where the first case of Ebola in Sierra Leone was diagnosed in May of this year. According to the researchers, the outbreak in the country may have stemmed from

the funeral of a traditional healer who had been treating patients with EVD in neighboring Guinea. The original Ebola patient at KGH had attended the funeral, and tracing turned up 13 more cases in women who were also present.

Study of the original patients and other infected individuals revealed that two genetically different strains of the virus appear to have spread to Sierra Leone from Guinea at around the same time – both were present in the original 14 patients and could have been contracted at the funeral.

The loss of five co-authors of the study to EVD is a reminder of the risks faced by researchers; they were all experienced members of the hospital's Lassa fever team and very familiar with the treatment of infectious disease. To date, Ebola has claimed the lives of more than 20 nurses, doctors and support staff at KGH. The World Health Organization (WHO) says that the number of medical staff now infected is "unprecedented" (4). More than 240 healthcare workers in West Africa have contracted the disease, and more than 120 have consequently died (5). *RM*

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FDA Crackdown on Labs

Plans to regulate laboratory developed tests could stifle innovation

The US Food and Drug Administration (FDA) has announced its intentions to regulate laboratory developed tests (LDTs). The agency has had the authority to regulate LDTs since 1976, but until now has refrained from doing so (1). US laboratories have instead been regulated by the Centers for Medicare and Medicaid Services (CMS) using Clinical Laboratory Improvement Amendments (CLIA), which have been in place since 1988.

So why is the FDA stepping in now? It cites the increasing complexity of LDTs, and their roles in critical decision making – in particular relating to personalized medicine.

The agency intends to take a "risk-based" approach (similar to the model it currently uses for assessing medical devices); LDTs considered high risk will be brought under the new regulations, while risk tests and tests for rare diseases, which do not have an FDA-approved equivalent, may not require no further guidelines (1).

Although some organizations have come forward to express their support for the new regulations, such as the American Association for Cancer Research, others aren't so pleased by the proposed changes. The American Medical Association (AMA), the American Clinical Laboratory Association (ACLA), and the Association for Molecular Pathology (AMP) have all met the proposed regulations with some skepticism, pointing to the regulations and accreditation procedures already in place. They also voiced concerns that further regulations could lead to the loss of patient access to required tests, increased cost of testing, and stifled innovation in the laboratory. *RM*

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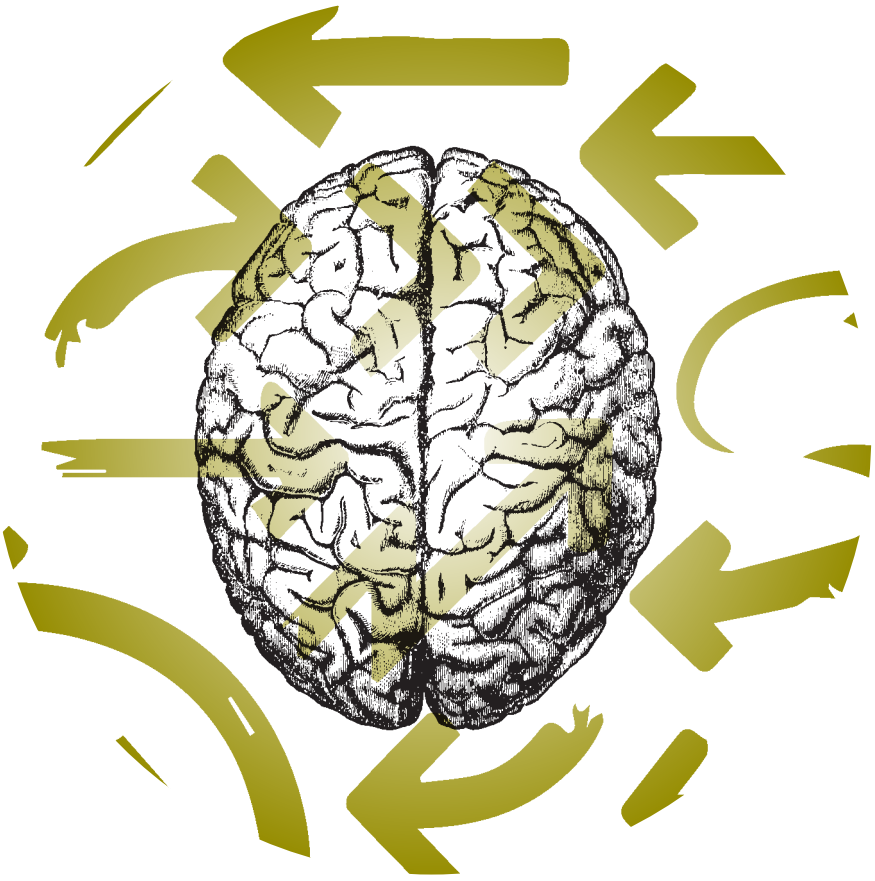
Unscrambling Schizophrenia



Despite numerous research efforts, schizophrenia remains a bit of a mystery. We know that both genetics and environmental factors play a part in its development, but the question of which genes and which environmental influences is clouded by uncertainty. Recently, two separate studies attempted to find new answers.

Team One: Genetic Factors

Could this GWAS result in the first completely new drug treatment for schizophrenia since the 50s?

The Schizophrenia Working Group (SWG) of the Psychiatric Genomics Consortium conducted a multinational genome-wide association study (GWAS), that has identified 108 loci associated with the risk of developing schizophrenia, 83 of them new. It marks the largest genomic study ever undertaken for a mental health condition (1).

"This paper is a landmark. We have never before had such a profound and important look into the inner workings of schizophrenia," says study co-author Patrick Sullivan, professor of genetics and psychiatry at University of North Carolina, USA, and director of the Center for Psychiatric Genomics. Genotype data was obtained and statistically analyzed from over 30,000 cases and more than 100,000 controls.

So how will this benefit patients with the condition? According to the authors, all current antipsychotics used in schizophrenia are thought to target the type 2 dopaminergic receptor – a mechanism discovered over 60 years ago. The SWG believe that a deeper understanding of the disease etiology is critical to breaking out of this therapeutic stasis.

Perhaps unsurprisingly, many of the genes identified are expressed in the brain, especially ones involved in neuron and synapse function, synaptic plasticity and cell signaling, although others were also active in the immune system.

Despite the new information, one of the authors, Michael O'Donovan, (deputy director at the Institute of Psychological Medicine and Clinical Neurosciences, Cardiff University, UK), cautions that we shouldn't get too ahead of ourselves and emphasizes that the study is only the beginnings of understanding the biology. "Follow-up experiments will be needed to understand the impact of these genetic variations on the disease," he says.

According to O'Donovan, there is already interest in genes encoding calcium channels and glutamate signaling, but he explains that it would be a "brave person" who expressed high confidence that these will be successful treatment targets. In addition, despite the growing body of information on schizophrenia risk factors, the likelihood of predicting risk with accuracy remains low. He adds, "I believe that at best, we may be able to add information to risk prediction. But I do not think that genetic testing in the general population will be accurate enough for diagnostic purposes. The role of other factors is important."

As for next steps, O'Donovan explains that even larger sample sizes should provide more information. Also, the current information needs to be used to its full potential; "People need to figure out how genetic variation in the systems we identify is acting," explains O'Donovan, "We need to link genetic changes to changes in the function of the genes and cells and brain. That will require a lot of non-genetic experiments from cell biologists, brain imagers, and psychologists." *RM*

Reference

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Genomics Consortium, "Biological Insights from 108 Schizophrenia-Associated Genetic Loci", Nature, 511, 421-27 (2014).

Team Two: Environmental Factors

Low levels of vitamin D may be linked to schizophrenia risk

A group of Iranian researchers took a different approach: delving further into the proposed link between vitamin deficiency and schizophrenia (1). "Vitamin D deficiency is relatively prevalent across the world and is associated with several disorders, including depression. So we were interested in exploring its role in psychiatric health further," explains Ahmad Esmaillzadeh, lead author of the study.

The team reviewed 19 studies that examined the blood of a total of 2,804 participants. Apparently, the work represents the first comprehensive meta-analysis of its kind and yielded unanticipated results. "We were very surprised by the significant 2.16 times increased risk of schizophrenia in vitamin D deficient individuals," says Esmaillzadeh.

It has long been suspected that vitamin D levels may affect the developing brain, and low levels prenatally may predispose to schizophrenia (2). Deficiency during development has also been suggested as a possible explanation for the varying incidences of schizophrenia in different populations – such as people born at different times of year or in different latitudes.

Esmaillzadeh says that the next step for his team will be to trial vitamin D supplementation in people with schizophrenia, as well as investigating maternal and neonatal serum vitamin D in relation to the condition in later life. *RM*

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Targeting Postpartum Depression

Could identification of a new biomarker offer hope for mothers?

Postpartum depression (PPD) is the most common complication of childbirth. It affects around 13 percent of mothers and is associated with over a ten-fold increase in suicide risk compared with healthy individuals. Researchers from Canada and Germany now hope they can develop new treatment strategies through their discovery of a new biomarker (1).

Lead author of the study, Julia Sacher from the Max-Planck Institute for human cognitive and brain sciences in Leipzig, Germany, says PPD is an immense public health issue. "It is often not diagnosed and in many cases not adequately treated. A mother's mental health and well-being have profound effects on her child's physical and emotional development and impact the entire family," she explained.

Sacher believes that the discovery of the biomarker – elevated monoamine oxidase A (MAO-A) in the brain – could open up new directions to improve diagnosis, treatment and effective prevention strategies.

The researchers used positron emission tomography (PET), to measure MAO-A density in the prefrontal and anterior cingulate cortex in the brain. They found that in women experiencing PPD, MAO-A values were 21 percent higher than in healthy controls.

"Our data argue for clinical trials of MAO-A inhibitors for PPD, and the development of new, well tolerated MAO-A inhibitors that either rapidly wash out of the periphery or which have high brain to periphery concentrations," says Sacher.

According to the study, the biomarker doesn't just identify depression; substantial MAO-A binding changes were also observed in the subclinical group; women who did not meet the criteria for full PPD, but who reported increased crying and sadness. This group also showed elevated MAO-A levels in brain regions important for balancing emotions and mood, such as the prefrontal cortex and the anterior cingulate cortex. For the researchers, this was an interesting find. "Either these women will go on to develop PPD at some later time or they have some sort of compensation mechanism protecting them from developing the full-blown clinical disorder," says Sacher. "Based on our neurobiological model for PPD, promoting normalization of MAO-A levels after the immediate postpartum period might reduce the probability of developing the full clinical disorder." *RM*

Reference

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The Survival Artists

We know mycobacteria can survive in the absence of oxygen. But what is their secret?

Mycobacterium tuberculosis is a pathogen known to survive in hostile conditions, but until recently, its ability to survive without oxygen has not been well understood. A recent study from researchers in New Zealand, Germany and the US has managed to shed some light on the subject (1). Up to a third of the world's population may have a latent TB infection (2), and the researchers hope that discovering mechanisms that allow mycobacteria to survive may lead to new drug targets for TB.

Michael Berney, assistant professor at Albert Einstein College of Medicine, NY, and one of the study's lead authors, tells us more.

What motivated your research?

Mycobacteria are survival artists; they need oxygen for growth, but they're able to survive months or even years when it's exhausted. *M. tuberculosis* can survive and persist in human lungs in granuloma, an environment known to be oxygen deprived. Likewise, many mycobacterial species isolated from the environment, such as the soil bacterium *M. smegmatis*, have been shown to survive long-term oxygen deprivation. Having an interest in mycobacterial metabolism and energetics, I wanted to pursue this metabolic conundrum: how does an obligate aerobe – a bacterium that cannot grow without oxygen – survive hypoxia?

Were there any surprises?

We found that *M. smegmatis* encodes three different hydrogenases – enzymes that are commonly found in anaerobic or facultative anaerobic organisms. Why would an obligate aerobe carry three of these enzymes? We learned that *M. smegmatis* uses these hydrogenases to produce hydrogen in the absence of oxygen and is able to quickly recycle the produced gas as soon as a suitable electron acceptor (for example, oxygen or fumarate) is available. This gives the bacterium a high degree of metabolic flexibility, as well as the ability to rapidly adapt to changing conditions.

In addition, we could demonstrate fermentation in a mycobacterium, which suggests that *M. smegmatis* can switch between fermentation, anaerobic respiration and aerobic respiration.

What challenges did you face?

The main challenge was to experimentally dissect hydrogen consumption and production by the bacterium. In order to determine the contribution of each individual enzyme to hydrogen metabolism, we

used genetic engineering to delete hydrogenases in the genome of *M. smegmatis* and create single, double and triple mutants.

With these strains in hand, we faced another challenge: measuring hydrogen consumption and production at extremely low concentrations (sub-atmospheric levels). We first used a hydrogen sensor, but these experiments were limited as we could only measure relatively high hydrogen concentrations. There are only a handful of groups in the world who can measure hydrogen at such low concentrations, using ultrasensitive gas chromatography. Fortunately, we were able to collaborate with Ralf Conrad of the Max Plank Institute in Germany, who has the necessary instrument and expertise.

What's next?

There are two main questions that we are currently examining:

1. Why are mycobacteria able to ferment and respire anaerobically yet are unable to grow without oxygen? It is very puzzling that mycobacteria are equipped with the tools to ferment and respire anaerobically, yet are unable to grow under anoxic conditions.
2. Do pathogenic mycobacteria, like TB, also rely on hydrogen metabolism or any other fermentative process to survive and persist in their host?

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To Use pCR, We Must First Define It

Pathological complete response can provide valuable information on survival in breast cancer, but is a standard definition within reach?

A pooled analysis of the relationship between pathological complete response (pCR) and breast cancer has highlighted an important issue: different studies are using different definitions of pCR, making it tough to compare results and to understand its prognostic value.

The analysis was conducted by Collaborative Trials In Neoadjuvant Breast Cancer (CTNeoBC), an international breast cancer working group established by the US Food and Drug Administration (FDA). The study is believed to be the first to use primary source data to investigate the relationship between pCR, event-free survival (EF) and overall survival (OS) in breast cancer patients.

pCR refers to the eradication of cancer in response to therapy, but its definition remains unstandardized; an issue that the CTNeoBC working group set out to address (1).

The study looked at 12 international breast cancer trials (a total of 11,955 patients) and found several different definitions of pCR were used. CTNeoBC compared the most common three: absence of cancer in breast tissue and lymph nodes (ypT0 ypN0); absence of cancer in breast tissue and lymph nodes regardless of the presence of ductal carcinoma (ypT0/is ypN0); and absence of cancer in breast tissue alone (ypT0/is).

The study revealed that eradication of tumor from both breast tissue and lymph nodes had a stronger association with improved EFS and OS than did eradication from breast tissue alone. As such, they propose that pCR is defined as either ypT0/is or ypT0 ypN0 in future studies; they found that ductal carcinoma had no effect on outcome in the studies they analyzed.

A key objective for the team was to establish pCR as a surrogate endpoint for assessing long-term breast cancer outcomes – namely EFS and OS. Unfortunately, the trial was unable to validate pCR as a surrogate endpoint, which the authors admit was disappointing. "This was also surprising in view of the substantial improvements in survival for individual patients who attain pCR," explains Patricia Cortazar, lead author of the research.

However, Cortazar remains positive, adding that the study does establish which pCR definitions best correlate to long-term outcomes – this may help to address the lack of standardization of pCR. They also found that individual patients who attain pCR have a 64 percent reduction in risk of death, compared with patients with residual tumor; the authors believe this confirms the prognostic value of pCR, which was found to be greatest in patients with aggressive tumor subtypes.

Perhaps pCR will eventually be established as a surrogate endpoint through further study. "We hypothesize that randomized trials of targeted agents in homogeneous tumor subtypes, with larger differences in pCR rates, will likely demonstrate a relationship between pCR and long-term outcome," says Cortazar. "Analyses of additional trials in a targeted population will be needed to demonstrate whether or not there is a relationship between pCR and long-term outcome at a trial level." *RM*

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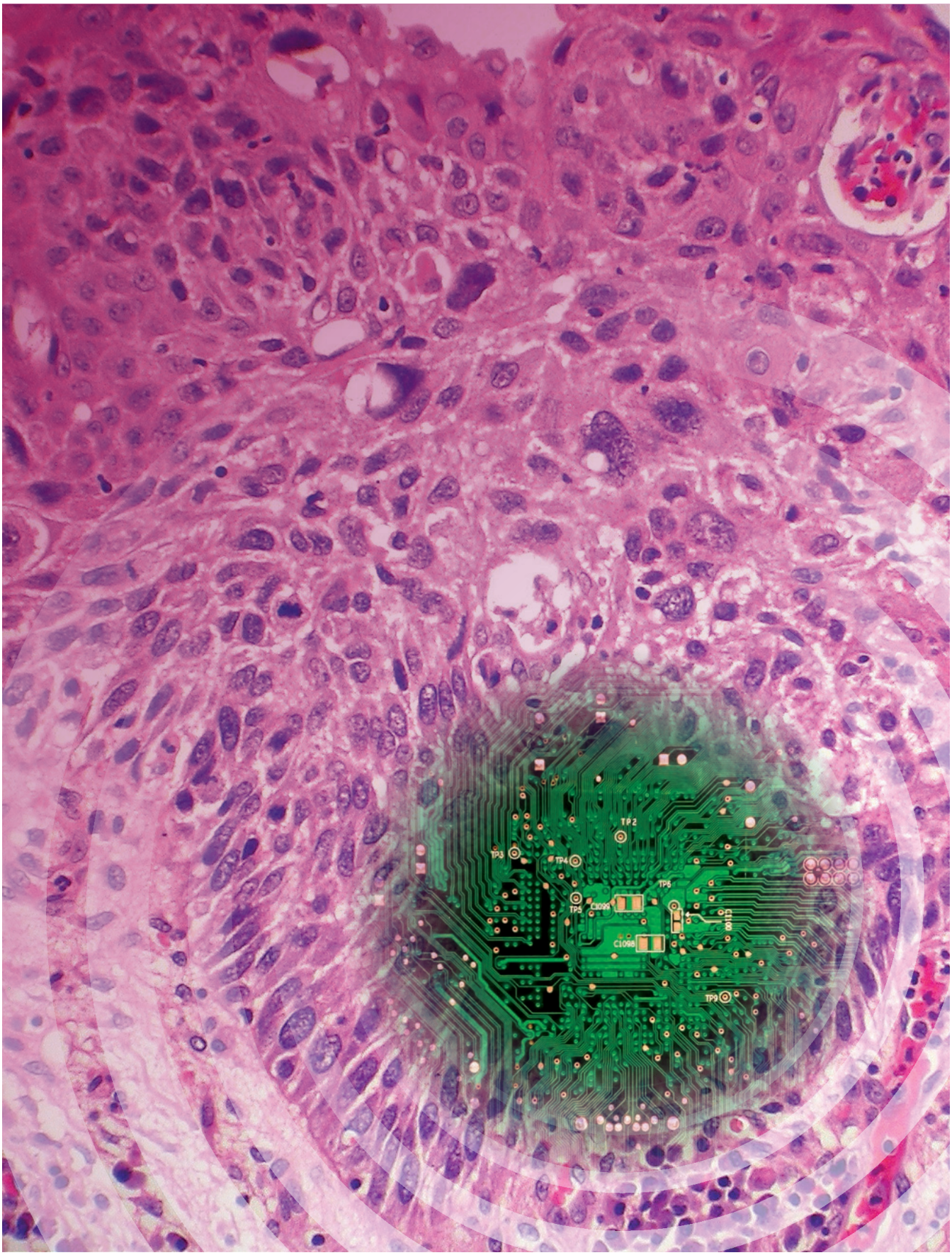
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Facing the Digital Future of Pathology

Digital pathology is pushing the boundaries of convention and dividing the community. Uptake of the technology is growing, but only slowly. Can its adoption be resisted forever? Here, we look at the benefits – and challenges – of implementing this inevitable technology.

By Iestyn Armstrong-Smith

Digital pathology is making its presence felt all over the world. For some pathologists, it's becoming a part of everyday working life; for others it is something to be viewed with skepticism.

Earlier this year England's National Health Service (NHS) published an overview of its National Pathology Program: "Digital First: Clinical Transformation through Pathology Innovation"(1). The document sets out how healthcare could apply new technology to help meet increasing demand, which is particularly pertinent for a health system that is financially stressed. Jo Martin (national clinical director of pathology for NHS England, and professor of pathology at Queen Mary University of London) prefaces by stating, "Pathology is leading the way in the use of digital technology, with the automated disciplines at the leading edge." Martin highlights how, in her own practice, technology has had a huge impact on improving communications, procedures, workload and quality.

The document is full of examples and references that support use of the technology, but it is clear that bridges must be crossed before we witness widespread adoption.

The plus points

You can do a lot more with digital pathology than you can with manual microscopy: instant sharing of results with multiple departments and colleagues; being able to include digital images with your pathology report; using computerized quantitative analysis for prognostic scores; removing the danger of breaking glass slides in transit; remotely interpreting frozen sections and so on. These advantages can all help speed up diagnostic accuracy or turnaround times.

It goes without saying that quality assurance (QA) is much improved with the technology – manual errors are reduced through its ability to perform automatic case reviews and tracking of slide assessments for completeness. Image analysis efficiency, precision and reproducibility are also much improved compared with manual microscopy (2, 3).

But, it's not only those of you who work in the clinical setting who have gained. For example, the inherent robustness and longevity of digital slide teaching sets are a big advancement on glass slides, which can fade, break or be misplaced. Other advantages include the ability to scan a single tissue sample

to provide slides for numerous teaching classes; it also enables students to experience a wider range of cases.

Whichever way you look at it, digital pathology technology is significant and the market for it is growing (see "The Digital Pathology Market" on page 25). The big question: why is there an apparent reluctance to implement it in every hospital? It seems there is no single, clear-cut answer. Indeed, The Pathologist welcomes your comments, which we hope you will be happy to share with the whole pathology community.

Problems and challenges

Pulmonary pathologist Timothy Craig Allen goes some way to explaining the apparent reluctance by highlighting a number of challenges that face digital pathology, including legal, privacy, security, confidentiality, and standard of care issues, in a recent article (4).

In practical terms, however, one of the first hurdles to overcome is the amount of bench space needed to site a system. Also, the workflow is something quite different; it isn't simply a matter of scanning slides, digitizing them, adding meta data and sending them to a computerized library to share with others. The very high resolution, highly detailed images result in huge files (think gigabytes rather than megabytes), so storage is also a real challenge. And because most files are in proprietary formats, you can't open them using standard software.

In addition, you have to consider how you make the files viewable to others and whether or not another pathologist will see the slides in exactly the same way, if they are using different monitors.

Perhaps more fundamentally, the quality of the image may not be assured. For example, the scale of an image displayed on a computer monitor is different to the same image viewed through a path lab microscope. And optical resolution is different from digital resolution, so correct equipment setup is a priority. The benefit of using a monitor, however, is a better field of view and the ability to view more slides at once, as well as being readily able to move them around to see more of the tissue directly on screen.

> *"In practical terms, one of the first hurdles to overcome is the amount of bench space needed to site a system."*

The strain on a lab's IT system – and the other systems it connects with – is another area of concern, with reliable network and Internet bandwidth being important factors.

Burgeoning patents

Patents have created unwanted obstacles too. As new technologies emerge, inventors and developers scramble to protect intellectual property. Even now, digital pathology patents run into several hundred according to research by Ioan. Cucoranu et al. (5). The group's investigation shows that the number of patents has quadrupled over the last 10 years, which goes hand in hand with developments in the field. Telepathology and whole slide imaging (WSI) account for the majority and there is a growth in digital image analysis and CAD. The researchers found that although the process of

Vendors' Viewpoints

Matthew Burke (MB), Sales Engineer from Hamamatsu Photonics UK Limited, Perry van Rijsingen (PvR), General Manager Philips Digital Pathology Solutions from Philips Healthcare, and Olga Colgan (OC), Director of Commercial Marketing Aperio ePathology from Leica Biosystems, offer their perspectives on digital pathology adoption and the future of the field.

What is pathologists' biggest concern about digital pathology adoption?

MB: The scarcity of time! Because of increased workloads – including identifying new markers needed for diagnosis – pathologists are short of time to commit to new training and to consider testing a digital solution compared with their current procedure.

Pathologists still need convincing of the benefits of sharing images and the fact that the time needed to view a case from a digital image can be as fast as viewing using a microscope. However, computers are getting faster and networking technology is providing more bandwidth for transferring large image files, so the gap is closing as the pixilation of large images associated with digital pathology is now becoming a thing of the past.

Also, the lack of clear guidance from regulatory authorities about the validity of using digital slides to report cases is an issue. Pathologists are very concerned about their legal position if they

securing a patent can be lengthy, the abandonment rate was 10.6 percent, which is relatively low.

The problem is the potential conflict between patents and standards that may arise when the implementation of standards necessitates use of technology protected by patents. As the market expands, we should expect to see growth in the number of patents too, and that will not help the problem. On a positive note, some manufacturers have recognized the need for an open playing field in terms of standards. Leica, for example, is helping to clear the way by making its Aperio technology patents, which cover technology included within international standards, available free of charge to other manufacturers.

The need for standardization

In general, pathologists are very good at implementing standardized technology, and a lot of what is already done in the path lab is automated. For example, barcoding helps with accurate labeling and identification of samples and with workflow. Laboratory information management systems (LIMS) are the norm and allow primary and secondary care clinicians to order tests, and view the results, electronically.

In terms of standards for digital medical images and related information, DICOM (Digital Imaging and Communications in Medicine) is the recognized international standard and is identical to ISO 12052. Published in 1993, the standard is implemented in almost every radiology, cardiology imaging, and radiotherapy device and increasingly in devices in other medical domains (for example, ophthalmology and dentistry). DICOM Supplement 145 is applied to WSI and defines the archiving and storing of image files. Integrating the Healthcare Enterprise (IHE) is an anatomic pathology group initiative that has also defined a standard that covers the manner in which systems communicate with each other.

Though some progress is being made in the development of standards, an open digital image format standard is yet to emerge, with vendors locked into proprietary imaging technologies. This creates problems with compatibility both backwards and forwards, which is something that Marcial Garcia Rojo discusses in "The Digital Pathologist's View".

Telepathology Networking

What? EURO-TELEPATH – Telepathology Network in Europe

When? Established in 2007, ended 2011

Why? To consolidate the best research references in informatics applied to anatomic pathology so that standards could be developed for representing, interpreting, browsing and retrieving digital medical images while preserving their diagnostic quality necessary for clinical, learning and research purposes

Who? Participants included COST (European Cooperation in the field of Scientific and Technical Research) Agency, with representatives from 16 European countries

How? EURO-TELEPATH participants took part in meetings, working groups, training schools

The end result? Collaboration with international health informatics standardization bodies to foster the development of standards for digital pathology. Also gave rise to the AIDPATH initiative.

misdiagnose a case using a digital slide displayed on a computer screen.

PvR: There are concerns over clinical (regulatory), technology and system integration and financial issues. In general, we hear from customers using our solution for high volume pathology laboratories and integrated pathology networks that digital pathology is important for moving their businesses forward. Most have some experience with digital pathology and know that they need help to make the full shift to digital. High image quality and system performance are a prerequisite for them, so the real discussion is about integration with their existing workflow, connectivity, IT infrastructure and scalability.

OC: Although there are a number of good reasons for adopting digital pathology, there are also obstacles.

Historically, the cost of systems combined with few research papers validating the return on investment (ROI) were a factor preventing implementation. The total-cost-of-ownership can be higher than expected too.

Also, as pathologists tend to be traditionalists and there is limited regulatory approval in some regions of the world, institutions are wary of it. While it makes collaborating quicker, compared with shipping slides or needing a pathologist to travel to different sites, the user experience when viewing slides can be slower than that of a microscope (if wide area networking is limited or if users need

The Digital Pathologist's View

Marcial Garcia Rojo of the Hospital de Jerez de la Frontera, Cadiz, Spain, is a key proponent and early adopter of digital pathology, having used the approach for more than seven years. Here, he shares his experiences so far.

Can you tell us why there is a need for standardization?

About seven years ago, digital scanners were appearing and pathologists were taking an interest in what they could offer. At the same time the EURO-TELEPATH initiative was investigating how we could automate many of the manual processes in the laboratory (see sidebar, "Telepathology Networking" on page 19). We concluded that digital imaging was something that needed developing as it could offer pathologists the opportunity to perform a complete scan of a digital slide or scans of sets of slides. However, we couldn't recommend digital imaging without a standard. So, we set about collaborating with various international standardization organizations – DICOM, IHE and SNOMED CT – to address the need, which would hopefully and ultimately encourage the use of digital imaging.

Two main standards have been developed. DICOM Supplement 145, defines how we archive and store the very large image files. The second comes from the IHE initiative, which defines how different systems communicate with each other.

What about validation?

In the USA, the Food and Drug Administration (FDA) insists on validation studies before pathologists can use digital images for diagnosis. We don't have this problem in Europe because we have sufficient validation studies. Here, it is the norm to perform validation studies once a lab buys a scanner and before using it for the first time. All the validation studies that I am aware of have demonstrated that these technologies are suitable for performing diagnoses.

However, we do need to perform further studies on efficiency; for example, we need to know that we are working efficiently with DICOM standard images. We also need to know the impact of using standards within our pathology workflows and that is something we are working on with the AIDPATH initiative (see sidebar "Collaborative Clout" on page 21).

How can we address the patent problem?

Patent problems are slowly being resolved. Various manufacturers were concerned about whether they could use technologies covered by DICOM because of patent concerns. Leica, for example, is allowing DICOM certified companies to use its technology, which is a step in the right direction.

I bought my first scanner about seven years ago, which used a specific file format and a specific viewer. Since

training or if they lack familiarity with the system, for example).

What is being done to address the concerns?

MB: There is more exposure to digital images these days, so greater familiarity with the technology is important. New trainee pathologists, for example, are taught how to work with digital images from an early stage of their career; also, there is more interest and use of digital pathology for the EQA (External Quality Assessment) scheme. The tipping point will come when the training norm will be to use digital images and pathologists will progress onto reporting from scans of their routine cases.

There are a number of ongoing tests and trials to show side-by-side comparisons between standard reporting and reporting from a digital image. These tests look at what is limiting the uptake of digital pathology – reporting time, image quality and the effect on workflow. We believe the results of these trials will encourage pathologists to accept that this is the future of pathology.

However, clear guidelines on reporting from a digital image and whether a standard process is required to integrate the workflow are needed. The FDA, EU and others must provide leadership and discuss with slide scanning companies how to optimize the process so that pathologists can benefit fully from this new technology.

then I have used several different file formats that are not interchangeable. Really, you should be able to use any format; if I can see any slide through my microscope then the same should be possible with viewing digitized images. So that's why we need technology companies to adopt a uniform standard, which should be possible now that patent problems are being addressed. Standardized technology will enable pathologists to scan images with the confidence that in 10 years' time they will be able to read those images without any problems.

Could you tell us about the technological hurdles?

Five years ago, we were debating whether or not this technology would be quick enough and produce high quality images. We've proven that it does and that it is suitable for performing on-screen diagnoses. However, the lack of standardized technology and the difficulty in implementing and using it needs to be addressed, if we expect to see wider adoption. In addition, we need to be able to provide adequate standardized training to users.

Scanning speed has reached a plateau and I doubt that it will get much faster before new technology emerges that captures the slide in one go. Feedback from the pathology community will play a big part in bringing forward the technological improvements we seek.

The AIDPATH initiative, for example, is enabling us to work with industry to drive such improvements. We are able to test new equipment and tell the manufacturers what they need to change. Also, the industry is working with university groups to improve imaging algorithms. Any successful work will be patented and distributed so that everyone will have access to standard algorithms.

Collaborative Clout

What? AIDPATH – Academia and Industry Collaboration for Digital Pathology

When? Established 2013

Why? To exploit the new and emerging digital pathology technologies effectively in order to process and model all data. The initiative aims to help with developing efficient and innovative products to fulfil the needs of digital pathology. Through training it will help professionals to develop novel image analysis solutions for future pathology diagnosis and solutions for biomarker evaluation and quantification

Who? Participants include universities across Spain, the UK, Italy, Romania and Lithuania, the European Commission, as well as technology manufacturers, such as AstraZeneca, Leica, Barco and Tissue Gnostics

How? AIDPATH participants engage in focused research and training. Activities include networking, workshops, summer schools and conferences

What about file compatibility?

As long as we have different technologies that use proprietary file formats and specific viewing software, we will always have compatibility problems. I don't think we should compress images using proprietary file formats because we may need to refer to them in the future. It's so important that new technologies take backwards compatibility into account.

PvR: Pathology is very demanding and digitization can provide great benefits if implemented correctly. But we recognize that this differs per lab, so together with the pathologist we define a solution that works for them – whether it be workflow, IT, or finance, for example. Providing the technology is half of the service, the rest is provided in support to ensure that the right steps are taken towards effective digitization.

OC: As an increasing number of institutions adopt digital pathology for routine diagnostics and second opinions (outside the USA), there is documented evidence of diagnostic equivalence with conventional light microscopy. Also, more use of the technology is providing independent and true total-cost-of-ownership evaluations. In addition, improved connectivity coupled with improvements in system throughput and performance provides a better user experience when reviewing digital slides.

The global trend towards big data, cloud-based solutions, reduced costs for server space and storage, and improvements in data security are also helping to reduce the uncertainty felt by some institutions and individuals around digital pathology. In addition, the clearance of certain digital pathology image analysis systems by the US Food and Drug Administration, combined with its adoption for primary diagnosis in Canada and Europe, is helping to increase overall confidence in, and exposure to, the technology.

Pathology Informatics Timeline

Early 1950s: Hans Elias analyzes the structure of mammalian liver using stereology (Europe)
1952: First computers used in clinical labs (USA)

❮ 1950's

1962: College of American Pathologists establishes the first computer education programme for pathologists (USA)
1965: Systematized Nomenclature of Pathology published (USA)
1968: National Committee for Clinical Laboratory Standards founded. First system for remote pathologic diagnosis demonstrated (USA)

❮ 1960's

1970 onwards: Laboratory Information Systems (LIS) in use in clinical labs (USA)
1976: SNOMED first edition published. First online surgical pathology system – Massachusetts General Hospital (USA)

1970's ❯

Early 1980s: US National Library of Medicine (NLM) sponsored informatics fellowships become available (USA)
1980s: Introduction of computerized tomography technology results in decrease in number of autopsies (Europe)
1986: First calls for pathologists as medical information specialists (USA)
1989: First book on pathology informatics published (ABCs of LIS) (USA)

1980's ❯

1990s: Hospital Information Systems adopted increasingly (Europe)
Mid to late 1990s: Implementation of PACS (picture archiving and communication systems) and DICOM standards (Europe)
1996: First virtual microscope system developed (USA)

❮ 1990's

2000: Association of Pathology Informatics receives its charter (USA)
2003: First US FDA clearance for quantitative image analysis of immunohistochemical cancer markers. HL7 creates a genomics working group (USA)
2005: DICOM creates Working Group 26 for Pathology (USA)
2009: Digital Pathology Association formed (USA)

❮ 2000's

Source: S. Park, et al., "The history of pathology informatics: a global perspective", J. Pathol. Inform., 1(7), (2013).

Which innovations are most widely adopted? Where is research and development heading?

MB: We have found that there are a large number of pathologists who are willing to use and diagnose from a digital image instead of a microscope, especially with regard to cellular pathology. For instance, it is now possible to scan a section in under one minute and therefore we are moving on from simply accepting the ability to scan and share a whole slide.

We believe that new research and development will improve features such as multi-level scanning of whole slides to replicate the z-axis focus function of a microscope. Also, extended focus imaging will enable us to merge multilevel images together so that a whole section is in focus at every point. This will take us to a point where an image from a slide scanner provides a new perspective that cannot be achieved on a microscope.

Current methods of evaluating slides lead to a degree of observer variation, which can be reduced by using digital pathology. New algorithms are being produced that can extract more information from a whole slide image or multiple slides to provide more numerical data. These improvements should progress patient diagnosis by reducing the number of possible mistakes and decreasing the time for a diagnosis.

PvR: Now, pathologists can interact with a digital image in an intuitive way and they can collaborate with others using

Are there any issues with LIS products?

Yes. The LIS companies are not evolving their products quickly enough to keep up with other areas of the market. Picture archiving and communication systems (PACS) and scanner companies are moving ahead but LIS vendors are trailing behind. It takes about five years to develop a LIS to ensure that a product is robust and reliable; the vendors need to speed up development. That said, I don't think we need other companies to get involved and flood the market with competing products – that's not the way to go.

We do try to involve LIS companies in AIDPATH by defining a project in which they can help. For example, seven years ago, we told the LIS vendors that they ought to produce web-based systems – at that time, there were no web-based solutions in Spain. We have learned that vendors only tend to respond when you ask them for something new; we need them to be more proactive.

Do you think that digital technology integration is moving too slowly?

On one hand, it is slower than I'd like it to be, but on the other, I think it is going as fast as the technology allows it to. For example, until about three years ago, scanners were slow and there were too many out of focus areas in an image. That has changed, but scanners remain difficult to implement, the images are very large and a PACS struggles with storing everything we'd like to archive.

Therefore, we need to get everything right with the technology so that we aren't worrying about it and so that we can concentrate on doing our jobs as pathologists.

"The LIS companies are not evolving their products quickly enough to keep up with other areas of the market."

What has changed since you began using digital pathology?

We are now much more selective about scanning. We select cases that could be problematic, need quantitative analysis and image analysis to measure the width of infiltration of a melanoma, for example. We also use it for making second opinions. This amounts to about 15 to 20 percent of my cases. Only when we reach the point that everything is standardized will I decide it is time to digitize everything.

Despite the challenges, do you feel digital pathology has benefitted your practice?

Yes. I actually think my digital pathology images are becoming as popular as X-ray film!

The main benefit is that I am more confident with image analysis and measuring. For example, I can use it to measure Ki-67 protein levels or the size of melanomas. It also reduces the time my colleagues need to wait for a second opinion – I might get the request first thing, and I can email my assessment to them in the same morning.

In addition, I am able to share my images with the other medical specialists in the hospital – I really feel this has made

this technology. However, innovation in healthcare is not just about technical developments. New ways of working are helping to achieve improved health outcomes in a cost effective way. Digitization, therefore, provides a backdrop for looking at new ways to improve the patient experience.

OC: Digital pathology emerged primarily in the education sector. It was then adopted by researchers. Its ability to capture whole slide scans and automatically analyze them for different phenotypes and expression for high-throughput assessment has been particularly popular in biomarker discovery.

Image sharing and collaboration for a variety of cases is another of the most widely recognized uses of the technology; this is validated by a number of studies across a broad range of providers. The technology is also enabling efficiencies in tumor boards, second opinions, and other applications requiring access to subspecialty expertise, which provides objectively verifiable ROI.

More recently, the use of automated image analysis in a clinical setting, such as a companion diagnostic HER2 assay, enables reproducible and objective stratification of patients into cohorts of likely responses to drug therapies and helps to eliminate inter- and intra-observer interpretation variability.

With increased subspecialization of pathologists, the ability to engage with experts in a given field is greatly enhanced by digital pathology. This is helping with difficult evaluations, streamlining access to

pathology more respected by other departments. You can see it in the faces of the dermatologist and hematologists, for example; they are impressed when you show them digital slides. They really appreciate being able to see whether their markers are correctly excised in a tumor or whether morphological features in a leukemia case correspond with those in their own specimens, for example. Collaborating with other specialists is much easier with digital pathology.

Where do you see your lab in 10 years?

In 10 years' time, I think I'll be fully digital. That's not to say I'll be getting rid of my microscope! I'll still need it, for example, to deal with polarized light or fluorescence, or to counter compatibility issues.

What is the general attitude to digital pathology in Europe?

I would say that the attitude is changing. Pathologists now view digital pathology more positively. They see that the technology is much more accessible and affordable; however, it needs to be easier to use and the pathology workflow it has introduced needs simplifying. We've been working on some of these issues at the hospital and have completely remodeled our processes, which has improved our workflow and made it easier to manage.

And in the next decade?

I think it will take longer than 10 years to see digital pathology fully embraced across Europe. Pathologists in private labs may not see the need, for example. However, I expect more hospitals to be using it. Also, as time passes, the pathology community will have access to the results of numerous validation studies, which should encourage wider adoption.

"I think it will take longer than 10 years to see digital pathology fully embraced across Europe."

What do you say to the cynics?

All patients need the same opportunity and no one should get in the way of progress. Doing it your own way may not be the best way and, in the future, the best diagnosis will come with advances in digital pathology. You have to think of the patient and how to provide the best service and outcome for them.

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the right experts, and ultimately improving turnaround time for decision support to the benefit of researchers, health care providers and patients.

What is your prediction for the role of the pathologist in the next 10 years; how will digital pathology affect the way they work?

MB: Although there has been significant investment into genomic research in recent years, without pathologists helping us to appreciate how those genetic differences affect tissue we will never truly understand disease. So, with advances in personalized medicine we believe that the workload and importance of pathologists will increase.

Digital pathology will enable pathologists and pathology departments to become more efficient. The ability to view images from any location in the world will allow them to be more flexible and to provide specialist or second opinions quickly. In addition, image analysis will allow them to provide responses rapidly and accurately, especially with routine cases, which will give more time for dealing with difficult cases.

PvR: First, there will be an intensified collaboration between pathologists as well as within cross-disciplinary teams. This opens up new opportunities for pathology labs, for example, to offer their expertise to regions beyond their current scope, where experienced or

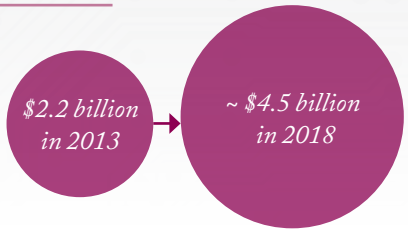
Digital Pathology Market

European pathologists are the second largest users of digital pathology technology behind North America. Some European countries have witnessed successful pathology projects, which are likely to lead to higher adoption of digital pathology in these countries (1).

North America dominates the digital pathology market, key reasons include favorable reimbursement scenario in the USA and the use of digital pathology to improve the quality of cancer diagnosis in Canada (1).

The Asian market, though it currently trails behind North America and Europe in its use of digital pathology, is expected to experience the highest growth in the next five years. This is attributed to the rise in awareness of digital pathology and its benefits, collaborative efforts by manufacturers, and federal health departments encouraging the use of digital pathology to improve the quality of cancer diagnosis (1).

Global Digital Pathology Market Size (2)



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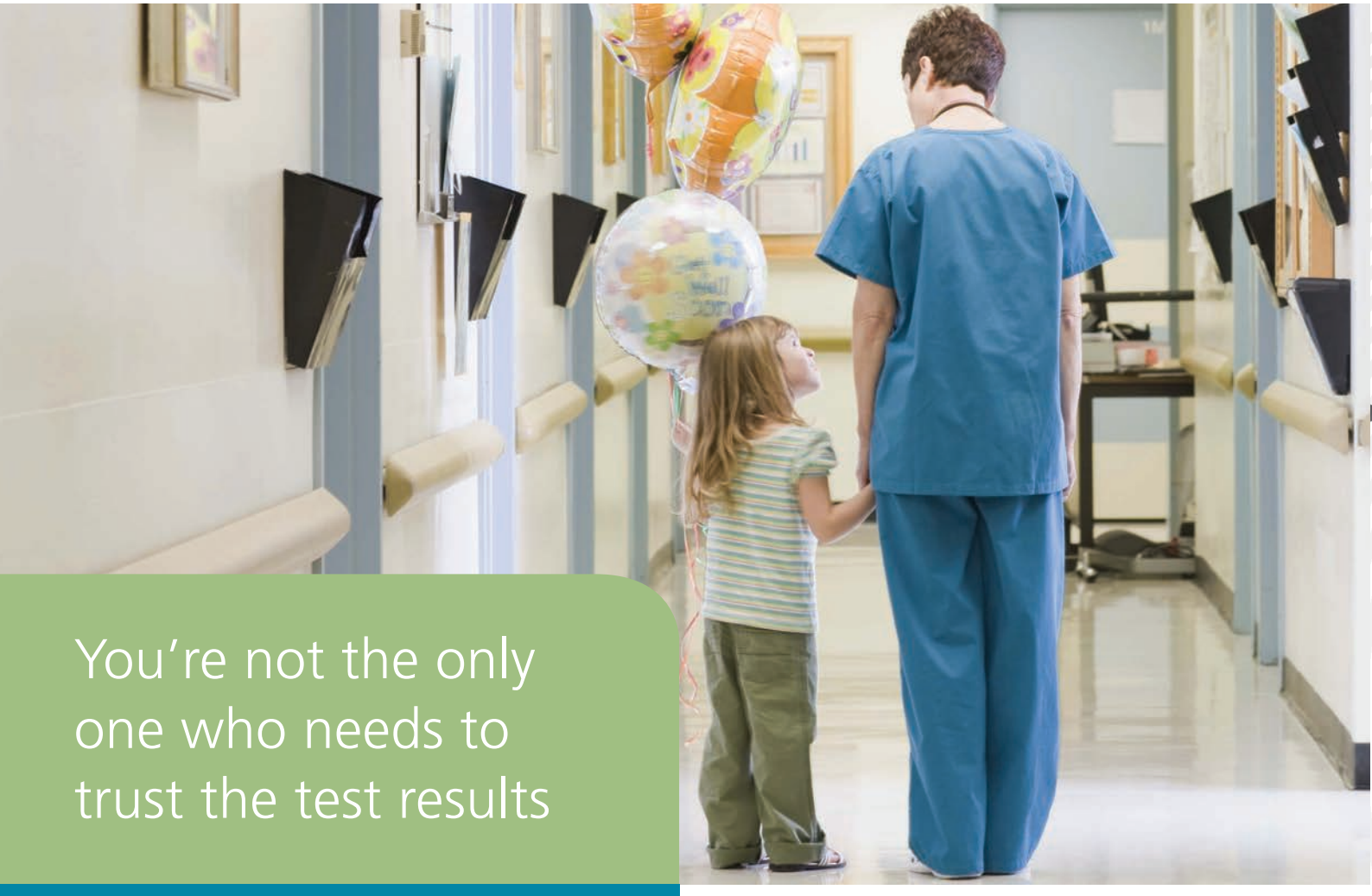
specialized pathologists are scarce. Second, the role of the pathologist in taking clinical decisions will increase based on their central role in extracting more data from tissue. Digital pathology will complement the increasing need to develop quantitative data sets to help develop predictive algorithms for personalizing cancer care.

OC: With the consolidation of healthcare resources, pathologists are working in distributed environments, often separated from colleagues and laboratory facilities, so digital pathology will help to improve efficiency in sharing slides and cases. Also, the implementation of electronic health records is optimized by digital images.

In addition, early detection and screening programs, combined with minimally invasive biopsy and surgery, often results in less tissue to analyze. This, coupled with the emergence of new biomarkers and increased trend towards companion diagnostics, is driving the use of multiplexing several markers on a single sample, which is best interpreted using automated image analysis.

In the end, digital pathology will lead to greater efficiencies in laboratory workflow, provide decision support tools, and transform the interaction between oncologists, pathologists and patients, as well as researchers, instructors and students. In 10 years' time, we predict that, digital pathology will be known simply as "pathology."

MASS SPECTROMETRY SOLUTIONS FOR *IN VITRO* DIAGNOSTICS



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Research advances
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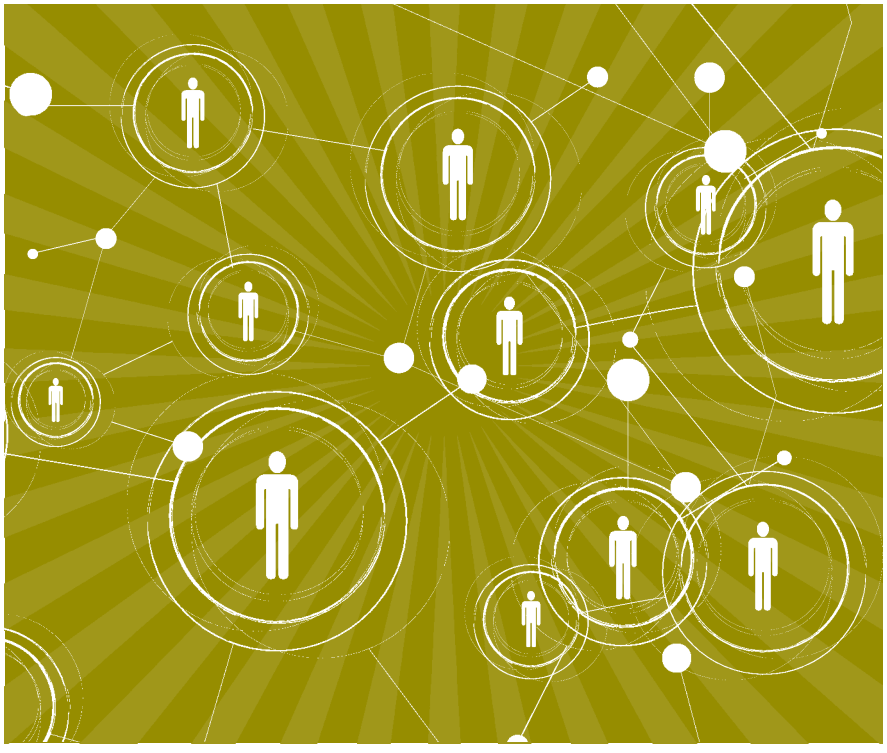
Human Proteome Maps – Two Perspectives

Now more than 90 percent complete, this project could prove invaluable for medical research.

By Roisin McGuigan



The sequencing of the human genome represented a game changing moment for science, but it didn't provide the whole story. The human proteome, which is still not fully explored, represents a wealth of information. Identifying which proteins are being expressed at a given time, in what tissues and in what volume, could provide completely new insights into disease conditions and aid drug discovery. It's not hard to see why so many would want to be involved in this important research challenge.

In May of this year, two teams published drafts of the human proteome in Nature; researchers at Johns Hopkins University and the Technische Universität München (TUM) (1, 2). The Pathologist spoke with Bernhard Kuster, lead author of the Munich team, about the progress of their research and the most important findings. Michael Tress of the Spanish Cancer Research Center queries the quality of the data and offers a counter opinion.

At a Glance

- *Two maps identifying over 90 percent of the human proteome were published this year in Nature.*
- *The information gathered from this research could crucially support the advancement of medical research, some results are also surprising.*
- *Several groups are collaborating to integrate all of the information available into online, free-to-access databases.*
- *Not everyone is convinced by the value of these projects, and question their accuracy.*

We've Come a Long Way Together

In an interview with The Pathologist, Bernhard Kuster, whose team has so far cataloged over 18,000 proteins, explained the next important steps for the mapping project.

"We have now joined forces with the Johns Hopkins team to take the research one stage further. By compiling all of our data into one central source, the ProteomicsDB, and partnering with others, such as the Human Protein Atlas [a Swedish team that is working to develop antibodies against all proteins; see sidebar, "The Human Protein Atlas"], our hope is to eventually provide as broad coverage as possible of the human proteome," says Kuster.

Clearly, the research efforts so far have generated huge amounts of data – data which needs to be accessed and used by the scientific community at large. Both proteome maps are available online (through the ProteomicsDB and Johns Hopkins Human Protein Map) and application programming interface (API) access has been enabled for the TUM database, which allows computers to "talk" to the database.

"Non-coding" coding regions

One of the most interesting findings from Kuster's work so far (mirrored by the findings of the Johns Hopkins group) was the discovery that some regions of the genome previously thought to be non-coding do actually code for protein. "This is especially significant as it implies that we don't yet fully understand which DNA

regions encode for proteins. I believe our findings are only the beginning; I suspect we will find a lot more 'non-coding' regions that have functions we aren't yet aware of. We do not yet know what biological significance these proteins will have, but uncovering their functions is an interesting future task for us," explains Kuster.

Missing proteins and our diminishing sense of smell

On the flip side are the so called "missing" proteins, that is, proteins thought to exist that weren't found during the course of the study. "There are several explanations for this," Kuster says, "the first is that the current technology simply isn't able to detect them. Another is that they are expressed in tissues we haven't yet looked at. The third, and possibly most interesting, is the hypothesis of "obsolete" genes. During the course of our work, we discovered that many olfactory G protein-coupled receptors (GPCRs) were missing, and in much higher proportions in comparison to other protein families. This pointed to the possibility that it was more than a technical problem or a case of examining the wrong tissue type." Added to this theory is the work of other geneticists who have proposed that many olfactory GPCRs are no longer functional (4). We also know that humans have lost a lot of their sense of smell compared with other animals in which these proteins are active (dogs and truffle pigs being two good examples). "Even though this finding may not have far reaching clinical implications, it is nonetheless extremely interesting from a scientific perspective, and will also help in the annotation of the human genome," adds Kuster.

The quest for 100 percent

It is clear that mapping over 90 percent of the proteome is a significant advancement for proteomics and biomedical research in general, but Kuster believes there is still some way to go: "While the majority of the proteome is now mapped, the last 10 percent is still missing, and it may transpire that getting that last 10 percent turns out to be ten times harder than getting the first 90! It is very difficult to say when, or if ever, we will be able to claim to have a complete map." He admits the idea of a 'complete human proteome' is rather a philosophical one: "We have currently set out to find one protein product per gene. But we all know that a single gene can have many protein products, perhaps even hundreds or thousands. We are still very far away from covering every variant of every protein. Despite this, we have come a long way and we are learning more than ever before."

Next steps

As well as continuing their current work on the human proteome, Kuster and his team also want to work with diseased tissues (most of their data is currently taken from healthy tissue) in order to gain more information on protein expression in different contexts. They hope to begin similar efforts for the mouse (an important disease model), the rat (an important toxicological model), other animal species, and plants (which could prove valuable for the food industry).

Working to map the human proteome is important in and of itself, but Kuster predicts that it will also help to progress clinical research and development by supporting the discovery of new molecular disease markers, or by tracking the progress of drug treatment. "There's a clear translational aspect to our work, although these developments will obviously arrive further in the future," he adds.

Despite the volume of work ahead, Kuster is happy with the progress made so far. "In terms of my hopes for this project, I'm pleased to say that we are already ahead of expectations, mainly because of the excellent technology that we have at our disposal (and its ability to analyze huge volumes of data), collaborations with our academic partners, and also because of the donation of data from fellow scientists. One of the best aspects of the scientific community is the spirit of collaboration. Many people are willing to share their discoveries to provide different pieces of the puzzle, and by doing this we are able to do so much more than we could alone. It is this emphasis on collaboration and this willingness to freely share information that I find truly heartening in scientific research; without it, we wouldn't be where we are today," he concludes.

The Human Protein Atlas

- Established in 2003
- Set up by a Swedish team, headed by Mathias Uhlén
- Key aim is to generate an antibody against every human protein
- Information on over 21,000 antibodies has been collected to date, targeting proteins from more than 16,600 genes
- Overall objective is to have a first version of the proteome by 2015, and a curated version by 2020

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Professor Bernhard Kuster is the chair of proteomics and bioanalytics at the Technische Universität München (TUM), Germany.

A Word of Caution

By Michael Tress

When the two proteome maps appeared in Nature, the numbers certainly raised some eyebrows. My colleagues and I are part of the GENCODE consortium, which is annotating the human genome, so we are very interested in large-scale proteomics information. We were also in the process of publishing our own analysis (1), and we were surprised by what these papers were reporting. How had they managed to find more protein products from genes than any previous experiment of this kind, finding several thousand more genes than the entire combined efforts of the worldwide human genome project, all without any kind of technological breakthrough?

When we looked at our data, we noticed we had not identified any peptides for olfactory receptors (ORs). Further, other databases, such as PeptideAtlas and PRIDE-Q (2), which I consider to contain high quality data, also identified very few ORs. We therefore reasoned that a study which identifies multiple ORs (Pandey's group found 108, Kuster's 200) is likely to be unreliable. We decided to investigate.

We carried out a quality test on the ORs the groups had found, and this produced some concerning results. For example, the Pandey data shows that ORs are most highly expressed in the liver (3). For us, this confirmed what we had suspected – the data was not reliable.

We carried out a reanalysis of the peptides detected in both experiments, and found reliable evidence for between 7,500 and 8,000 of the genes they identified. The Pandey group's data was entirely their own, published previously in the Journal of Proteomics Research. The Kuster group carried out comparable experiments on a similar number of tissues (using CellZome technology), but in their paper they also included results from a reanalysis of the spectra from previously published large-scale experiments. However, they did not provide the results of their re-analyses, meaning we could only analyze the CellZome data, which is 25 percent (roughly 4,500 peptides) of the Kuster data (although the CellZome data alone identifies genes for 36 ORs).

"I think, at best, this data will not aid good scientific research."

The Pandey group reported 17,296 genes and the Kuster group over 18,000. I personally believe that the Mann Group (4,5) identified as many if not more protein coding genes than the Pandey group and Kuster's CellZome experiments. We carried out a comparable analysis of these experiments at the same time as the proteome map data, and after filtering the peptides we found that the various studies had identified 8,050 (Nagaraj et al), 8,929 (Geiger et al), 7,972 (Kuster CellZome) and 7,458 (Pandey). This led us to conclude that the two proteome maps contained questionable data.

Our analysis identified many factors which I think contributed to this data inflation: the inclusion of poor quality spectra, using a single peptide to identify multiple genes, confusion between leucine and isoleucine, the use of two search engines to increase the peptide coverage rather than to increase the reliability of the peptide spectrum matches, and the combination of multiple experiments (which ratchets up false positive rates). Some of the problems we identified only affected one of the two data sets and some affected both (3).

These two studies stand out because they analyzed a wide range of human tissues, rather than cell lines. It's possible that research groups carrying out tissue-specific experiments will use this data as a gold standard, and even now will be writing proposals based on it. This concerns me because I think, at best, this data will not aid good scientific research. At worst, I suspect using this data could be a poor use of time and resources. In situations like these, the onus is on the authors to provide information that is as accurate as possible.

Large-scale evidence for cross-tissue peptide expression would be a real step forward for proteomics. However, the information provided by these draft proteome maps cannot be used without first filtering out large amounts of possibly unreliable data.

Michael Tress is a staff scientist at the Spanish Cancer Research Centre (CNIO), Madrid, Spain.

Have an opinion on this topic? Please feel free to join the debate, email fedra.pavlou@texerepublishing.com

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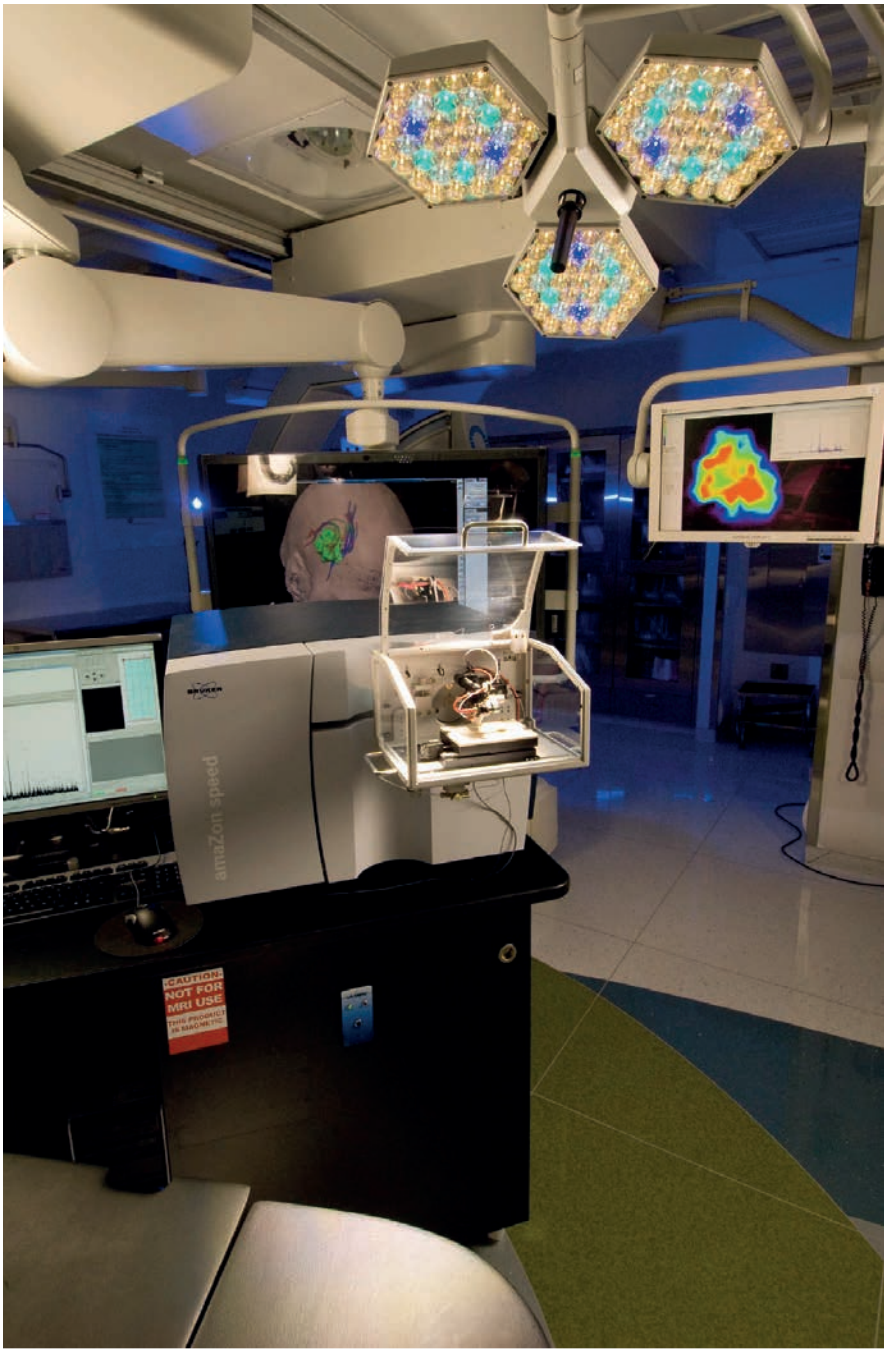
Operating Within Molecular Margins

Is the accurate identification of tumor types during surgery – in real-time – a realistic possibility or a pipe dream?

By Sandro Santagata and Nathalie Agar

Today, we still rely on a century-old technique – microscopic review of H&E stained frozen sections – to analyze tissue in an intraoperative setting. And while the value and diagnostic expertise provided by the pathologists who use such traditional techniques are unquestionable, knowledge is advancing around us. Despite progress in other fields, we lack advanced tools in pathology that allow us to quickly assess the molecular make-up of biopsy specimens during a tumor resection. Consequently, molecular information remains hidden in the tissue until later diagnostic evaluation with immunohistochemistry, genetic analyses or other molecular techniques. The ability to conduct molecular analysis during surgery would offer big advantages to pathologists from a cost and workflow perspective, but more importantly, it could have a life-saving impact on the patient.



At a Glance

- *Frozen section still remains the cornerstone of intraoperative diagnostics.*
- *New tools, such as desorption electrospray ionization mass spectrometry (DESI MS) may provide 'real-time' diagnostic information during tumor resections.*
- *Using DESI MS to define molecular margins of a tumor marks a new paradigm in surgical thinking.*

Stepping away from tradition

In the operating theatre, time is of the essence; there is a real need for creative new approaches that allow pathologists and surgeons to make diagnostic decisions based on detailed molecular information. Using mass spectrometry (MS), we have been able to rapidly detect molecules and distinguish tumor from normal tissue during surgical procedures in real-time (1).

DESI MS in action

Desorption electrospray ionization (DESI) targets the tissue surface with a stream of charged solvent droplets, which extract molecules from the sample and introduce them into the mass spectrometer. An MS profile is quickly acquired in a line scan or a more detailed two-dimensional molecular image, a fact that extends its use to tissue sectioned on a slide.

Corporate Backing

Waters Corporation recently announced an exclusive agreement with US-based instrument manufacturer Prosolia for DESI technology for clinical mass spectrometry applications (June 2014). One month later, it announced its acquisition of rapid evaporative ionization mass spectrometry (REIMS) technology from MediMass. Clearly, the company sees real potential in the technology. Here, Jeff Mazzeo, Senior Director, Health Science Business, Waters Division tells us why.

What promise have you seen so far with use of ambient ionization mass spec technology in surgical applications?

During an operation to remove cancerous tissue, surgeons can be unsure of exactly where the diseased tissue ends and healthy tissue begins. The result is that healthy issue is sometimes excised, or worse, parts of a tumor are missed and a follow up operation must be scheduled to remove the remaining malignant tissue. I believe the work conducted by Santagata, Agar and team, as well as work by Zoltan Takats (1), have shown that ambient ionization MS has the potential to one day transform surgical resection procedures.

Do you foresee any immediate challenges to more routine use of MS in this setting?

Like many, we are encouraged by the early research with DESI and REIMS techniques. While still in their conceptual stages of development, the technologies must continue to demonstrate application benefits to a range of diseased tissues in much larger patient populations. There is also ongoing development work to be completed to make the instruments more feasible for routine surgical use in terms of installation, maintenance and use. Lastly, regulatory strategies must be discussed and agreed in order to develop solutions that can meet regulatory requirements so that clinical trials can be performed.

The advantages for the surgeon and patient are obvious, but what do you think this would mean for the histopathologist?

Just as we believe that MS has the potential to transform surgery, we also believe that imaging MS has the potential to transform histopathology. While more work is needed to correlate the results of MS investigations with traditional histopathology techniques, objective chemical information will hopefully add to the understanding of the morphology of tissue sections.

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The spatially resolved data can then be overlaid on top of a histology image for validation of the methodology outside of the operating room, which allows correlation of histology with signatures (multiple peaks) or specific single peaks that target one molecule. Intraoperatively, single point analyses are performed in seconds, providing molecular information on the tissue at stake. We believe this approach has several advantages over traditional molecular evaluation:

- It requires minimal to no sample preparation, and can be performed in ambient air conditions
- It can reliably measure small molecules, such as lipids and metabolites, with masses below 1,000 Daltons
- It can acquire useful molecular information in a matter of seconds.

It's important to note that this two-dimensional molecular imaging approach allows us to validate MS data against the gold standard of histopathology, which also offers real value in research.

By using lipid profiles acquired by DESI MS, we have been able to discriminate different types of brain tumors (for example, meningioma from glioma), different gliomas subtypes (for example, astrocytoma from oligodendroglioma) and different grades of tumor (for example, WHO grade II glioma from WHO grade IV glioma).

In our latest study, we used DESI MS to detect a single metabolite that is generated by gliomas with mutations in isocitrate dehydrogenase (IDH) 1 and 2 genes (1), found in the high majority of low grade gliomas. These mutated enzymes generate an oncometabolite – 2-hydroxyglutarate (2-HG) – which accumulates to high levels in these gliomas and can be used to trace tumor cells.

DESI MS approach, step-by-step

The full clinical protocol is described in our recent paper (1); however, we can summarize the DESI MS process in three key steps: 1) Smear or touch prep from tissue on glass slide; 2) Place glass slide on the instrument; 3) Acquire data in single points analysis intraoperatively; (2D imaging in the lab).

We have been able to reproducibly detect 2-HG in regions containing tumor, but not in normal tissue or regions of hemorrhage, which supports the use of DESI MS in defining the margins of a tumor and, therefore, guiding surgery. The high sensitivity and specificity was exciting to see,

"As the expertise using these approaches increases, validation studies will be required to determine the elements of pathology practice that might be redundant and those where complementary information is added to existing modalities."

as was the ability to detect tumor cell concentration down to under 5 percent. We have validated our findings using a complete DESI MS analysis system installed in the Advanced Multimodality Image Guided Operating (AMIGO) suite at the Brigham and Women's Hospital (BWH) in Boston, MA, USA (see Figure).

Mutations in IDH1 and IDH2 are not only found in gliomas but also in intrahepatic cholangiocarcinomas, acute myelogenous leukemias (AML) and chondrosarcomas, so we believe the detection of 2-HG or other metabolites with DESI MS could be useful in other clinical applications. Moreover, DESI MS could have applications in the diagnosis of a broad range of tumor types and could also provide a good alternative to intraoperative MRIs – without the associated high cost and disruption to standard operative workflows.

Tools of the future?

We hope that our work will pave the way for further development and clinical trial testing of metabolite guided surgical approaches; we have proof of principal studies underway both in the area of brain tumors as well as for resection of breast cancer (our manuscript on this study will soon by published in PNAS). These are the first steps in what could be a revolution in the way we conduct surgery. Admittedly, implementation of these technologies will require a long period of rigorous testing and validation. As the expertise using these approaches increases, validation studies will be required to determine the elements of pathology practice that might be redundant and those where complementary information is added to existing modalities. Indeed, it seems likely that the new intraoperative approaches being developed by us and other groups around the world will provide truly complementary tools – based on mass spectrometry and other analytical tools – for the pathologists and surgeons of tomorrow.

Sandro Santagata is an assistant professor in pathology at Harvard Medical School and practices neuropathology at Brigham and Women's Hospital and Children's Hospital, Boston, USA.

Nathalie Agar is the founding director of the Surgical Molecular Imaging Laboratory (SMIL) in the Department of Neurosurgery at Brigham and Women's Hospital, and an assistant professor of neurosurgery and of radiology at Harvard Medical School.

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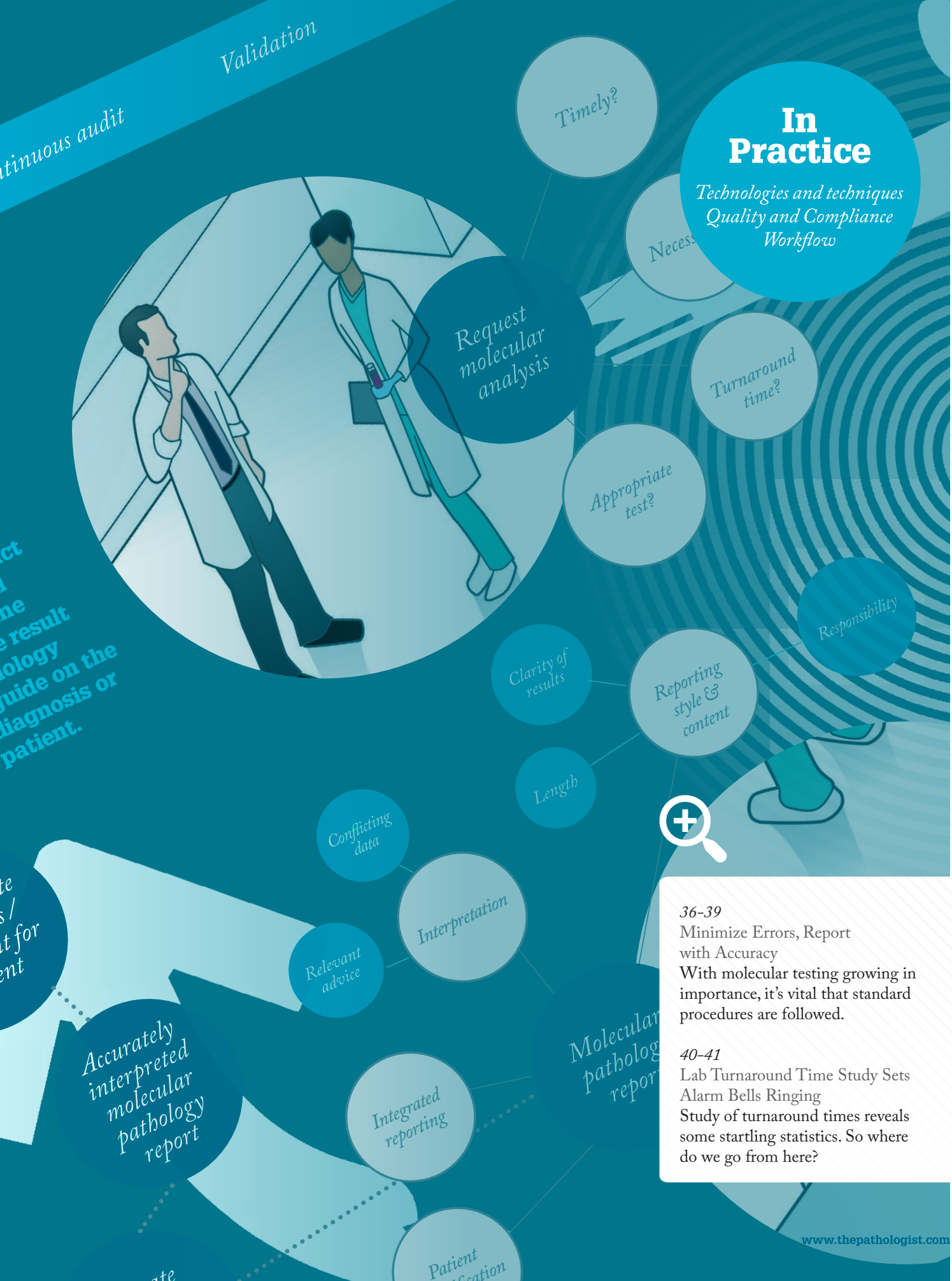

In Practice

Technologies and techniques
Quality and Compliance
Workflow

Minimize Errors, Report with Accuracy

Best practice guidance to ensure that molecular pathology labs get the best possible result

By Ian Cree

Molecular pathology is growing at an astonishing rate. It's an area of medicine that continues to generate excitement, not only amongst health care professionals, but also the public. Rarely a week passes by without an announcement from the press about a medical 'breakthrough' and everyone appears to be sold on the merits and promise of personalized therapy. Often, these breakthroughs are the result of molecular research and many targeted drugs are now reaching the clinic.

This is an exciting time for medical research, but what does it mean for those involved in performing molecular pathology tests for cancer patients?

At a Glance

- *Molecular testing is becoming an increasingly important part of the diagnosis of any patient with cancer.*
- *The molecular pathology process consists of many stages, each of which can be a source of error.*
- *A European, multidisciplinary team has developed guidelines for laboratories that aim to minimize the occurrence of errors and to facilitate an accurate report on which to base cancer treatment.*
- *The ESP and RCPath are now recommending this guidance as best practice to laboratories performing molecular pathology tests for cancer patients.*

The new drugs require new testing processes and have challenging requirements for both equipment and staff. Inevitably, pathology laboratories are faced with greater workloads, greater resource requirements, greater training needs – and greater room for error.

Given the large number of processes and people involved – from the moment a molecular pathology report is first requested to its finalization – the importance of standardizing procedures and implementing guidelines is obvious. Progress is certainly being made in this regard. For example, in the US, the College of American Pathologists (CAP) in collaboration with the International Association for the Study of Lung Cancer and the Association for Molecular Pathology (AMP) have recently issued guidance for laboratories operating lung cancer molecular pathology services (1).

Recognizing the need to develop a more general guideline – or a best practice document – for laboratories performing molecular pathology tests in Europe, a large team made up of pathologists, geneticists, scientists, industry representatives, oncologists, quality assurance experts, and others, was assembled from across Europe. We focused our initial efforts on developing a guideline for those involved in performing tests for patients with cancer since the majority of advances in personalized medicine have been made in this therapy area.

We are now one year on and have produced a consensus document (2), which has been recognized and is supported by the European Society of Pathologists (ESP) and the UK Royal College of Pathologists (RCPath).

Beyond the obvious

The modern challenge to pathologists is to think beyond the diagnosis and classification of a disease, and to produce information that guides treatment more efficiently and accurately. To be effective, we must be clear about our responsibilities at every stage of the molecular pathology process – from requesting molecular analysis to pre-analytical sample handling to nucleic acid extraction and analysis to the reporting of results. Furthermore, the requirements for the laboratories offering those services need to be clearly outlined.

The infographic on page 38 summarizes all of the individual steps (and key considerations) involved in the molecular pathology process, which are discussed in more detail in the guidance (2). All steps (and factors or technologies related to them) share the risk that any deviation from standard operating procedures is likely to have a negative, knock-on impact on the overall process, leading to an inaccurate result. If this guidance is followed as a minimum precaution, we believe the resulting molecular pathology report will not only be accurate, but it will also provide the optimal treatment for the patient. With multiple stages and people involved, the catch is getting everyone on the same page.

Request or reflex

For those requesting a molecular pathology test, it's very important to consider what type of test is needed; when the result is required and, perhaps most importantly, whether a test is needed at all. Currently, not everyone who would benefit from a cancer test is getting one. There will always be workload and budgetary concerns within pathology, but these can be better balanced through integration of molecular pathology with other departments. And while this is already happening (there are improvements across Europe), it is still very challenging. Our ultimate goal is to ensure that those in need have access to testing. A standard operating procedure that supports the multidisciplinary team (MDT) requesting process can help, but much comes down to good communication between the clinic and the laboratory.

Another way of tackling the problem is to consider reflex testing. In other words, pathologists are made directly responsible for the molecular analysis request based on a patient's diagnosis and tissue availability. Given that more than 10 percent of patients with any particular diagnosis need molecular analysis, reflex testing has great potential. For example, we routinely do HER2 testing for all breast cancer, and a similar approach to EGFR mutation testing in lung cancer can save time in deciding treatment in patients who are often very ill at diagnosis. There are many circumstances where a pathologist should exercise his or her clinical judgment and simply order the test.

For the laboratory, reflex testing has a lot to offer in terms of speeding up the process. It is also financially attractive to hospitals in some instances, because it can reduce the number of MDT discussions and the number of outpatient appointments. It does, however, need to be balanced against unnecessary testing in patients who do not need further treatment. With that in mind, the RCPath and ABPI (Association of the British Pharmaceutical Industry) are in the process of developing planning tools that should help departments decide when reflex testing might be beneficial.

Common blunders

As you move along the pathway outlined in the infographic on page 38, you will all see potential problem areas. From experience, the majority of issues that lead to inaccurate results occur during the pre-analytical stage, starting as early as the discussion about which biopsy to take.

Thereafter, DNA or RNA extraction can often be prone to errors. Many people still use manual processes, but there are good automated systems available that help eliminate some errors and help to achieve better consistency of extraction. Analytical methods vary, and comparative studies of these are needed. Such studies can generate economic data that not only convinces pathologists, but also – and more importantly – helps gain backing from national health care regulators.

Aside from processes, one very important aspect that is discussed throughout the guidance is the need for accreditation of laboratories in accordance with the External Quality Assessment (EQA) scheme, which is applicable to all laboratories in Europe. It is extremely important for laboratories offering molecular testing to participate. For those who do, I would advise that you look at the results of EQA schemes, and the mistakes made by others, which may help highlight areas where you might be introducing errors in your own lab.

Those laboratories who believe they can perform molecular pathology tests without the sort of oversight that accompanies EQA participation are taking big risks and should be aware of that fact.

Clearing clinician confusion

With the high (and growing) number of processes involved in performing a molecular test, it's no surprise that the final complex report can result in clinicians scratching their heads in puzzlement. We must aim to produce coherent reports and accurate advice that guides treatment in the clearest possible way. We have provided recommendations in this area, but we will increasingly need to provide tools that will allow clinicians to easily and accurately interpret and act upon reports. The US is making a lot of headway in this regard. The CAP Cancer Committee has launched 70 cancer protocols in total that aim to standardize pathology reporting across a large range of cancers; these are now an integral part of routine pathology practice across the country. The RCPath and ICCR (International Collaboration on Cancer Reporting) minimum datasets are another part of the solution, but much depends on their implementation by the commercial providers of laboratory information systems.

Just the beginning

Here, we have only touched on a small number of points included within the overall guidance. The figure provides an overview of the critical considerations when conducting a molecular pathology test. The authors of the guidance certainly acknowledge that further guidance and standards can and should be developed for each of the separate elements of the process, but we've made a good start by covering all of the core processes.

While the new guidance is specific for cancer, there are many elements that are applicable to other facets of molecular pathology. Our scientific understanding and technology are evolving all the time, so we acknowledge that revisions will be needed in the future.

Where next? Well, work is ongoing to develop the guidance even further, and is currently focusing on internal quality assessment. In the meantime, the ESP and RCPath are disseminating the guidance as best practice for laboratories performing molecular pathology tests for cancer patients. Our ultimate goal is to support everyone working in molecular pathology laboratories to provide the right diagnosis and treatment for patients accurately and efficiently. If you share that goal, we hope you will join us on the journey.

Ian Cree is the Yvonne Carter Professor of Pathology at Warwick Medical School, UK.

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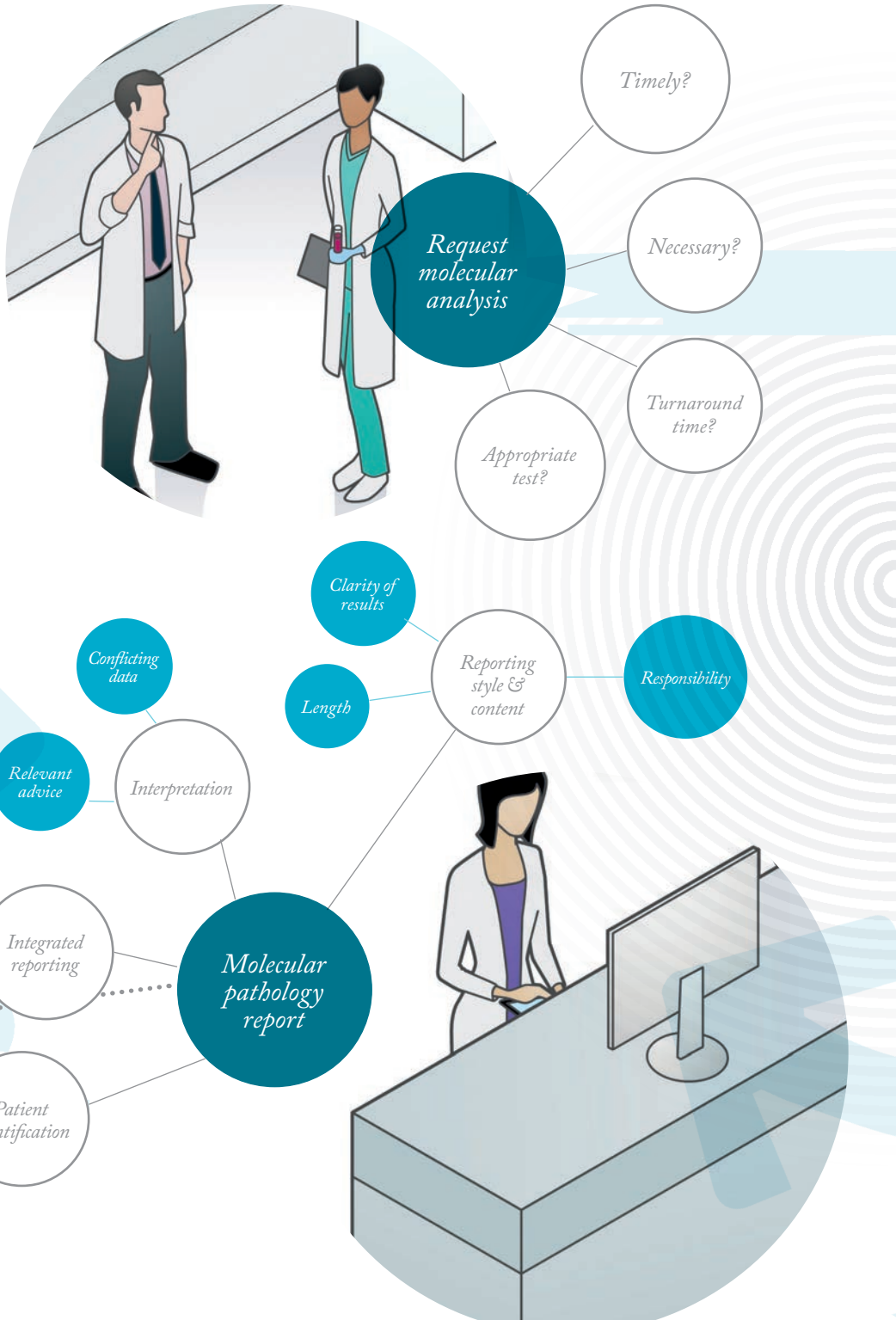
Best practice guidance for molecular pathology labs

Processes and key considerations when conducting a molecular pathology test for cancer patients. Errors introduced at any stage along this pathway are likely to impact negatively on the overall process, and the outcome could be an inaccurate result and a molecular pathology report that fails to guide on the most appropriate diagnosis or treatment for the patient.



Accreditation → Staff training → SOPs → Checklists

- Sample handling & receipt
  - Labeling
  - Specimen type and origin
  - LIMS
  - Barcoding
  - Tracking
  - Transport time and temperature
  - Fixation requirements
- Sample processing
  - Micro-/macro-dissection
  - Labeling
  - Centrifugation
  - Temperature
  - Cross contamination
- Analytical methods
  - PCR/NGS/Sanger, pyrosequencing
  - Cross contamination
  - Single gene assay/Panel testing
  - % Mutations to be tested for
  - # Genes to be tested
  - # Samples
- DNA/RNA extraction
  - Quantification
    - Spectrophotometry
    - Fluorometry
    - PCR
  - Automated/Manual
    - System trials
    - Cross contamination
    - Labeling
  - Storage
    - Temperature
    - Labeling

Lab Turnaround Time Study Sets Alarm Bells Ringing

Pathologists in high-throughput laboratories are working as fast as they can to return results as quickly as possible. But are clinicians actually looking at them?

By Enrique Rodríguez-Borja

In any fast paced pathology laboratory, turnaround time (TAT) of results is extremely important. As laboratory pathologists, we may imagine our clinical colleagues sitting anxiously in front of their computers waiting for our reports. But actually this often isn't the case. Sometimes they don't access our results for days. And in a few cases, they aren't accessed at all.

Why is TAT important?

As pathologists, we're consistently expected to work efficiently – so too are clinicians – and various models are used to assess our performance in this regard. But total TAT (defined here as the time from the clinician requesting a test to receiving and interpreting the results) is very rarely studied. Last year at our clinic we established a maximum TAT for our outpatient day hospitals. But even if my laboratory meets these standards and validates results within this timeframe, the information still needs to be accessed by the clinician in order to be of any value to the patient. I know how efficient my lab is, but I was curious about my clinician colleagues. Could I find out when my results were consulted? This motivated my investigation into post analytical TAT, in other words, how long it takes for a clinician to access patient test results, once they left my lab at the University of Valencia Hospital Clinic in Spain (1). Some of the results were surprising – and alarming.

In many of today's labs, the majority of results from pathologists are "in the cloud", so not only do we no longer print hard copies, but we can see when our results are accessed by clinicians. For two months we collected two specific times concerning each request: the time the results were made available on the intranet, and the time the results were first accessed by a clinician. We also established that the latest time for consulting results on the day in process (the time limit) would be 3 pm.

Based on the advice of clinicians, we established a maximum TAT of two hours for processing requests from our day hospitals. This means that from receiving samples in the laboratory to reporting basic biochemistry results on

At a Glance

- *Investigation into turnaround times (TAT) reveals alarming statistics – 27 percent of "priority requests" are not looked at for several days; seven percent are not consulted at all.*
- *TAT is no longer just a problem for the laboratory, everyone involved in the process – from requesting and taking a sample to consulting the result – must take responsibility for efficiency.*
- *Total TAT needs to be defined and agreed by all clinical services.*
- *Measuring total TAT will be a challenge and new methods must be established.*

our intranet, no more than two hours should elapse.

Good news, bad news

Let's start with the positive results from our study, which included 945 requests; the vast majority (73 percent) of clinicians accessed our results the day they became available, which is the ideal scenario. However, one-fifth were not accessed for between one and eight days (despite the results being available). Surprisingly, 27 percent of the tests we carried out were consulted late or not at all (see Chart). It's a shockingly high number, which implies that the initial requests were perhaps less crucial than the clinicians initially thought. Were these results just unimportant from the start or had there been a failure to follow up? After discussing this with them it seemed that they were largely made because of oncological protocols attached to treatments and "just in case" scenarios.

Finally, a small number of cases were consulted before the complete results were available. This was our fault because our laboratory failed to provide the results within the two-hour timeframe, but I was pleased to note that after this initial enquiry by the clinician, full results were made available fairly quickly (between 13 minutes to an hour after the clinician initially accessed them), so the waiting time for results in these cases was not too long.

Our study turned up some interesting findings about what happens to our results once they've left the lab. But using TAT as a measure of efficiency is not always straightforward.

No measurement, no improvement

"If you cannot measure it, you cannot improve it". Lord Kelvin's quote perfectly illustrates the dilemma we are currently facing in our pathology labs: how can we possibly improve TAT if we cannot measure it accurately? Currently, there is no system in place to do so; there are huge variations in lab workflows and there is no standardized method for measuring TAT. For example, TAT for our lab would usually only include the intra-laboratory tests or "pure analytical phase" part of the work, but why? Most laboratory errors occur before and after lab testing (2), and these two phases may also be responsible for up to 96 percent of total TAT (3,4).

"No matter how capable your laboratory is, a failure to communicate and establish standards with other clinical services will result in inefficient practices"

The majority of laboratory information systems (LIS) do not measure total TAT (the time from initial clinician request through to their consultation of the results) or even the individual TATs for the pre and post analytical phases in the testing process. In effect, our laboratory is operating blind. How do we know exactly how much time has lapsed since the sample was obtained to when it arrives in our laboratory? How do we define the time the sample is in the laboratory? Before or after centrifugation? And which machine or device is recording the time? And how?

As pathologists, we must be able to prioritize our work. If all requests are equally urgent, then in reality, none of them are deemed urgent. So clinicians must make us aware of those requests that are high priority.

But to be truly effective as a laboratory, we must agree with the rest of the clinical services (such as clinicians and phlebotomists) a total TAT for the requests we receive. We must also define what we mean by those TATs – what specific stages in the process do they include?

Once TATs are agreed and defined we must continue to measure the degree of compliance with them.

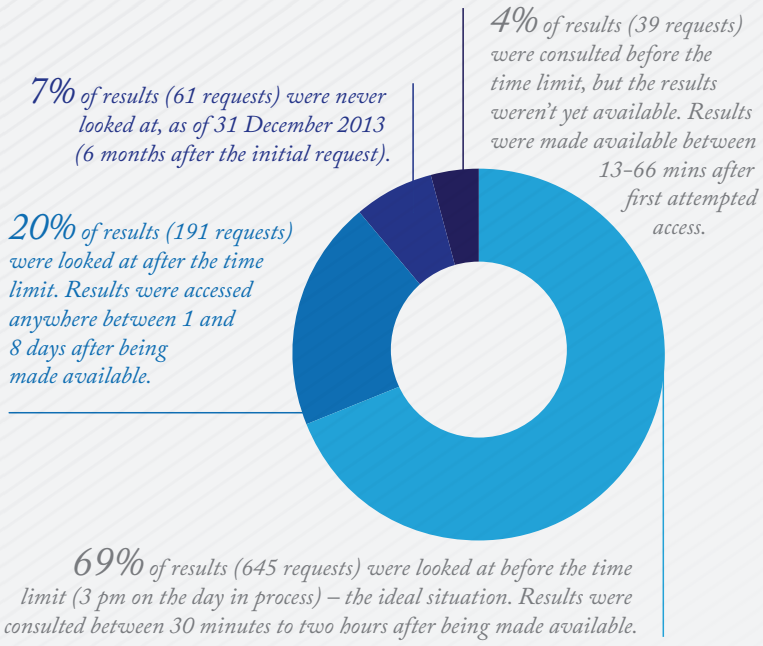
What needs to change?

The information from our study demonstrates the value of measuring TATs. In this case it has also served to highlight a serious issue: the volume of requests that are not consulted.

As pathologists, we must always aim to improve our TATs by lowering our delivery non-performance rate (found to be four percent in this particular study). But, improvement has to come from both sides. Communication with clinicians is essential – our colleagues must be aware of when our reports will be available in order to encourage them to consult results earlier.

LIS could play an important role. We would recommend that LIS developers implement a software function, which allows us to measure TAT both during the time the specimen is in our laboratory, but also before it arrives and after it leaves, giving us important information on the pre and post analytical stages. This would result in much closer collaboration and transparency between various groups within the healthcare system. As an example, the phlebotomist could record the initial venipuncture step and collection of the sample, our laboratory could then record arrival and analysis of the sample, the time we

Clinician consultation of lab results in an outpatient hospital



validate it and make it accessible to the clinician. Finally, the time the clinician accesses the result could be recorded, giving us a full and clear picture of the sample's journey from the moment it was taken. Ideally, all of these times would be monitored by software, using a completely computerized physician order entry system.

Pathologists, clinicians and patients would all see benefits if our processes are optimized. In our case, these results have led us to implement several improvement measures. Importantly, we have encouraged clinicians to consider which of their requests are really in need of prioritizing, and which are not. We've also urged them to consult available results earlier since we have demonstrated that our lab meets its TAT targets 96 percent of the time.

Think outside of your lab

The most important thing we have learned from our study is that improving TAT is no longer just a "laboratory problem". The time it takes to obtain a sample, the length of its journey to your laboratory, the hour at which the clinician consults your report – all of these things have an impact on your efficiency and your workflow. To focus simply on speed within the laboratory does not provide the full picture and will not optimize delivery of a test result from initial request. The fact is, no matter how capable your laboratory is, a failure to communicate and establish standards with other clinical services will result in inefficient practices. To tackle the challenge presented, a new method has to be created, established and controlled by both laboratories, clinicians, and other health professionals working in close collaboration.

If we have no information on TATs at all phases of the testing process, we can't detect inefficiencies and potential drawbacks, making it very difficult to introduce strategies to improve. If my laboratory is analyzing samples it receives at lightning speed but the samples arrive very slowly or doctors consult my results very late, then what am I actually achieving?

Total TAT is a crucial, bottom-line measurement of the efficiency of all the services involved in testing a patient and one which deserves much more scrutiny as we strive to continually streamline and improve our services.

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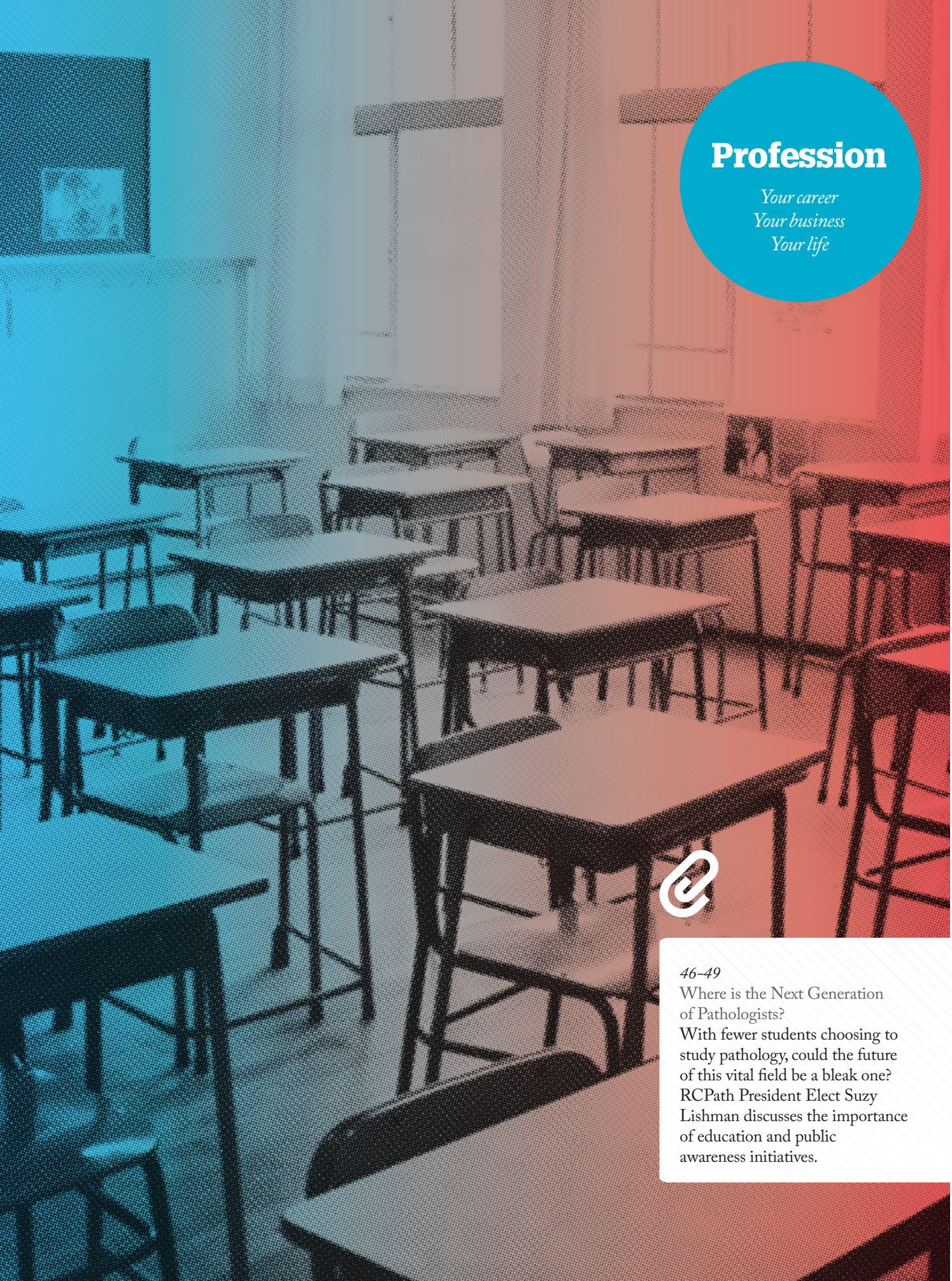

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Where is the Next Generation of Pathologists?

Inadequacy of course content, lack of awareness, poor perception, changing healthcare priorities – it's no wonder pathology is struggling to attract new talent. Can the UK's Royal College of Pathologists help buck the trend?

By Fedra Pavlou

You're a pathologist. Obviously something happened during your academic studies that made you think: I'd like to get involved in that! Now that you work in the profession, you understand the crucial role that pathology plays in supporting high standards in patient care and in the advancement of scientific research. So why aren't more medical students choosing the profession of pathology? Certainly, numbers are dwindling, and given that a large portion of pathologists are nearing retirement age (1), it's now more important than ever to reinvigorate interest in this field of medicine.

At a Glance

- *Fewer medical students are choosing pathology today.*
- *Course content must provide more extensive coverage of pathology if its value is to be recognized.*
- *Ever-expanding curricula, economic pressures and healthcare reforms are negatively impacting pathology teaching.*
- *Profile-raising public awareness initiatives demonstrate the value, and increase the attractiveness, of the profession.*

But that's easier said than done. Television programs, such as CSI and Quincy, M.E., have led to the public thinking that pathology is solely about performing complicated analyses to help cops catch criminals. For most pathologists, this couldn't be further from the truth. This misapprehension is causing problems for the profession, and it needs to be tackled in two key ways. The first: pathology's profile in general needs to be raised – we need to show that it goes well beyond the autopsy slab and a quizzical detective. The second: the way that pathology teaching is delivered needs to be improved in a way that reflects the true value of the field. With medical students being under increasing pressure to learn non-clinical skills, such as communication and leadership, the teaching of other disciplines is being squeezed. Pathology, sadly, is one of those.

Returning to form

"I do think there's a lack of knowledge and understanding about the range of career options in pathology. Students don't have the sort of exposure that they do to other specialties and therefore it means they often don't consider it as a career choice," admits Suzy Lishman, Royal College of Pathologists' (RCPath) President Elect.

Reflecting on her experience in the UK, Lishman believes the move away from solid blocks of didactic pathology teaching, and towards its integration into a systems-based approach is not helping. "It's great for putting the patient at the center of care, which is where they should be. But it's not so good for students learning the basic science that underpins diagnosis and treatment," she explains. "I believe we've possibly gone too far in the wrong direction. We need to bring it back. Students need a basic understanding of pathology, physiology, anatomy, etc., before they can understand how disease affects the patient and how they can care for them," she says. Right now, she thinks a lot of work is needed to boost the understanding of the importance of pathology, but first and foremost, actually getting students to recognize it as an independent subject is even a challenge.

Lishman believes the demise of the hospital autopsy hasn't helped. "The number of consented autopsies performed in the UK has plummeted in recent years. This, I believe, is a global phenomenon and means that students don't have the opportunity to see autopsies on patients for whom they've cared so they don't have the chance to see how valuable they can be," she says. Although she believes that medical students have a huge appetite for pathology, with other subjects competing for crucial curriculum airtime, something's got to give.

Having spoken with many pathologists around this subject recently, it's apparent that the issues described by Lishman extend into Europe and beyond. In fact, a Canadian research team felt compelled to look into the factors that lead to a career choice in pathology, citing manpower shortage as their reason for conducting the study (2). While they highlighted the importance of good course content and access to pathologists as key factors to attract students to the profession, also made some interesting observations around the influence of rumors and negative perception amongst students. Hearsay, perception and stereotype were actually three of the six key factors that they found influenced career choice (see "Six Factors Influencing the Career Choice of Pathology"). Raising awareness of pathology more generally, ensuring good course content, but also providing students with access to pathologists, should improve the appeal of the profession. In other words it all starts with education.

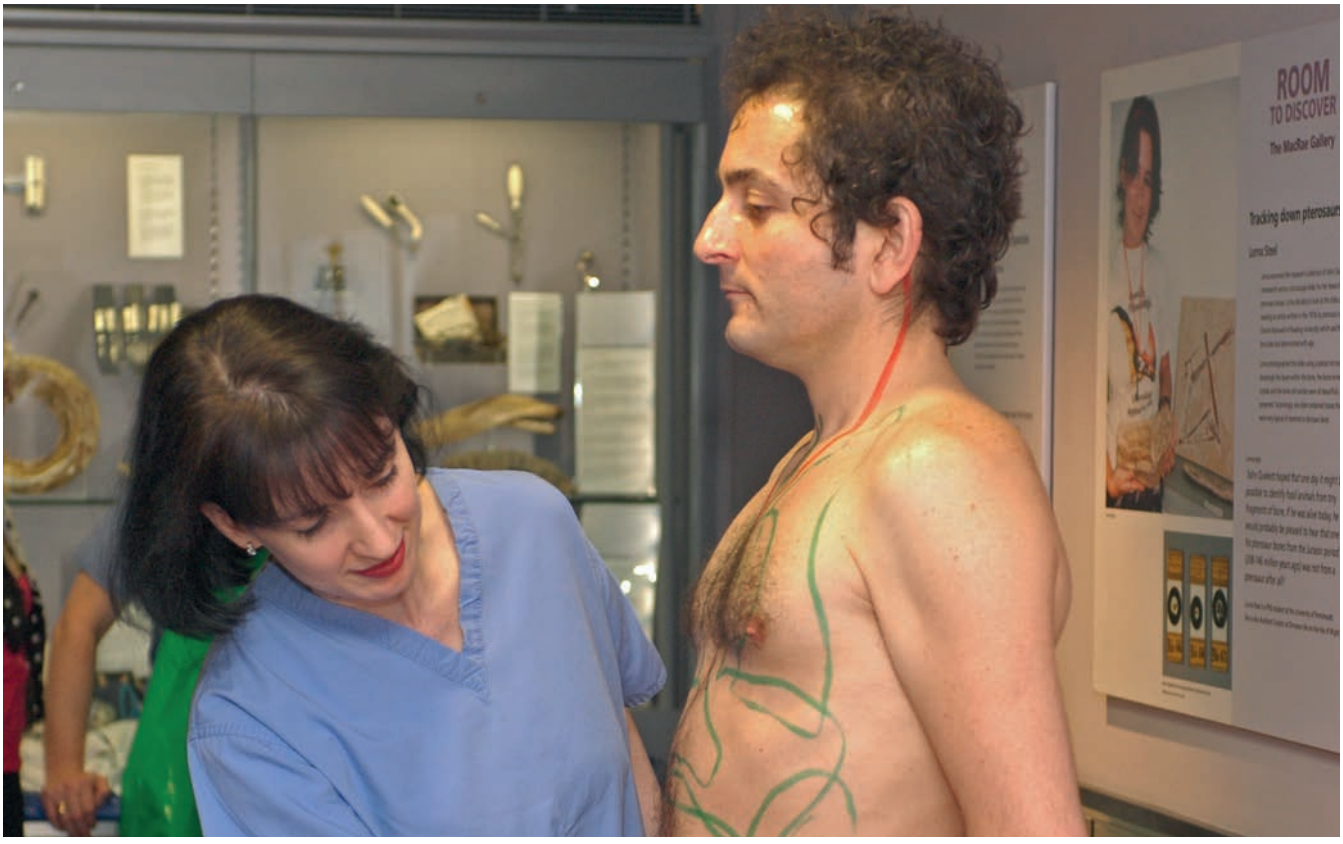

Figure 1: Suzy Lishman performing a "virtual autopsy".

"Training doctors of the future who are fit to practice and understand and value pathology is one of our biggest challenges."

Overhaul obstacles

In the UK, the RCPath is taking an active role in tackling these issues. The first step is working towards standardizing the undergraduate medical student curriculum, to ensure that every student has a basic grounding in the science of pathology, irrespective of where they study. The second was to introduce an undergraduate membership category of the College, encouraging students to learn more about the specialty by providing careers advice, talks, bursaries, competitions and awards. Increased collaboration with other medical and pathological societies formed the third step, particularly with the introduction this year of the Pathology Summer School, attended by 80 students from around the UK. Finally, the College encourages medical students to get involved in its public engagement program – either attending an event aimed at increasing their understanding of pathology or helping to deliver events for schools or the public.

However, one potentially huge hurdle to progression is the planned overhaul to the way in which junior doctors are trained in the UK. The emphasis is being firmly placed on flexibility, with doctors becoming generalists for several years after qualification, before deciding on a specialism. The main reason? To make a much larger resource pool available to over-stretched accident & emergency departments. "It could go one way or the other; this overhaul could encourage more people to come into pathology because we have well-developed curricula and clear career paths that are attractive to trainees. Or it may put people off because they'll think it's too general and takes too long

Six Factors Influencing the Career Choice of Pathology

1 Medical students' perceptions (accurate and inaccurate) regarding the role of pathologists in medical care

2 The role of the course as a career choice. The course was most important in medical student and pathologist group. Non-content related factors such as teaching style or personality more important than content for medical students.

3 Lifestyle of students, residents and pathologists. Most prominent factor in the resident group.

4 The influence of rumor among medical students. Students expressed that many career decisions were based on class rumors.

5 The influences of clinical experience and role models. All groups agreed that these were important influences, both in discovering or confirming pathology as a career as well as excluding other specialty choices.

6 Overcoming the negative stereotype of the pathologist. Negative stereotype known to even junior medical students.

Source: T. Hung et al., "Residency Choices by Graduating Medical Students: Why Not Pathology?", Hum. Pathol., 42, 802-7 (2011).

– if you do three or five years of general medical training, you're probably not going to want to do another five years of pathology training. So I think the reconfiguration of training is probably going to be one of the factors that determines how pathology evolves over the next decade," says Lishman.

The RCPath's work on postgraduate curricula is particularly important; over 50 different exams are already developed for the 19 pathology subspecialties. Depending on the outcome of planned overhauls, they may need to revise the curricula for every one of those 19; no enviable task. Lishman acknowledges that "training doctors of the future who are fit to practice and understand and value pathology is one of our biggest challenges."

I love pathology

A second key challenge is raising awareness of the value of pathology. Not only is this important for attracting the next generation of pathologists, but it's crucial in raising the profile of the profession more generally – the work you do affects everyone. As pathology services continue to be financially squeezed, a positive (but a realistic) public profile helps.

In the UK, the I Love Pathology brand and website, and National Pathology Week are making some real headway.

First launched by Lishman in 2008, National Pathology Week is a unique initiative that aims to build the profile of pathology amongst the public through simultaneously-run events across the UK. "The original plan for the first National Pathology Week in 2008 was for 40 events to be held around the country where pathologists would either go out into communities and hold events, or invite the public into their labs. In the end, 320 events actually took place – which is far more than we expected!" says Lishman.

National Pathology Week takes place in the first week of November and the number of events is growing year on year. The I Love Pathology website was born out of the annual initiative and is the RCPath's year-round public engagement program. It hosts information about past events and provides educational

"It's no good doing all the hard work and then letting somebody else make the announcement; we need to be out there communicating it to the public and to policy makers so that they value pathology."

and branded materials, the aim being to allow pathologists to select a tried and tested off-the-shelf event that they can just deliver. "One of the most heartening statistics we gained from feedback was that over half of the people who have attended National Pathology Week events had never attended any sort of science related event in the past," remarks Lishman.

And it's not just the public who have benefited. "The initiative has a real feel-good factor. Many event organizers have said that it has been great for teamwork in their departments. It has also allowed them to get together with different disciplines with whom they rarely speak. Some said that it has reignited their passion for the subject because teaching it, or communicating it to members of the public, reminded them of exactly why they liked it in the first place," she says.

According to Lishman, the "virtual autopsy" (Figure 1) is by far the most popular event amongst attendees. "It's important to remind people that the majority of the work that pathologists do is with, or for, the living, but this event has always been the most well-received. I've given it many times now, to rooms of 30 to 500, aged from eight to 80 years, and at venues ranging from medical institutions and schools to music and arts festivals. I always get the same level of enthusiasm," she says. Now pathologists up and down the country are perfecting their own virtual autopsy events. Not only have these sessions been important in raising the profile of pathology, but they've also educated the public on the dignified and respectful way in which autopsies are performed.

"One of the things I've been particularly keen to highlight is the cross over between arts and science and to work with less traditional audiences," explains Lishman. One such event focused on the heart, where attendees were invited to view striking images of the organ and to admire its beauty and symmetry. "When you step back, you see that pathology really is beautiful," reflects Lishman.

This year sees the very first International Pathology Day on Wednesday, November 5th. Working with more than 40 international organizations, the aim will be to raise the profile of pathology on a global scale. "We're hoping that there will be hundreds of events happening all around the world on that day, all focusing on pathology," says Lishman.

Communication is key

These initiatives have so far proven to be a hit in the UK; given their relative infancy, the overall impact on the future of pathology remains to be seen. It will certainly be interesting to see how the international community responds once events are rolled out globally.

Certainly, National Pathology Week has been great for encouraging pathologists to step outside of their labs and to get closer to the public that they serve. This needs to happen more often. Pathology is at the forefront of the molecular revolution that is transforming the way that diseases are diagnosed and treated; indeed there are very few news stories about innovations in medicine today that aren't underpinned by pathology. But how many people are aware of that fact?

"It's no good doing all the hard work and then letting somebody else make the announcement; we need to be out there communicating it to the public and to policy makers so that they value pathology," concludes Lishman.

The exceptional achievements already made by pathologists can only be built upon if a healthy pipeline of new talent can be secured – and that means attracting government and public support for your endeavors. Admittedly, it's not going to be easy. Hurdles will continue to present themselves, but by working together, we can make a difference. Promoting the amazing work that you do, for example, by giving talks to students at your old University department or by speaking with the press, will help make your vital field more attractive to everyone. You're shaping the future of medicine – why not shout about it?

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If you'd like to tell us about awareness-building initiatives that you're involved in, or give us your thoughts on the issues discussed in this article, I'd love to hear from you: fedra.pavlou@texerepublishing.com

Always Pushing the Boundaries

Sitting Down With…
Stephen Minger, Chief Scientist,
Cellular Sciences – Life Sciences,
GE Healthcare, London, UK

What initially attracted you to neuropathology?

I got interested in the human brain in the 1980s working at a leading diagnostic neuroepilpsy clinic at the University of Minnesota – I thought it possessed tremendous complexity, but its susceptibility to diseases such as Alzheimer's disease (AD) also fascinated me. A fantastic talk by Peter Davies inspired me further, and he actually ended up being my PhD mentor at Albert Einstein College of Medicine in New York. Everything I know about neuroscience I learned there. It was an amazing place.

You're disappointed with lack of progress in AD. Why?

Significant advances have been made in the diagnosis of AD. But, if you look at the therapeutic advances, they still unfortunately amount to very little. Thirty years on from starting my PhD there's not a single drug on the market that does anything to really impact on the disease. There are some medicines that can help slow it down or help with symptoms, but these only work on a subset of people and only provide some benefit.

Back in 1990, my then boss said to me, "Once you get AD, it's all over. You need to understand what happens 50 years before it gets to that." He was absolutely right. Looking at postmortem tissue from people with AD tells you very little. Disease susceptibility and factors that impact AD development happened long before you see the clinical features. I felt really despondent and thought, "I'm in a dead-end field – how am I going to make an impact?"

What ignited your interest in stem cells?

I read a study by a Swedish group who, in the 1980s, transplanted human fetal tissue into the brain of Parkinson's patients – their long-term clinical recovery was phenomenal. I thought that was very cool! But would it work in AD? So I did a post-doc in a neural transplantation lab at UCSD where we developed some of the first fetal-derived neural stem cells during the 1990s. When I moved to the UK from the US I brought that technology with me to Guys Hospital, London.

When I started my lab in London, I planned to use human stem cells to develop therapies for brain diseases. It was a frustrating process; I could make the cells I wanted, but very quickly I'd lose them, because they'd change state. That's why neural transplantation never really took off. And then – boom – human embryonic stem cells arrive.

And that was your next tricky step…

Right. What started out as an email to Peter Braude – board member of the Human Fertilization and Embryology Authority (HFEA) and Head of the Assisted Conception Unit at Guys – led to the creation of a small group at Kings College London that consisted of me, Peter, and Susan Pickering. We had one goal: to produce human embryonic stem cells. We lobbied parliament, overcame slammed doors, and one day in 2002 I heard the lead story on BBC Radio 4: the HFEA had granted the first license in the world for human embryonic stem cell research. We did it! That was a really seminal event in my life. It categorically changed everything.

What tempted you to join GE?

At that time they were exploring some pretty cool areas related to stem cells. I'd never linked GE with cells or cell therapy, but they think way out of the box. And I'm not a conventional scientist; I push boundaries. So when GE asked me to join them, I was astonished. The first time I met my manager, he said, "You're the kind of guy that's going to keep me awake at night."

I'm now responsible for what we call "blue skies", a tactic that explores where we might want to be in 20 years. It could be tissue printing, nano-neural prosthetics, microbiomic diagnostics, which are at the top of the list, but they're actually more like five to ten years away.

"We lobbied parliament, overcame slammed doors, and one day in 2002 I heard the lead story on BBC Radio 4"

My CEO, John Dineen, is not your typical CEO of a Fortune 500 company. He's a visionary. I was on the phone with him recently and he said, "Any company can make stuff that makes money, we're making stuff that changes the world".

Are you still following AD?

Yes. I read an interesting paper the other day. Researchers are tracking thousands of patients who are double *ApoE4* positive; apparently, these people have a roughly 80% chance of developing AD, independently of other amyloid mutations. Why haven't others been doing this? We've known about the *ApoE4* gene for 20 years! I'm going to follow up on it.

Do you ever regret moving away from academia?

When I washed up in the UK in 1996 I had nothing. When I got my own lab, it was pretty much empty, aside from a rusty water bath. But things turned around for me and though I loved academia, I would never go back. I never thought I'd work for a big company, I always thought I would have to give things up, but that's not true. In fact, I've accomplished more in the last five years than in the last 20. I receive comments from people who think I've "sold out", but what we do makes a huge impact. So, I'd unabashedly say, "No, I haven't."

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