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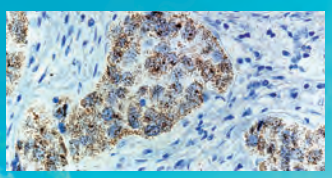

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Online this Month

The Pathologist on Twitter

What got you talking this month? Here are some of our most popular tweets…

Top Tweet

We know the positive impact of lab medicine on healthcare. But does anybody else?
The Pathologist @pathologistmag
What can be done to make lab medicine more visible? http://ow.ly/F8dwQ
10:45 AM - 3 Dec 2014

Alan Jackson @AlanPath
@pathologistmag @ilovepathology Even in retirement I explain lab medicine to friends and colleagues, and have just joined "The Pathologist"

Lab Tests Online AU @LabTestsAu
MT @pathologistmag @ilovepathology How to make lab medicine more visible? Time to get out of the lab & communicate. http://ow.ly/F8dwQ

Ebola infographics: charting death tolls and infection rates
The Pathologist @pathologistmag
#Ebola in graphics: http://econ.st/12q5JnE
11:00 PM - 8 Dec 2014

A synthetic blood-brain barrier for pediatric studies
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#bloodbrainbarrier on a chip could stand in for children in pediatric research: http://bit.ly/1vE4eOY
3:40 PM - 8 Dec 2014

World's 27th richest person to spend US$100 million on cell research
The Pathologist @pathologistmag
Microsoft billionaire launches institute for cell science: http://bit.ly/1yKNvdx
1:00 PM - 9 Dec 2014

Dutch researchers: "Kissing is a great example of exposure to a gigantic number of bacteria in a short time"
The Pathologist @pathologistmag
Is one kiss worth 80 million bacteria? http://bbc.in/11cZyTF
7:30 AM - 24 Nov 2014

Nature Communications study investigates cancer using evolutionary principles
The Pathologist @pathologistmag
Applying evolution and computational modeling to the Darwinian struggle between normal and cancerous cells: http://bit.ly/1xVzOa2
9:00 AM - 22 Nov 2014

Ron H. N. van Schaik on the undisputable value of pharmacogenetic tests
The Pathologist @pathologistmag
Pharmacogenetic tests – are they useful and reliable? What are the recommendations? http://ow.ly/FwtJN
10:25 AM - 9 Dec 2014

US researchers divide the world into regions using disease prevalence
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A global map of human disease – what factors influence where you'll find a particular pathogen? http://bit.ly/11XZs2J
12:30 PM - 4 Dec 2014

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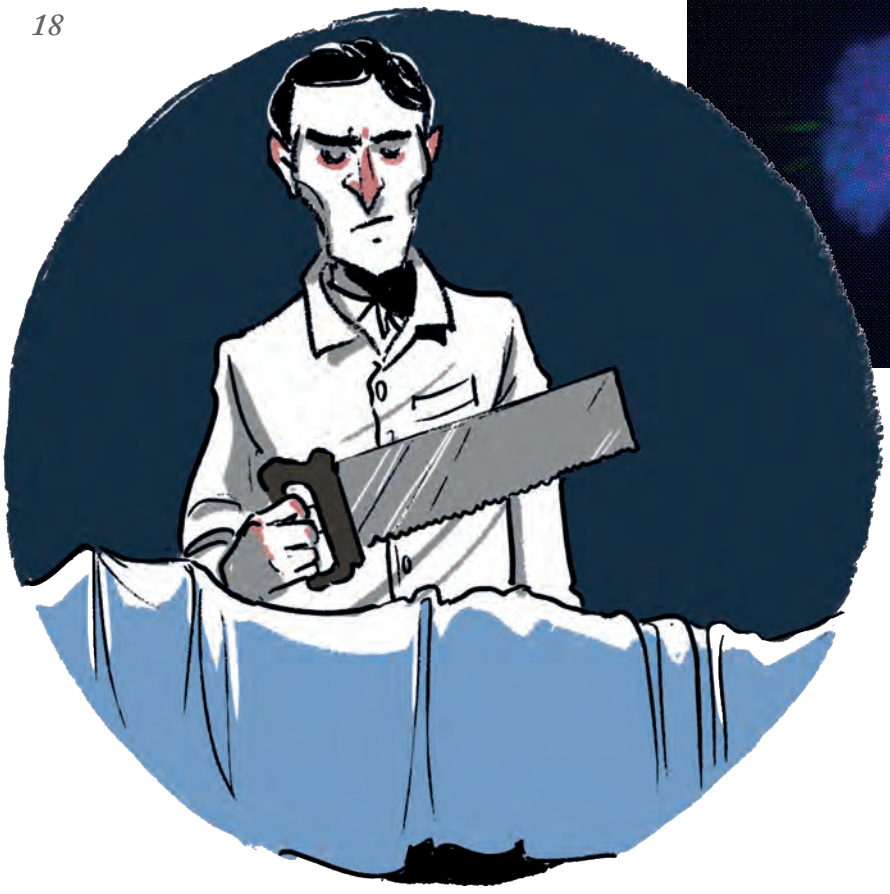

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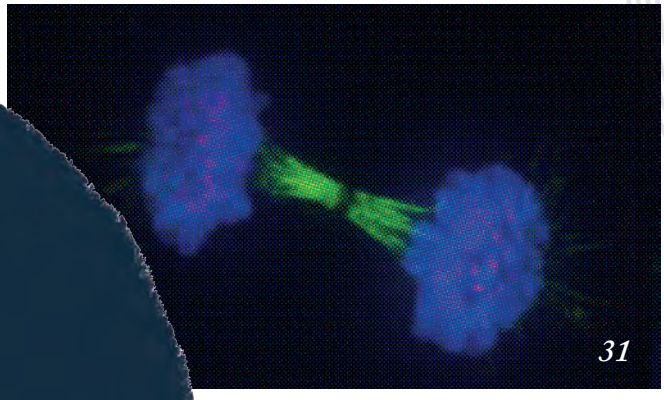

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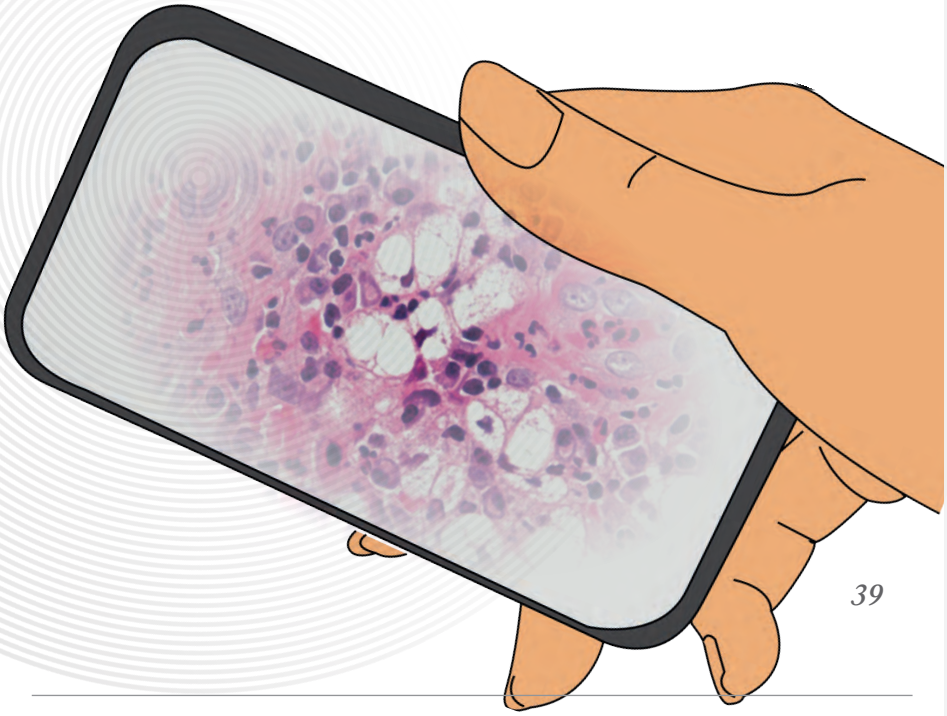
On The Cover

Stereotype of the pathologist who doesn't like people
Credit: Giles Crawford, Illustrator



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Opening the Floodgates

The controversial approval of a home-based DNA test kit in the UK raises eyebrows.

Here's a hypothetical scenario: someone uses a home DNA test and presents to their healthcare practitioner (HCP) with grave concerns because they are "at risk of developing" a whole host of diseases. The HCP sees more than one patient that day with similar concerns. Healthcare horror story or positive progression?

Whatever your view, this could soon be a reality – at least in the UK. Earlier this month, the country's Medicines and Healthcare Products Regulatory Agency (MHRA) agreed to allow California-based DNA service providers 23andMe to market its saliva collection kit and personal genome service (PGS). Interestingly, just over a year ago the FDA banned the company from promoting its service in the US. Why? According to the warning letter issued in November 2013 (1), 23andMe were doing so "without marketing clearance or approval" and the healthcare regulator did "not have any assurance that the firm has analytically or clinically validated the PGS for its intended uses" despite numerous information requests. According to a spokesperson, however, those things that were a concern to the US watchdog have been removed from the CE marked test (2) and a subsequent letter to 23andMe confirmed the violations had been addressed (3).

However, cautions of the potential health consequences that could result from false-positive or -negative assessments remains, in particular for high-risk conditions, such as BRCA-related genetic risk and drug responses. Nevertheless, 23andMe CEO, Ann Wojcicki, believes providing information on 254 diseases and conditions (which includes categories such as carrier status, health risks, and drug response) to customers "is empowering" (2).

The company's intended use of the data generated from these tests has also set alarm bells ringing for some. In fact, director of the Center for Law and the Biosciences at Stanford University in California went as far as to query if the firm's long-term business plan was to make money by selling the data. Perhaps that's not an entirely surprising accusation given 23andMe's recent partnership with Google to supply genomic data for the tech giant's latest endeavor: building a complete database of the human genome (4).

The actual impact that public availability of these tests will have on UK consumers, HCPs and pathology labs remains to be seen and I'd really like to hear your thoughts. Do you welcome these tests? Could they have a positive impact on your work or indeed the profile of your profession? Let us know by commenting on our website (www.thepathologist.com). For now, the MHRA, as well as the Department of Health and patient societies, like the Alzheimer's Society, warn to approach them with caution.

Fedra Pavlou
Editor

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1. *FDA Warning Letter issued to 23andMe, Inc. (22 Nov 2013) http://1.usa.gov/1avFitx.*
2. *M. Roberts, P. Rincon, "Controversial DNA Test Comes to UK," BBC News (2 Dec 2014) http://bbc.in/1CARHQQ.*
3. *FDA Close Out Letter issued to 23andMe, Inc. (25 Mar 2014) http://1.usa.gov/1ukDayG.*
4. *M. Schubert, "The Google Genome," The Pathologist, 2, 42–43 (2014).*

Michael B. Prystowsky

Professor and university chairman of pathology at Montefiore Medical Center and the Albert Einstein College of Medicine, New York, Michael oversees a pathology service line performing over 11 million tests per year at more than 200 sites to support clinical programs at the Montefiore integrated healthcare system, which trains pathologists to be fully integrated as physician members of healthcare teams. He serves as governor for the College of American Pathologists (CAP) and as a counselor for the Association of Pathology Chairs.

Michael offers his opinion on the practicality of biosensor-based testing of drug resistant pathogens on page 38.

Jackie James

In 2004, Jackie was appointed clinical senior lecturer at Queen's University Belfast (QUB) in Ireland and a consultant pathologist at The Belfast Health and Social Care Trust. She is currently based in the Northern Ireland molecular laboratory, delivering a diagnostic service for solid tumors. Jackie led the development of the Northern Ireland Biobank and has been its director since 2010. Her current research focus is the biology of squamous cell carcinomas, in particular the development of new strategies for molecular classification of upper aero-digestive tract cancers.

Manuel Salto-Tellez

Professor and chair of molecular pathology at QUB, Manuel is also the deputy director of the Centre for Cancer Research and Cell Biology, and a consultant pathologist at the Belfast Health and Social Care Trust. He has authored 200 peer reviewed articles, and has edited and contributed to key textbooks on pathology and oncology. Manuel serves on key committees of RCPath and Cancer Research UK and leads the Molecular Pathology Program at QUB and Northern Ireland – Molecular Pathology Laboratory. His main research interest is the interface between genotype and phenotype.

One page 47, Jackie and Manuel discuss the need for improved molecular diagnostic training and their vision of the future role of the pathologist.

Elena Castro

Elena received her MD and PhD from Universidad de Salamanca in Spain, and worked as a clinical research fellow in cancer genetics and prostate cancer at the Institute of Cancer Research & The Royal Marsden Hospital, London, before joining the Spanish National Cancer Research Center (CNIO). Her research focuses on populations with high prostate cancer risk. "There is growing evidence for the role of DNA repair defects in prostate cancer carcinogenesis and tumor progression. We have demonstrated that *BRCA* mutations not only increase the risk of prostate cancer, but are associated with more aggressive disease".

Elena discusses the high impact of *BRCA* mutations on survival rates on page 12.

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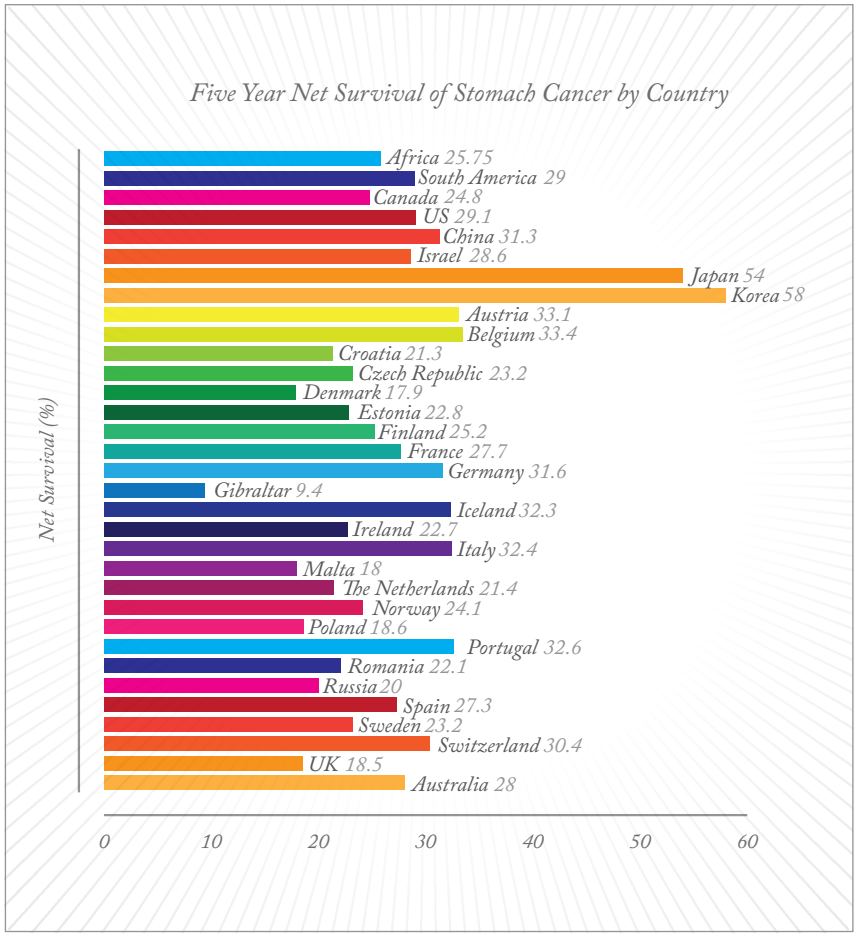
Global Cancer Study Reveals Shocking Statistics

Study of over 25 million people highlights huge geographic differences

The most comprehensive comparison of worldwide cancer data ever published has uncovered some striking disparities, highlighting both the extremely low survival rates in some countries, and also the large differences in treatable cancers. Among the starkest examples are differences in net survival of childhood acute lymphoblastic leukemia – ranging from just 16 percent in Jordan to 80–90 percent in Canada and many parts of Europe (1). However, huge variations aren't only seen in the divide between developing and developed countries, which one would expect – even within Europe, survival rates vary significantly.

The study, published in The Lancet, includes data from 279 cancer-based registries, originating from 67 countries (23 of which are considered low or middle income), and involving 25.7 million adults and 75,000 children – accounting for roughly two-thirds of the world's population. Ten common adult cancers were included: stomach, colon, rectum, liver, lung, breast, cervix, ovary, prostate, and adult leukemia. The authors found that survival of some cancers was universally low; less than 20 percent for lung and liver cancer in almost every country studied, demonstrating that both conditions are still lethal in the majority of cases. Unsurprisingly, the numbers also demonstrate that in most cases, patients in developing countries were much less likely to survive all types of cancer.

What might have been less expected is the variation observed between developed nations. An illustrative example is stomach cancer net survival from 2005 to 2009 – this was highest in Korea and Japan (58 percent), while for some countries with comparably well-equipped healthcare systems it was



less than half that – under 25 percent in Canada, Norway, The Netherlands and the UK (see Chart). The authors note that this is likely to be down to more intense diagnosis and radical surgery; cancer types with a more favorable prognosis may also be more common in these countries. Conversely, survival of leukemia in East Asian countries is low (19 percent in Japan) when compared with many European countries (40 to 60 percent).

On a more positive note, prostate cancer survival has seen marked increases; 22 countries saw a 10 to 20 percent rise in the last 20 years, but the gap is still wide – under 60 percent survival in Thailand, versus more than 90 percent in Brazil and the US.

Even when making allowance for artefacts and comparison problems in such a large dataset, the numbers make it clear that successful treatment of cancer is not simply a question of medical resources – attitudes to screening and treatment, political forces, public awareness and genetic predispositions of the population in question could all potentially come into play when it comes to surviving cancer, no matter where you live. *RM*

Reference

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Non-Invasively Diagnosing Endometriosis

Gene expression profiling could reduce surgery and increase diagnosis

Endometriosis can result in pain and infertility, among a host of other symptoms, and is thought to affect up to 10 percent of women of reproductive age. Despite this, the time between symptom onset and diagnosis can be more than 10 years (1). Why? Traditionally, the disease is diagnosed and staged during surgery, but University of California San Francisco researchers have now developed an alternative that is less invasive but highly accurate – gene expression profiling.

In a study of 77 women with endometriosis, 37 with other uterine or pelvic problems, and 34 controls, the research team analyzed the expression patterns of endometrial tissue samples, acquired using a catheter, and developed genetic "classifiers" for disease and non-disease states. The system was able to identify endometriosis with 90–100 percent accuracy, including stage (i.e. minimal, mild, moderate or severe) (1).

The authors now intend to validate their method in a larger study population, and the National Institute of Health Reproductive Medicine Network has launched a multisite clinical trial. *RM*

Reference

1. *J.S. Tamaresis et al., "Molecular Classification of Endometriosis and Disease Stage Using High-Dimensional Genomic Data", Endocrinology, 155, [epub ahead of print] (2014)*

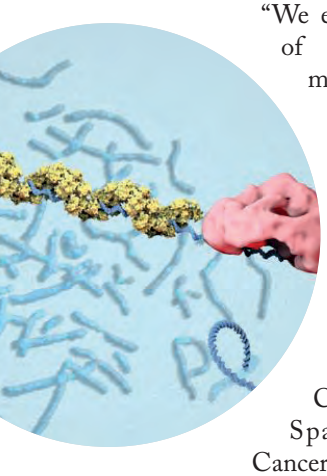
BRCA Mutations Could Reduce 10-Year Survival by Up to 50 Percent

Carriers of *BRCA* gene mutations appear to be less responsive to conventional prostate cancer therapy

	3-Year Survival	*5-Year Survival*	*10-Year Survival*
Non-carriers Surgery	99%	97%	91%
Carriers Surgery	96%	89%	67%
Non-carriers Radiotherapy	96%	91%	80%
Carriers Radiotherapy	85%	57%	39%

Table 1. Metastasis-free survival rate and treatment type for *BRCA* carrier and non-carrier prostate cancer patients.

It has previously been reported that carriers of *BRCA2* have over eight times the prostate cancer (PrCa) risk of non-carriers by age 65 (1), and for the first time last year, a link was made between PrCa prognosis and both *BRCA1* and *2* mutation status (2). Now, a further study has cemented the link, and raised the questions: Should patients with PrCa be screened? And do they need different treatment approaches?



"We evaluated the role of germline *BRCA* mutations in PrCa in 2013, and demonstrated that they not only increase risk, but are associated with more aggressive disease," (2) explains Elena Castro of the Spanish National Cancer Research Centre (CNIO), a senior author of both studies. "We showed that *BRCA2* mutations are a prognostic factor for PrCa, independent of other classical factors, such as PSA levels at diagnosis, TMN, and Gleason score. In our second paper, we wanted to study the response of carriers to conventional treatments for localized cancer – radical prostatectomy and external radiation therapy," (3).

This second, more in-depth study involving over 1,300 patients (67 of which had mutations) demonstrated that carriers may have very different reactions to treatment. In patients who received radiotherapy, 10-year survival was less than half that of non-carriers (39 versus 80 percent). "The poor response to radiotherapy in *BRCA* carriers may be due to either radio-resistance or to the development of new primary tumors," explains Castro. For surgery, the difference in 10-year survival was less pronounced, though still large; 67 percent for carriers and 91 percent for non-carriers (Table 1).

The results of the two studies make it clear that more research is needed into the link between *BRCA* mutations and PrCa, and the resulting impact on prognosis. Further, only inherited mutations have been investigated so far: "Germline mutations occur in less than 2 percent of sporadic PrCa, but somatic *BRCA2* losses have been described in approximately 15 percent of cases. There is currently no indication for genetic screening, but as technologies evolve and the cost of genome sequencing continues to decrease, it may prove cost-effective," says Castro.

Screening could also lead to more tailored treatments. "Our results support close monitoring of *BRCA* mutation carriers following conventional treatment, as these patients tend to present with metastatic relapse earlier and more often than non-carriers," adds Castro. "The most appropriate management of PrCa in this population is still unknown, but PARP (poly-ADP ribose polymerase) inhibitors may be a potential approach, and these patients may benefit from taking part in clinical trials."

The team is now working on the molecular characterization of *BRCA*-mutated tumors to try and figure out why they are more aggressive and what treatments might best benefit patients who may not respond well to more traditional approaches. *RM*

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Pathology in a Tube

Biopsy tissue sample preparation in a tube promises to be cheap, fast, reproducible and automated

University of Washington (UW) scientists and engineers are working on a low-cost device that will help pathologists diagnose pancreatic cancer faster. The first-generation device is extremely simple. It uses a fluidic transport system to expose a needle biopsy tissue sample to the sequential steps involved in fixing and staining samples for diagnosis.

We spoke with Ronnie Das, a UW researcher in bioengineering and lead author of the published paper (1).

Figure 1. The simple fluidic transport system designed to help automate and streamline biopsy tissue sample preparation and handling. (Photo courtesy of the University of Washington).

How did you get started?

The inspiration came from a related project to image tissue biopsies in 3D to aid in cancer detection and diagnosis. Pancreatic cancer development is not fully understood, and we think 3D visualization of whole tissue may provide (for a lack of better words) an added dimension to detection and diagnosis. However, before biopsies can be imaged and evaluated by a pathologist, they must be processed. This can take days. Since we were dealing with small tissue and fluid volumes, we thought "why not use microfluidics?" This resulted in our instrument: a disposable, silicone-based, credit card-sized device consisting of several circular cross-section microfluidic channels that can replicate the rudimentary processes of a pathology laboratory in minutes (see Figure 1).

Our device may provide a route for human-free handling, and since we are processing whole tissue for 3D imaging, the device also preserves specimens so that traditional pathology may still be performed. This could help maximize the information from patient biopsies while causing minimal disruption to the pathologist's workflow.

Any surprises?

This whole project continues to surprise us on both a scientific and engineering level! Microfluidics R&D is everywhere, so it surprised us that no one (to the best of our knowledge) employed microfluidics to transport and/or process whole intact tissue directly obtained from a patient. The sheer novelty and simplicity of the idea, along with the ease of creating and implementing it, means it has been well-received by the scientific community, and we have recently been awarded a National Institutes of Health exploratory grant to continue our work.

What were the challenges?

An ongoing challenge is effective tissue staining. The last significant study on whole tissue staining and processing was performed in the 1960s, when 3D optical imaging was not yet invented, so in some ways, we are rediscovering the art of staining. Specific and controlled diffusion and absorption of stains in slices is quite different from whole tissue cores that are 50–5,000 times larger in volume.

Ultimately, we are servicing medical doctors, pathologists and clinical professionals, who make the hard calls. The challenge is simple: our device must be able to reproduce exactly what pathologists are used to seeing on a daily basis, by matching or emulating traditional processes that have been established for nearly half a century.

What impact could the device have?

Processing biopsies takes time, and a pancreatic cancer diagnosis can be terrible for patients. We hope our device could eventually help reduce patient wait times, inconvenience and cost in delayed decision-making. Combined with our imaging system, and collaboration with Melissa Upton, professor of pathology at UW, we hope the tissue staining ability of the device could lead to highly informative 3D visualizations of biopsies to aid in early detection of cancer. Other applications could include processing biopsies outside of cancer, and combination with other clinical technologies, such as ultrasound elastography.

What's next?

Our main aim is to characterize and optimize our device and its functions to pathology standards. We are attempting to flow tissue from the device to the 3D imaging platform. Future designs under consideration will incorporate onboard optics or even include an interface for smartphone cameras to collect imaging data.

Reference

1. *R. Das et al., "Pathology in a Tube: Step 1. Fixing, Staining, and Transporting Pancreatic Core Biopsies in a Microfluidic Device for 3D Imaging", Proc. SPIE 8976, Microfluidics, BioMEMS, and Medical Microsystems XII, 89760R (2014).*

Diagnosing HIV With No Lab Facilities?

Point-of-care molecular diagnosis could make a big difference to disease control in remote communities

Imagine receiving a patient's blood sample and being asked to test for HIV without any lab equipment, refrigeration, trained healthcare workers or electricity. A tall order, but global health non-profit PATH scientists intend to do just that, using non-instrumental nucleic acid amplification (NINA) (1), coupled with an innovative way of modulating temperature. The system has been designed to allow diagnosis of HIV and other infectious diseases in remote and isolated communities that don't have access to laboratory services.

In low-resource locations, the lack of access to molecular testing is a significant barrier to controlling infectious disease. Transporting samples from rural communities to a central laboratory means expense, delays in getting results, and often a failure to follow up; individuals who have samples sent to a distant facility may not return to their local clinic to discover they have a disease, and therefore may not get treatment. If the lab isn't an option, over-the-counter tests might be available, but these are antibody-based and cannot detect HIV in its early stages, when patients can be most infectious.

According to the authors of a recent report, the NINA system could offer a cheap and clever alternative. The reaction is carried out in a small, portable incubator that uses the galvanic corrosion of magnesium iron alloy (only around €0.05 per reaction) when mixed with saline solution to provide heat (2). The assay, which requires a blood sample, uses reverse transcriptase-loop mediated isothermal amplification (RT-LAMP), which can be carried out at a constant temperature and does not need a thermal cycler to detect pathogen nucleic acids (in this case for HIV). Once the test is complete, the results can be visualized

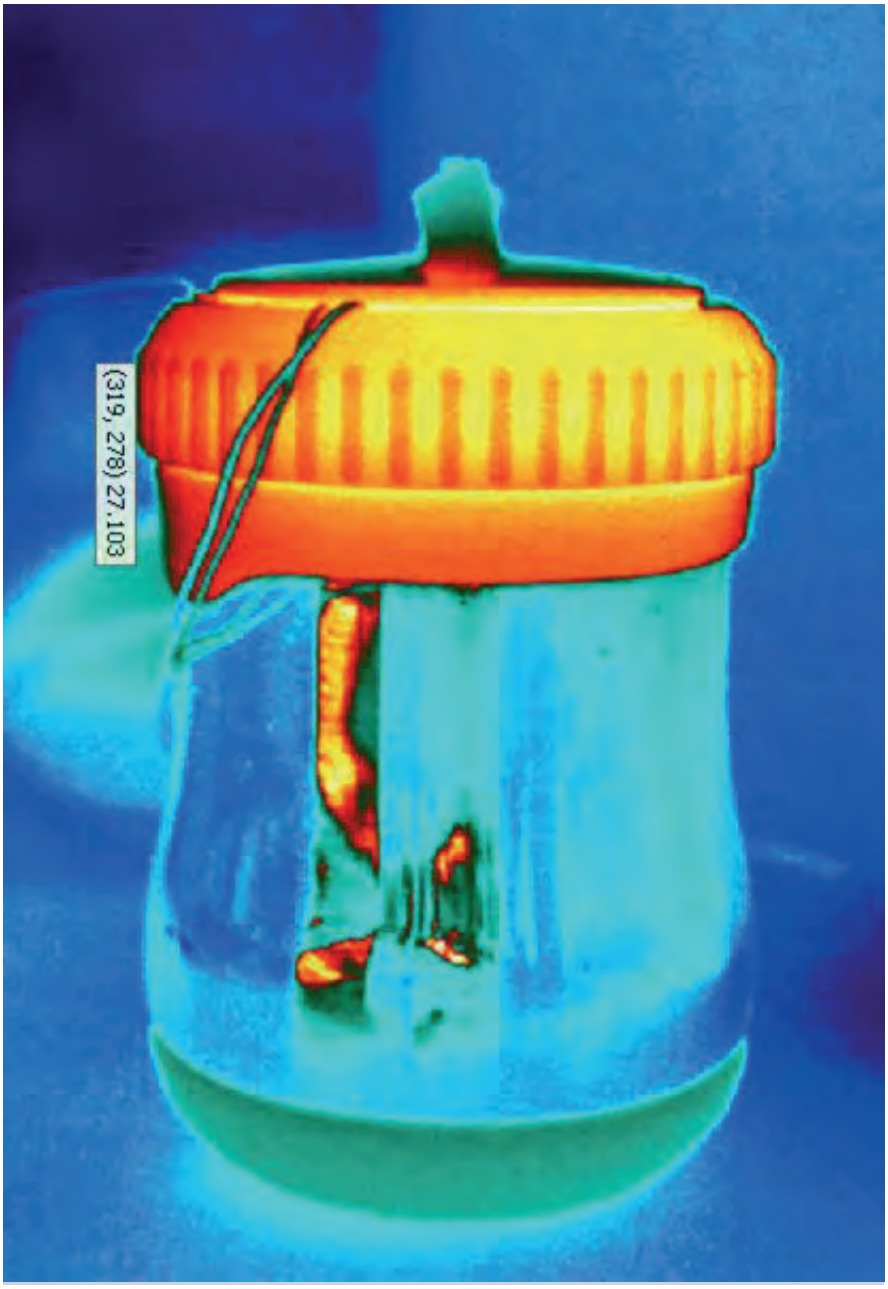

Figure 1. Thermal imaging of the NINA device was used to assess heat losses and compare insulating materials (Paul LaBarrre, PATH).

using a simple dipstick test, with a color band indicating the presence of disease.

Studies by the PATH scientists have shown that the incubator can maintain a stable 60°C environment at multiple ambient temperatures (see Figure 1), so testing won't be compromised by surrounding conditions. It could also be adapted to other diseases, like malaria, and help improve the control and surveillance of multiple diseases, by allowing for advanced molecular testing to be carried out cheaply, without access to modern diagnostic equipment. To achieve this, a way of preparing nucleic acids from blood samples is also needed, as PATH senior technical officer Paul LaBarre explains: "To complete this low-resource setting diagnostic, one remaining need is the integration of a simple method for isolating nucleic acids from patient blood samples before amplification. Current methods are expensive and technically difficult. Fortunately, there are several methods we are testing that look promising."

And with detection in less than 80 minutes, the test could also become part of a point-of-care health service, with patients diagnosed and treated within a single visit – something which could be of huge benefit to underserved communities. *RM*

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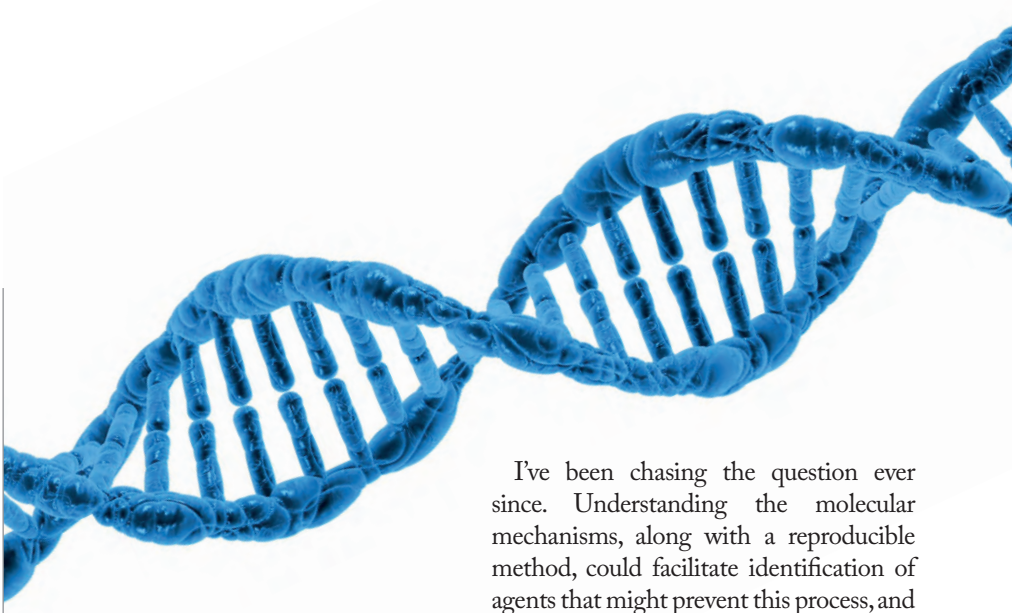
2. *J. Singleton et al., "Electricity-Free Amplification and Detection for Molecular Point-of-Care Diagnosis of HIV-1", PLOS ONE, 9, e113693 (2014).*



In Pursuit of Immortality

Cell lines that have avoided senescence but kept their normal genome could provide new avenues for cancer research

How do human cells become immortal? Despite the important implications for cancer development, the process is not well understood. Now, a research team based in the Berkeley Lab, US, have developed a new method to create and study immortal human mammary epithelial cells (IHMECs). It is already possible to do this but the oncogenic agents used to create the cells result in multiple genomic errors, meaning the cells are not accurate models of cancer etiology. The new method generates cells with normal, stable genomes, providing a more accurate model for studying the process in the same way it actually occurs in human cancers; while human cancer tissue may contain many genomic alterations, only a small number of these are thought to play a role in disease development.

This is the culmination of over 30 years of work for Berkeley researcher Martha Stampfer, lead author of the associated paper (1). "When I started this work, I was fascinated by the observation that rodent-derived cultures from both normal and tumor tissues could spontaneously immortalize in culture, but in humans, it only occurred in cells derived from tumors. I've been chasing the question ever since. Understanding the molecular mechanisms, along with a reproducible method, could facilitate identification of agents that might prevent this process, and thus halt malignant progression," she says.

It is believed that immortalization is mainly due to the upregulation of telomerase, the enzyme responsible for maintaining the telomeric ends of chromosomes, but very little is known about how human epithelial cells reactivate telomerase during cancer development in vivo. Creating the immortal cells involved overcoming two senescence barriers; using *C-Myc* to reactive the enzyme which maintains telomerase and allow division to continue, and using small hairpin RNA to silence the tumor suppressor p16 – a straightforward and reproducible method.

Studying cells created in this manner could provide researchers with an invaluable tool for analyzing the underpinnings of immortality and potentially developing new approaches to cancer therapy. The Berkeley team intends to continue unravelling the mysteries of immortality, as Stampfer explains, "We are currently examining the molecular changes that occur during the process. Several molecules with observed changes in expression are now being studied, and will be tested for to see if they are necessary to attain or maintain immortality. The goal would be to identify therapeutics that could prevent immortalization in pre-malignant cells." *RM*

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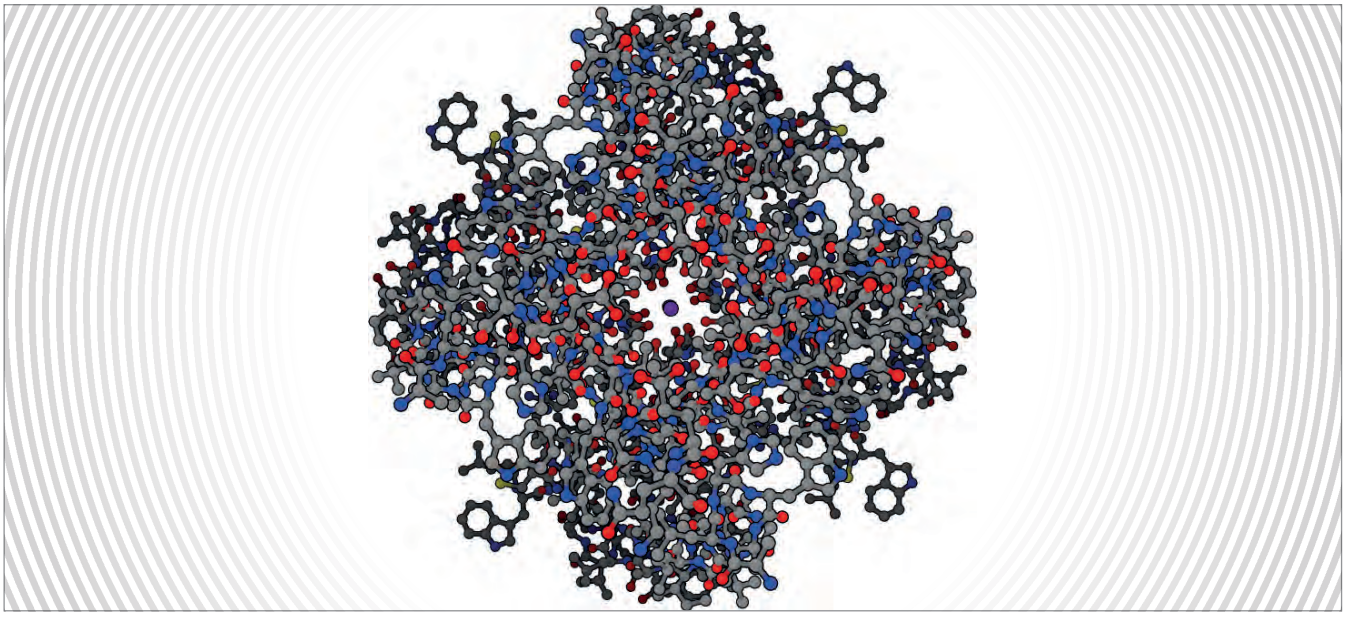

WGS Unravels Idiopathic Epilepsy

Potassium regulation appears to be the culprit in three case studies

A research team led by scientists at Scripps Translational Science Institute (STSI) have uncovered a previously unknown basis for a rare and severe form of epilepsy: defects in a gene involved in potassium regulation. STSI's IDIOM (Idiopathic Diseases of Man) study aims to use whole genome sequencing (WGS) to hunt down the origin of diseases in both adult and pediatric cases – and the advent of modern sequencing methods means they're uncovering genetic causes for conditions that have long been a mystery.

The research began with the case study of a nine-year old girl with a severe and complicated form of epileptic encephalopathy (EE) that had no known cause. EEs are a heterogeneous group of conditions with childhood onset, neurodevelopmental impairment and often a poor prognosis (1). Recent progress has seen 12 new causative genes identified for this group of conditions, and the number is still growing – WGS of the patient uncovered a de novo missense mutation in the gene *KCNB1*, which wasn't previously associated with EE.

KCNB1 encodes the kv2.1 voltage-gated potassium (K^+) channel, which regulates the flow of K^+ in neurons, affecting how cells communicate, and in the kidneys, affecting K^+ excretion and fluid balance. Two further patients with the same condition were identified, and whole exome sequencing (WES) uncovered similar mutations. The Scripps researchers feel the identification of the mutations in three patients, along with previous functional studies demonstrating that mutations in the pore region of the channel can result in altered ion selectivity and therefore dysfunction, point to the fact that these mutations may be causative of EE. They also suggest that clinical WES will be a valuable tool for molecular diagnosis of future cases (1).

"We are continuing to learn the impressive power of whole genome sequencing for making a difficult – and heretofore impossible – diagnosis," says Eric Topol, director of STSI. "These findings can serve as a model on how to treat this particular form of epilepsy in other patients. The *KCNB1* mutations might also have a role as a diagnostic biomarker for this condition, and they could help to direct the discovery and testing of new drugs to treat epilepsy."

Uncovering the mutation also has a more immediate effect – the original patient's physician feels this discovery has made a huge difference to her outlook, and believes expanded medical treatment and monitoring of hydration could see her condition improve over time. *RM*

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On a Mission to Banish River Blindness

A new diagnostic test could help wipe out the neglected disease for good

Onchocerciasis (AKA river blindness), caused by the parasitic worm *Onchocerca volvulus* and spread by the black fly (Figure 1), affects over 17 million people (1). Although pharma giant Merck has committed to donating the antiviral ivermectin until the disease is eliminated, diagnosis remains a big problem. Current testing methods are time-consuming and painful, leading some patients to avoid them altogether. Researchers at the global non-profit organization PATH believe a simple, less invasive alternative is needed to get rid of the debilitating disease for good – so they've released one.

Onchocerciasis causes itching, skin lesions, visual impairment and often blindness. The ocular pathology is caused by the worm releasing microfilariae (MF) into the bloodstream of the host; they travel through the scleral and subconjunctival tissues to the cornea, where they die and release bacteria causing inflammation, damage, and eventually blindness. Some patients will have worms visible in their eyes, but not all those infected will present in this manner. The current gold standard diagnostic is a skin snip examined for worms in saline solution, but this test can have poor sensitivity if MF levels in the skin are low, so a negative result will require DNA extraction and PCR analysis. This multi-step method takes time and requires a painful skin biopsy, causing some at-risk individuals or even whole communities to avoid it.

Finding a better way to diagnosis the disease could be critical, and PATH believe they have found an answer: their IgG4 rapid test, which requires just a straightforward fingerprick. The sample is run through an immunochromatographic assay, and a result is presented in under 20 minutes.

David Kaslow, PATH vice president of product development, thinks the test could prove to be a game-changer: "The proven technology behind this test makes it a powerful and reliable tool in the multinational collaboration to eliminate river blindness. The availability of a rapid, point-of-care diagnostic is a harbinger of a world free of the suffering caused by this insidious parasite. What's needed now is quick action to add this simple test to control and elimination programs."

The US Centers for Disease Control and Prevention, however, is less effusive, stating, "These tests cannot distinguish between past and current infections, so they are not as useful in people who live in areas where the parasite exists, but they are useful in visitors to these areas" (2).

It's not a bug, it's a feature, say PATH: by detecting unique antibodies to the parasite, it quickly identifies previous exposure (3). Perhaps that's not the point. Although river blindness has been eliminated from many regions of Africa (4) and scores of people have been successfully treated with ivermectin, many have not. A rapid, reliable method that doesn't require skin biopsy, should definitely aid screening – and as that's the first step on the path to eliminating this pernicious disease, it's certainly a commendable endeavor on the part of PATH. *RM*

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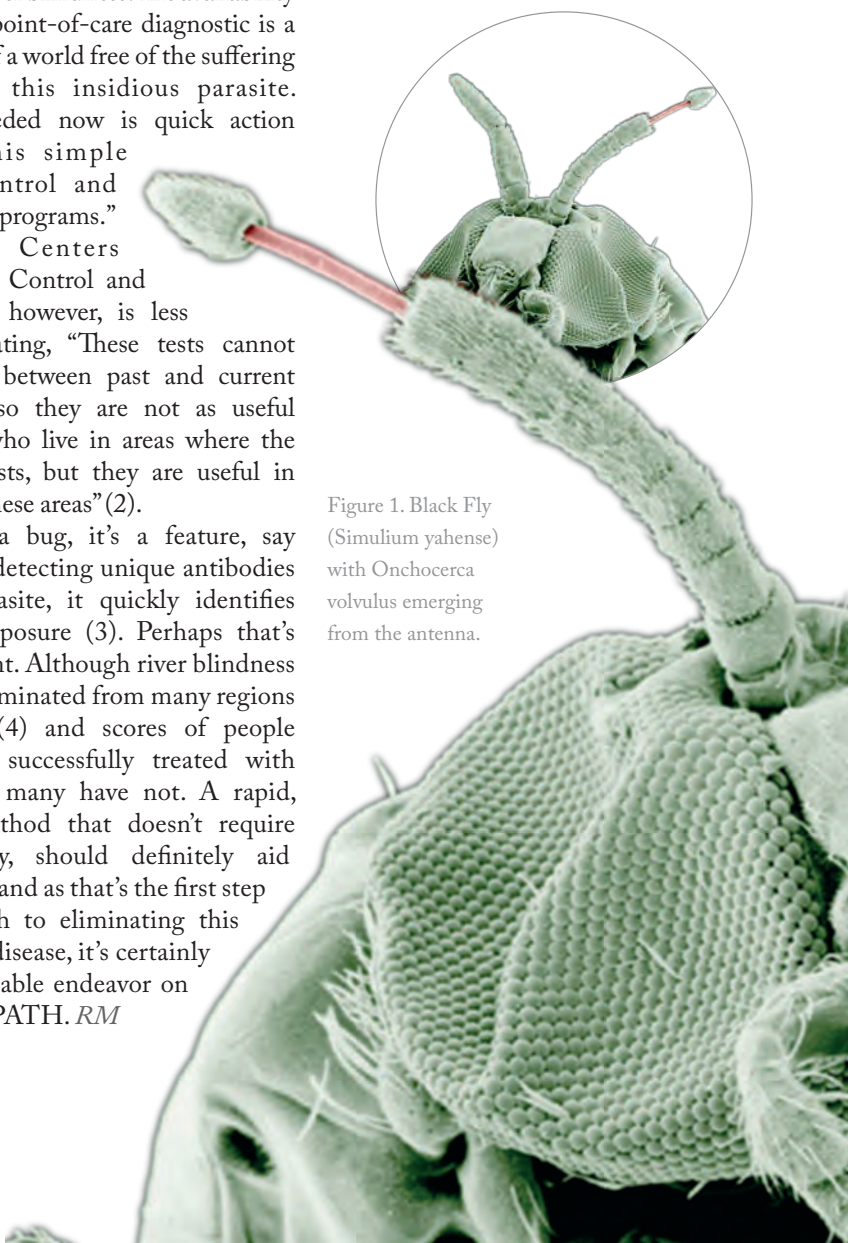


Figure 1. Black Fly (Simulium yahense) with Onchocerca volvulus emerging from the antenna.


PATHOLOGY

The Last Respite of the Socially Inept?

Negative stereotypes about pathology are damaging the field – but exactly what are those stereotypes, and how do we defeat them?

By Michael Schubert
Illustration by Giles Crawford

Most people have heard the stereotypes about pathologists. They're an unfriendly lot who chose their careers because they didn't like patients – or indeed, people at all – preferring to spend their time in the company of corpses and assorted taxidermy. Pathologists don't want to talk to anyone, lack a sense of humor, and spend their ample time off watching Quincy and Silent Witness. As pathologists, you know these stereotypes aren't true – but do other people know that, especially young medical students who will eventually have to choose a specialty? And are stereotypes like these ones harmful to pathology as a discipline?

When trainees were asked by the Royal College of Pathologists (RCPath) about the stereotyping they had encountered, the responses were surprisingly conclusive. Almost all had heard that pathologists didn't like people (85 percent), that they had poor communication skills (76 percent), or that they spent all day with dead bodies (83 percent). They'd also heard other comments – anything from having a morbid fascination with death to being considered a technician, rather than a "proper doctor." And these stereotypes weren't coming from the general public; alarmingly most of them were coming from doctors in other specialties, both consultants (63 percent) and trainees (83 percent). Other pathologists had also been involved in stereotyping the trainees (1). One head of department even claimed that "histopathology is the last respite of the socially inept." (2)

Though this kind of labelling within the medical profession is harmful enough, the misconceptions held by members of the public are even more extreme. In a National Pathology Week survey in 2009, RCPath asked people in schools and communities a range of questions about the field. To them, pathologists are considered "creepy," "scary," and, in 45 percent of responses, were related specifically to corpses, dead bodies, or autopsies. Of the people surveyed, over a quarter were aware of forensic pathology as a subspecialty (28 percent), probably because of publicity from popular television; some were also aware of hematopathology (22 percent) or histopathology (9 percent), but no other subspecialties were mentioned (2).

When asked why someone might choose to become a pathologist, a number of the answers were positive – liking science or problem-solving, wanting to help others, or being interested in how the body works. Unfortunately, people also felt that pathologists might be interested in crime, fascinated with death, uninterested in patients, "weird," or "geeky." One respondent even stated that people might enter pathology because they "couldn't get into medicine." Perceived qualities needed to specialize in the field were similarly diverse, ranging from accuracy and intelligence to statements like "lack of a sense of humor" and "lack of personality." Perhaps most telling of all, when asked what pathologists did in their spare time, only 12 percent of respondents said "normal things," while other answers included talking about corpses, stuffing animals, going to graveyards, and collecting roadkill or pigeon claws... (2)

To anyone with an understanding of the pathologist's role in disease diagnosis, monitoring and treatment, these stereotypes are laughable. But their effect on pathology is much less humorous. It's already an unpopular residency choice for medical students, attracting only 1 to 3 percent of medical graduates (3) – a situation resulting in a severe and longstanding shortage of personnel to the point where it has even been referred to as a worldwide crisis (4). Of those trainees who did make it into pathology, 15 percent said that their experience of stereotypes had made them less interested in a career in the field, whereas 59 percent believe that stereotypes deter other trainees from entering the specialty. Numbers in the literature seem to support this conclusion – in one study of clinical residents who chose not to enter pathology, 17 percent said it seemed boring or repetitive, 7 percent felt it didn't have enough contact with other people, 4 percent wanted to avoid death and autopsies, and 1 percent thought the field carried low prestige and a poor reputation (5). One resident in the study reported that pathology was "not well recognized among peers," and they were, "not exactly sure what they do."

Clearly, stereotypes about the nature of pathologists are costing the specialty some of its best candidates – but to understand why, it's important to look at the worst offenders and ask how they've gained such a strong foothold and what can be done to counteract them.

Pathologists spend all their time with corpses

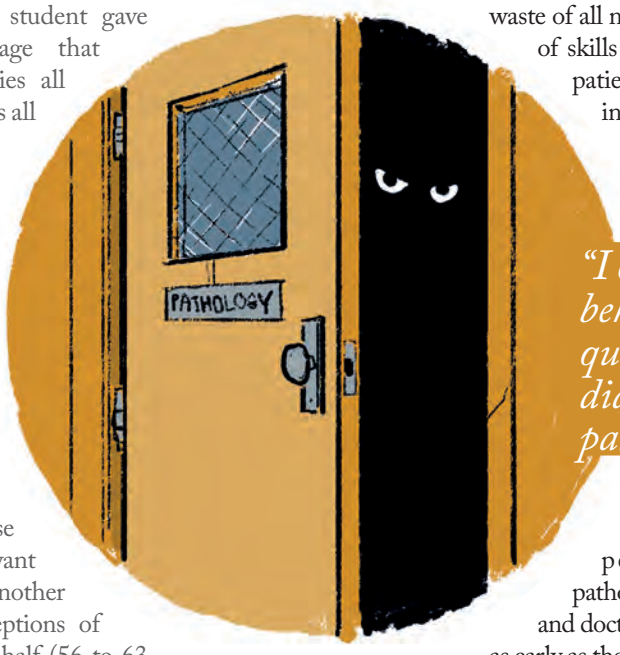
With the recent proliferation of forensic pathologists on television, it's no surprise that they're everyone's idea of the essential pathologist. A list of "favorite TV pathologists" from The Guardian newspaper features 10 entries, all of whom are involved in murder investigations (6). There doesn't seem to be much else out there – in fact, in many popular medical shows, doctors from every medical specialty can be seen either performing their own laboratory analyses or bypassing the lab altogether! "I watched a lot of X-Files as a teenager and I remember quite often FBI agent Scully would be found in a white lab coat hovering over a dead body with a scalpel in hand in a white clinical laboratory with low-level lighting", says Hannah Jean Gregson, a histologist at the University of Manchester in the UK. With popular media portrayals linking pathology only to the examination of dead bodies, it's easy to see where the general public might have gotten this particular misconception.

"One postgraduate student gave the 'model' stereotypical image that "pathologists look at dead bodies all day." I'm not sure where she thinks all these dead bodies come from!"

It's a little harder to understand why people in the medical field think the same way, though. It's likely due at least in part to the "CSI effect," where incoming medical students view pathology through the media's macabre lens and therefore view pathology with active distaste from the start. One resident who chose a different specialty said, "When I think of pathologists, I think of TV shows like CSI and get an 'eerie feeling' and honestly feel scared!" (5) Even without this influence, though, the stereotype arises – medical students surveyed between 1967 and 1971, before even forensic pathology entered popular media, considered pathologists to be "morbid characters who enjoyed constant contact with the dead." The reason for these judgments,

students claimed, had to do with perceptions of pathologists as "insecure, uncomfortable, and ill at ease with others, and inept in interpersonal communication, shy, introverted, aloof, and cold." (7) When asked whether the stereotypes still apply nowadays, doctors agreed that they did – one replied, "Definitely. When I tell people I'm a pathologist, they start talking about TV programs like Silent Witness and dead bodies," and another said, "Even people I know well presume I spend all day working with the dead." (2) Gregson asked medical and postgraduate students in her University of Manchester research group how they thought pathologists filled their days; and she reports, "One postgraduate student gave the "model" stereotypical image that "pathologists look at dead bodies all day." I'm not sure where she thinks all these dead bodies come from!"

That isn't great publicity for pathology – no one wants to be greeted on the ward with, "Oh, dear, what's the bad news?" as one pathologist reported. That desire to avoid being seen as morbid or associated with death is keeping good candidates out of the discipline; 4 percent of clinical residents who had chosen to specialize elsewhere said that it was because they "want living patients, and want to avoid death and autopsies." Another study of medical students' perceptions of pathology showed that well over half (56 to 63 percent) could identify autopsy as one of the duties of a pathologist, whereas the numbers for most other duties were much lower (8). It's difficult to combat an image that most incoming medical students believe before their training has even begun, and even more difficult to do so when a lifetime of influence from popular culture only reinforces that image. But this apparent fascination with death may be the most negative – and certainly the most untrue – stereotype that pathology faces in trying to attract promising new candidates to the field.



Pathologists don't like people

At every stage of their careers, pathologists report hearing from others that they apparently don't like people. Pathologists are supposed to be unfriendly, uncommunicative and socially awkward, hiding away in their laboratories because they don't want to – or are unable to – interact with patients or colleagues. Chella van der Post, a pathology trainee and doctoral student at Radboud University Medical Center in The Netherlands, says, "I often hear that I behave and communicate quite normally, so why did I *have* to become a pathologist?" Clinical residents in other disciplines overwhelmingly cite lack of patient contact as a reason for avoiding pathology; in one study, 75 percent of respondents raised it as a concern even if they had enjoyed their experiences in pathology during medical school (5). They accompanied their reasoning with statements like, "I thought it would be a waste of all my clinical training and development of skills in diagnosing and interacting with patients if I ended up in a job that didn't involve patient contact," or, "I went into medicine to work with people, not specimens."

"I often hear that I behave and communicate quite normally, so why did I have to become a pathologist?"

Many people feel that this perceived separation between pathologists, who are presumed introverts, and doctors, who want patient contact, begins as early as the medical school application process – explaining, "the way that the selection happens for medical students now, with the interview being a big portion […] it kind of almost weeds out some of the people who don't want to be people-people." (3) In an attempt to explain why pathology is supposedly incompatible with most aspiring doctors' personalities, another student specified that medical school is geared toward selecting "those people that would be great extroverts and great at dealing with the population." The perspective that doctors must be good at dealing with patients, while excluding pathologists from that definition, seems to begin early and continue largely unchecked – and, apparently, pathologists themselves often do little to ameliorate the stereotype. During their training, medical students emphasize the impressions made by teachers and mentors, focusing on enthusiasm and approachability rather than encyclopedic knowledge. Focus group discussions with graduating medical students elicited comments like, "My experience actually wasn't so positive with my PBL tutor, who was a pathologist. He was a bit

stuffy, talked over us – and that's sort of where some of my hesitancy with pathology comes from." Another student noted, "Something that interests me in terms of what I'm going to go into is actually the interaction that you have with colleagues, and I got the sense that there was very little of that with pathology." (9)

Unfortunately, this impression of unfriendliness often continues on into postgraduate training and beyond. Negative encounters with pathology seem to be quite frequent – one resident labeled teaching pathologists as "socially difficult to be around," while another shared an unpleasant experience. "[We] had a very eccentric and rather negative pathologist give us our training, [who] scared me off from the field." (5) People who managed to enter the field despite this undesirable stereotype find themselves having to defend their choice. When asked, specialists from other fields claimed that pathologists were "very isolated" and did not have enough contact with other people. One pathologist told a story of a chance encounter with someone they hadn't seen in over 20 years. "She said that she was surprised to hear that I'd become a pathologist, as I'd always liked talking to people so much." (2)

The good news is that the myth of the unfriendly, isolated pathologist is an easy one to counter. Medical students were surprised to discover that pathologists could be "people who were really animated, lively people" and that "if I spent all my time in the lab with these people, they'd be really friendly individuals." (9) Among trainees who chose a career in pathology, 50 percent of those surveyed by RCPath said that they'd made their decision after a positive experience of the specialty as a student or junior doctor, and 46 percent were influenced by a role model. Nearly all (85 percent) said that positive role models were important. Of those surveyed by Jason Ford (5), 15 percent cited good pathology experiences during medical school as their reason for choosing the field, describing them as exceptionally good teachers and role models; a further 14 percent entered pathology training after admiring the personal qualities of pathologists, with one student referring to them as "one of the happiest groups of physicians that I worked with." It's clear that the experiences young trainees have with pathologists can reinforce the stereotype of the misanthropic pathologist – but they can just as easily debunk it.

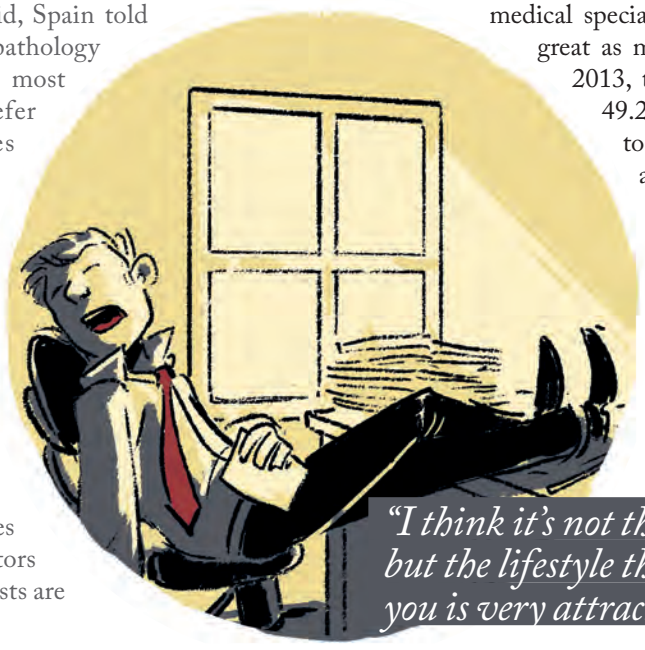
Pathologists aren't real doctorss

The idea that pathologists are actually scientists, lab technicians, or "surgeons' servants" is far more common than it ought to be. It's understandable that the general public is, at best, shaky on its knowledge of pathology training and duties – surveys reveal that they think people choose careers in pathology because they "couldn't get into medicine" (2) – but this shouldn't be true even of medical students, let alone doctors who are past their school years. Nevertheless, the stereotype of pathologists not being "real doctors" persists.

"The students had no clinical exposure to pathology, believed that electives were either unavailable or undesirable, and claimed they had "never seen" a pathologist in the wild."

In surveys of second-year medical students, over a quarter believed that there was no residency requirement to become a pathologist (8). Many said that, before medical school, they "didn't even know it was a medical specialty," and despite preclinical lectures, they remained ignorant of their teachers' actual roles. One student said, "Here we are getting a lecture by pathologists, and we're like, "what the heck do these guys do?" You know, like I remember seeing people and going like, "I don't even get what you do"." After 16 months of clinical clerkship experience, the same students gained very little understanding of the need for pathologists in clinical care – "You sent the specimen and then it's done, and then, Oh! Miraculously, a result comes back." The students had no clinical exposure to pathology, believed that electives were either unavailable or undesirable, and claimed they had "never seen" a pathologist in the wild. One of the students, explaining his lack of interest in pathology as a career, commented, "I don't think you see the pathologist who examines the tumor afterwards and makes the diagnosis ultimately as being a doctor – you sort of see them as a technician who sits in the background." (3)

Even pathologists who are well settled in their careers experience this stereotyping. They report being referred to as "just a lab rat" and being told that they're "not a real doctor and must have a lot of free time!" (1) Trainees express concern over the lack of pathology teaching in their undergraduate medical curricula, pointing out that they were able to become qualified physicians without ever setting foot in a pathology department or being aware of meeting a pathologist. And these were the residents who were more dismissive, saying that pathology "seems more like a technician job." (5) Alberto Berjón García, a pathology resident at La Paz University Hospital, Madrid, Spain told us, "I got very little exposure to pathology as a student. It is true that most medical students tend to prefer surgical or clinical specialties and maybe that's why it is underrepresented, but I think it is a mistake because every doctor should understand what a pathologist does." It appears that most people outside the specialty are only peripherally conscious of its existence, aren't aware of encountering pathologists in the course of patient care, and don't fully understand their duties – and this combination of factors leads to the belief that pathologists are not actually doctors at all.



"I think it's not the actual pathology, but the lifestyle that pathology offers you is very attractive."

Pathologists are lazy

One of the most widely perceived benefits of a career in pathology is its good lifestyle. Incoming trainees are generally of the opinion that pathology offers flexibility and a good work-life balance; in fact, 43 percent of residents in one survey listed it as a primary reason for their choice of specialty (5). But it's possible to have too much of a good thing, and sometimes, this positive aspect of the job can be perceived as laziness or an unwillingness to work. Pathologists are thought to put in fewer hours than other specialties, leave earlier in the day, or even do less in their time at work – an impression reinforced by the fact that so many doctors in other fields don't fully understand the duties of a pathologist.

Comments made by both medical students and pathologists were generally positive with respect to lifestyle. One student observed, "I think it's not the actual pathology, but the lifestyle that pathology offers you is very attractive." (9) It's an opinion that seems to be shared not only by students, but by residents and experienced pathologists as well. In discussing the upsides of the career choice, one pathologist said, "As far as lifestyle goes, it's fantastic… If I have to leave early or nip out for an hour or something, just the control of the hours that you have, the flexibility, is very, very good." It's true that pathologists as a whole tend to have fewer working hours than other medical specialties, but the difference isn't as great as most people seem to think – in 2013, the average pathologist worked 49.2 hours per week, as opposed to about 55 hours per week in all specialties (10). The field is particularly welcoming to women; female students and qualified pathologists emphasized the appeal of control over the hours that they worked and the time they were able to take out of their careers for family.

Though it seems as if this lifestyle advantage should attract more people to pathology, it unfortunately also contributes to negative stereotypes about the profession. Pathologists report being told, "Oh, you must have a lot of free time," or that they have easy jobs – some were even told that they must have chosen pathology as a "last resort" after failing to get into other specialties. Attitudes like this contribute to outsiders' views of it as a choice with low prestige or a poor reputation. A concern a medical student expressed after hearing it "from a lot of people, so it kind of just keeps creeping up" is the idea that, "in terms of careers in medicine, [pathologists] are not thought as highly of as some of the others." (9) A friendlier lifestyle than most other medical specialties offer, coupled with a lack of visibility in direct patient care and a poor understanding of a pathologist's work, seems to result in a false view of pathology as an easy field and pathologists themselves as lazy doctors.

Pathologists are nerds

The image of the pathologist as a "weirdo in a bow tie" is probably the least damaging of the preconceptions out there. Plenty of people regard this as a negative – but there are also plenty of people who consider it a positive characteristic. When RCPath asked members of the public why people might choose to become pathologists, "weird" and "geeky" were two of the reasons offered, but many respondents also used phrases such as "like science" (16 percent), "like problem solving" (12 percent), or "interested in how the body works" (10 percent) which suggest that this particular stereotype can work in pathologists' favor as easily as it can work against them (2).

"You need to like to study a lot, to go into your books and puzzle until you find the answer to the image under your microscope."

Residents who opted not to enter pathology reported that they didn't want to be seen as "geeky and boring" or "having Asperger's personalities" (3), making it clear that this image is giving some medical students a reason to avoid the specialty. When discussing what she likes most about her job, Chella van der Post agreed with the stereotype of the studious thinker – "You need to like to study a lot, to go into your books and puzzle until you find the answer to the image under your microscope." The theme of the scientifically inclined laboratory recluse seems to warn away young doctors who equate "geeky" with "boring," or who feel that pathology appeals only to a very specific personality type – the Mister Spocks of clinical practice.

Many trainees do acknowledge the grain of truth that gives rise to the stereotype. Some even feel that pathologists emphasize their quirky or eccentric natures, deeming them desirable rather than problematic (1). Asked about the truth of such perceptions in today's environment, one pathologist admitted, "There are some more positive stereotypes about pathology – that you have to be clever, have a scientific approach, perhaps be a bit geeky. These ones are probably true!" Fortunately, the "nerd cred" conferred by a career in pathology doesn't scare everyone away – one RCPath survey respondent admitted, "If pathologists have a stereotype of being a bit cerebral and wanting to understand the mechanisms of what's gone wrong, whether or not it makes any difference, then that stereotype attracted me to the specialty." (2)

Practicing without preconceptions

It's plain that all of these stereotypes – the ghoul, the hermit, the technician, the late sleeper and the nerd – are damaging to the field of pathology. Not only do they cost the discipline the recognition and respect it deserves, but they discourage promising young medical trainees from choosing pathology as their specialty. The loss of incoming personnel is so great that it's now led to an international shortage of pathologists – and so the question is: what's the best way to combat these negative impressions?

In order to attract medical students to pathology, promotion needs to begin early. Students have expressed surprise at the lack of pathology exposure in their medical training, reporting that it was possible to make it all the way through their medical school careers without ever being aware of meeting a pathologist, much less entering a pathology department themselves. The traditional teaching block has been replaced in many universities by an integrated curriculum, which may result in students who aren't sure which doctors are pathologists, or what they do all day. But even in schools with block courses, the current methods could use an overhaul – a study of students' perceptions of pathology before and after their second-year course showed that their understanding of pathology increased only modestly, and their interest in it was actually decreased (8). Students need information not only on the practice of pathology, but on its place in the clinical setting. For many students another study suggests, "Pathology is a mystery: its introverted practitioners work behind the scenes, engaging

in unknown activities that miraculously lead to diagnostic reports." (3) The authors of this report suggest that, "Preclinical medical students should be explicitly taught the role that pathologists play in patient care, and senior students should be given insight into the actual daily responsibilities of pathology practice."

"That my colleagues – old and young – from other fields/specialties do not know what a pathologist does or can do for them and the patient, is something that makes me a bit sad. But, I also see this as a challenge and a big motivation to improve the image of pathology," says Chella van der Post, who is a member of a multi-specialty board of residents. In fact, she uses every opportunity to explain the field and how critical it is in diagnosis and disease management. "To step into the spotlight and improve our image to our colleagues and to lay people is the first step to take," she adds.

Exposing students to pathology as an integral part of clinical care motivates them to consider further training. The positive effects of clerkships on perceptions of many disciplines are well documented – and it's a good understanding of the pathologist's role in diagnosis and treatment that spurs a student to consider an elective clerkship in pathology. Explaining the day-to-day work of the pathologist in as clinically-oriented a way as possible, highlighting case studies, and making pathologists visible in other disciplines by inviting their involvement in conferences, rounds and lectures; all of these are ways to make a difference to students' opinions of pathology early in their training, which in turn encourages them to consider it when choosing a specialty. It isn't as simple as involving pathologists in medical education, though – the doctors who participate in teaching and training are essentially the "face" of pathology, and it's important to be selective about the tone and source of students' early introductions to the discipline (5). Nearly one-fifth of residents who chose other specialties gave insufficient or inadequate contact with the field during medical school as a reason, and among those, many students cited encounters with teachers who were eccentric, negative, or socially awkward. In contrast, doctors who did specialize in pathology often state that their role models "definitely didn't fit into any of the stereotypes," describing them as "passionate about their subjects, excellent communicators" or "extroverted, funny, even a bit zany." (2) Positive mentorship experiences like these dispel unwarranted stereotypes about pathologists and encourages a more balanced view.

As the pathologist population grows more diverse, it becomes more and more difficult to hold onto these stereotypes. Visibility to the general public, to medical students, and even to specialists in other fields, is a key part of combating preconceptions with facts. At the conclusion of one National Pathology Week event for medical students in the UK, every attendee said that they would at least consider a career in pathology, and several added that a single afternoon had taught them more about it than they had learned in their entire undergraduate careers (1).

Public engagement, medical school training, and exposure at all levels of practice are vital to clearing up misconceptions about who pathologists really are and what they do – but all of these things rely on active and positive representation, because the only people who are truly in a position to fight back against stereotypes are pathologists themselves.

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Join the debate

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Have you been exposed to these stereotypes?
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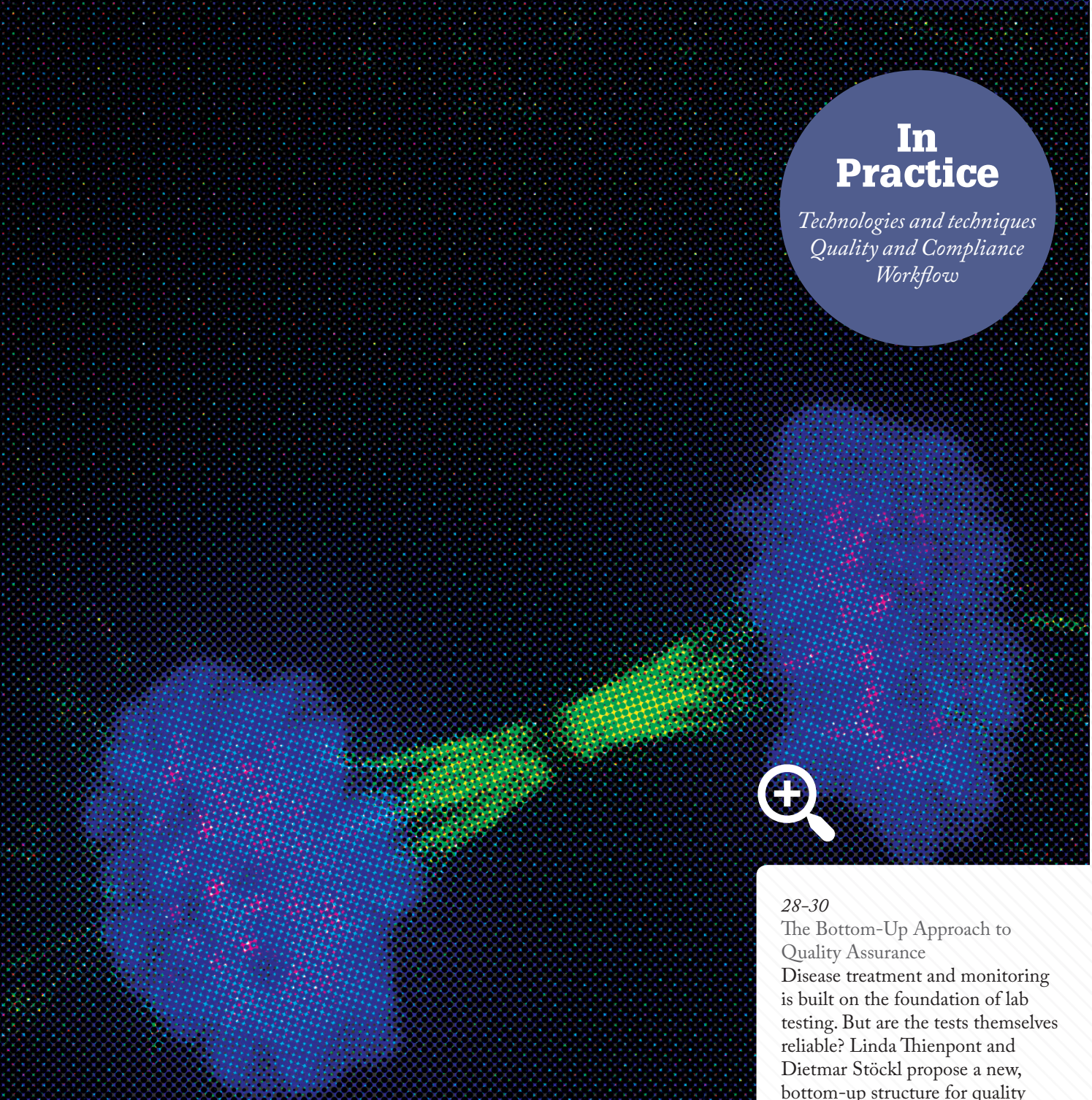


The Bottom-Up Approach to Quality Assurance

Laboratory testing is critical for disease diagnosis and monitoring – but how can we be sure the tests themselves are fit for optimal patient care?

By Linda Thienpont and Dietmar Stöckl

The importance of quality assurance in laboratory medicine seems so obvious that there should be no need to spell it out, but despite the criticality of measures to ensure reliability of laboratory testing, they are still plagued by problems. The key issues faced today fall into two groups – systematic problems with the way quality assessments are conducted, and poor communication between the concerned parties.

A major issue of internal quality control and external quality assessment (IQC/EQA) is the use of "processed" materials – that is, samples that have been pooled, stripped, dialyzed, and so on. These kinds of materials are cheap and available in high volumes, which makes them desirable for use as controls; they are also easy to alter if needed, for instance by supplementing to obtain pathological levels, or by lyophilizing to keep them stable. The problem is that these materials don't necessarily reflect the reality of patient testing. In metrological terms, this is called "noncommutability." If noncommutable materials are used for IQC/EQA, they may point to biases that don't exist in patient samples, and vice versa. It also means that IQC/EQA across assays isn't possible; quality assessment can only be done at the peer group level.

And building proper peer groups isn't an easy task. Peers should ideally be homogeneous – that is, grouped by testing system (combination of reagent, calibrator and assay from the same in vitro diagnostic (IVD) manufacturer). However, small EQA schemes may never have enough laboratories using a single system to form homogeneous peer groups. They do peer grouping by method principle, which is inadequate because IVD manufacturers design and optimize their own testing systems differently – so, despite being based on the same principle, one company's test may not be equivalent to another's. We estimate a need for about 15–20 laboratories before homogeneous peer grouping can provide any meaningful conclusions on performance. That's why we recommend that small EQA schemes join forces or participate in a program like the Empower Project (see sidebar "An Empowered Approach to Quality Control/Assessment") to benefit from proper peer grouping.

Communication issues mainly center on access to data. For instance, in many commercial schemes offering combined IQC/EQA solutions, the external assessment is often only available on a monthly basis. This means that laboratories become aware of bias problems only after the event, rather than in a timely manner. As a result, they're not able to remediate at the earliest possible stage. Laboratories are not the only parties affected by limited data access, though; IVD manufacturers can't obtain extensive data records from individual customers, which limits their ability to detect analytical problems in their assays when applied to patient samples. This is why we advocate that both laboratories and IVD manufacturers would benefit from access – within

At a Glance

- *Quality assurance in laboratory medicine suffers from both systematic problems and issues with communication*
- *Materials typically used for internal quality control and external quality assessment (IQC/EQA) may not show the same testing biases as patient samples*
- *Inappropriate peer grouping and limited data access are hurdles to improving IQC/EQA processes and follow-up*
- *Laboratories and in vitro diagnostic (IVD) manufacturers can benefit from a "bottom-up" approach where motivation comes from within and all parties collaborate and communicate*

confidentiality constraints – to externally maintained QC databases.

The bottom-up approach

Every health care provider's goal is to provide the best possible patient care. For those working in laboratory medicine, focusing on test comparability and stability is a key component of reaching this goal. To achieve it, though, current quality systems need to improve. We suggest that shifting from a "top-down" to a "bottom-up" approach is an important first step. What this means is that, rather than a system imposed by authorities and associated with penalties for failure, we recommend one that involves voluntary participation. This could move the goalposts for some labs – instead of aiming for performance at a "reasonable" level, participants aim for a "desirable" level. The involved parties must, of course, be in agreement over what constitutes desirable quality and be willing to closely collaborate and communicate. Only this can ensure that problems identified by QC processes are easily traced to their sources and resolved. The use of commutable samples that resemble patient samples as closely as possible is another change that would improve existing QC systems – which means that, if any problems are discovered, their effect on patient results is clear.

Of course, the changes don't stop there. Along with restructuring to a bottom-up QC system, laboratories need to establish appropriate performance specifications. Modern quality assurance systems can help define realistic, but meaningful, quality goals.

This might seem to the laboratory community to be a lot of changes to make, but we suggest that the changes first be implemented for common, high-volume tests, so that any bugs can be ironed out. Only once the community feels confident enough that the major problems have been resolved does it make sense to tackle the more complicated tests.

An Empowered Approach to Quality Control/ Assessment

What?

The Empower Project is a bottom-up approach to quality control/assessment that facilitates collaboration between laboratories and IVD manufacturers. The aim is to offer involved parties evidence of performance quality on patient samples, better data access, and communication.

Why?

Laboratories need QC systems that offer better access to data from commutable samples. This should enable them to obtain a global picture of comparability of results across assays, detect analytical problems in their own assays and performance, trace the origins of the observed issues, and remediate them. The systems should also use proper peer grouping, so that laboratories can join forces in making claims for improvement to their IVD manufacturers. Companies themselves should also benefit from the opportunity for evidence-based dialogue with their customers.

When?

The Empower Project started in 2012. The pilot phase is still underway and will last until September 2015. Until then, laboratories are invited to enroll free of charge.

Who?

All kinds of laboratories are welcome. In the master comparison surveys, 125 laboratories can enroll; after this number is reached, a rotation system is implemented to allow other laboratories to participate from survey to survey. Manufacturers' in-house laboratories also join the appropriate peer groups. In patient percentile monitoring, more than 120 laboratories are enrolled thus far, which translates to over 240 test systems and appropriate peer groups in the program.

Key achievements?

The project has seen a good level of participation, with a global distribution of laboratories from more than 20 countries. The project founders have also successfully established collaboration with IVD manufacturers and LIS providers.

Next challenges?

The main objective is for the performance standards adopted in the Empower Project to become accepted in the community, and for more LIS providers to adapt their software for automated participation in percentile monitoring. New software is currently being developed; one example is the "Flagger," which will allow investigation of the effect of performance instability on the frequency of flagged results. The master comparison surveys are ongoing on an annual basis.

For further information, or to get involved in the Empower project, email linda.thienpont@ugent.be or dietmar@stt-consulting.com

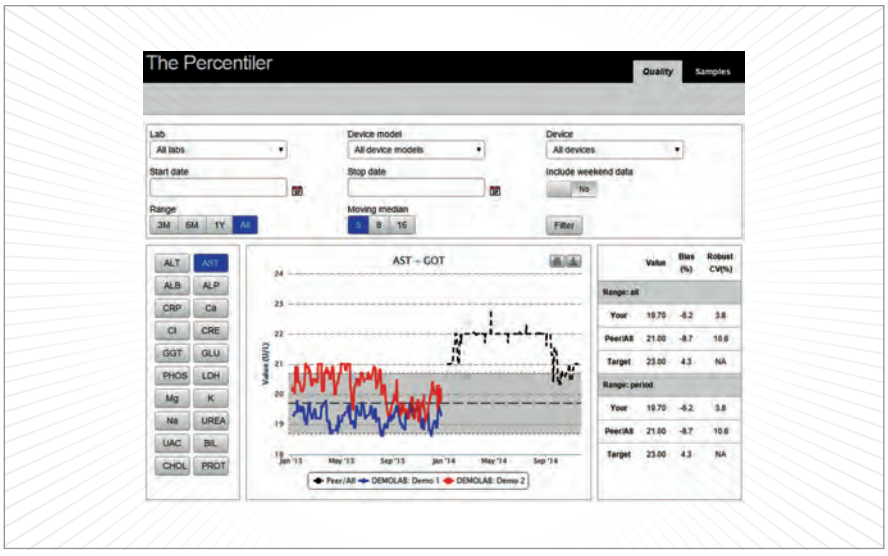


Figure 1. Demonstration of "The Percentiler," which allows a laboratory to track its moving medians over time, even by individual instrument. The dashed grey line represents the long-term median of the laboratory, whereas the dashed black line gives the peer group's comparative value. The shaded zone is the "stability" zone between quality specifications.

"No proposal is truly useful without a "product," a practical solution that can be used"

Practical implementation

Discussing systemic changes like the ones we've mentioned is easy, but when the discussion is over, how many of the ideas are actually translated into practice? No proposal is truly useful without a "product," a practical solution that can be used. The Empower Project is structured around several products that can help turn intention into implementation.

One such product is the master comparison survey. These studies provide the participating laboratories, divided into homogeneous peer groups, with a panel of 20 samples to examine for eight different analytes. The samples, which consist of unprocessed clot serum from single blood donations, are commutable. This allows the surveys to provide comparability across assays and laboratories, and to set benchmarks for the intrinsic quality of commercial assays and for laboratory performance. All of these attributes ensure that master comparison surveys add value to conventional EQA – they provide evidence for quality of performance on real samples under "field" conditions.

Laboratories that want to add value to IQC as well as to EQA can make use of a second product, patient percentile monitoring. With this system, laboratories can monitor their performance for 20 common analytes by calculating their daily medians and sending them to the Empower Project's database. A number of laboratory information system (LIS) vendors offer free solutions for automatically calculating and transferring daily medians, which makes the percentile monitoring program easy to join. For online monitoring, participants have password-protected access to a user interface ("The Percentiler"), which enables them to plot the course of the moving median over time for each analyte and even for individual instruments (Figure 1).

With the Percentiler, laboratories can identify aberrations in their own performance and trace their origins, and compare performance with their peers. The patient results stored and shared within this tool enable discussion between laboratories, but they also assist communication with manufacturers; laboratories can use the results to suggest improvements.

From thinking to doing

The biggest challenge in updating QC processes lies in moving from "thinking" to "doing." The shift to a bottom-up approach with large networks of laboratories is the key to future progress, because when the motivation for good QC exists, all of the stakeholders work together to provide the best possible patient care. This leads to the adoption of better performance standards and to improved channels of communication. The addition of easy-to-implement products like master comparison surveys or patient percentile monitoring turn the wealth of ideas for improvement into real possibilities. The result is better comparability and stability of laboratory results. And, ultimately, better outcomes for patients.

Linda Thienpont is professor of instrumental analytical chemistry, statistics and quality control and head of the mass spectrometric reference laboratory, at the University of Ghent, Belgium.

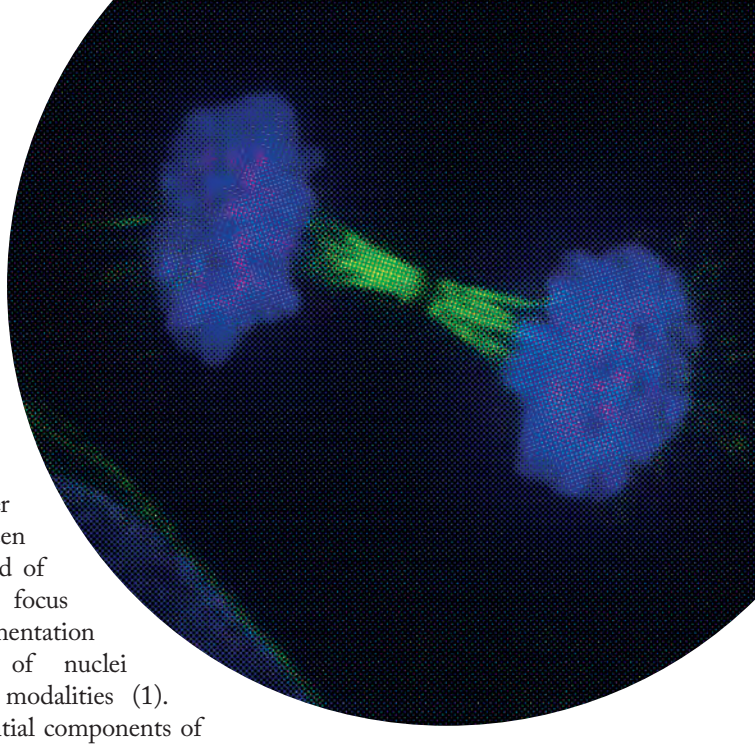
Dietmar Stöckl is owner of STT-Consulting, Horebeke, Belgium. He is co-founder of the Empower Project.

Taking On the Challenge of Automating Mitosis Detection

Two frameworks developed to detect mitosis in color and multispectral histopathology images

By Humayun Irshad

We all know that pathological exams not only constitute the gold standard in most medical protocols, but also play a critical and a legal role in the diagnostic process. Diagnosing a disease after manually analyzing numerous biopsy slides represents labor-intensive work for pathologists. But, thanks to recent advances in digital histopathology and the ability to recognize histological tissue patterns in high volumes and definition, this laborious task has been made somewhat easier. And in my opinion, although digital pathology presents us with challenges in training, investment, standardization and computational requirements, it's also one of the biggest evolutions in modern medicine.



Over the last decade, a huge number of articles have been published in the field of histopathology that focus on the detection, segmentation and classification of nuclei in different image modalities (1). These tasks are essential components of many histopathological applications; in breast cancer, for instance, they are involved in detection of malignancy, extraction of prognostic features, nuclear pleomorphism grading as part of a computer-aided prognostic system, detection of lymphocyte infiltration, and assessment of tumor proliferation.

Mitotic count is known to be an important parameter for disease prognosis, particularly in cancer – but actually detecting mitotic nuclei, even with digital histopathology, is a real challenge to us; they're small objects that vary widely in shape and texture. This has never been addressed well in the literature, mainly because of the lack of available data, so in a bid to plug this research gap, an international contest, the MITOS benchmark (2), was launched at the 2012 International Conference on Pattern Recognition (ICPR). The contest challenged teams to identify all mitotic figures in a region of interest of H&E-stained tissue, using three scanners – the ScanScope XT (Aperio ePathology from Leica Biosystems), the NanoZoomer 2.0-HT (Hamamatsu Photonics), and a multispectral microscope. The mitotic nuclei had been annotated manually in each high-power-field (HPF), but the goal of our research was to develop frameworks that were able to automatically detect mitosis in breast cancer tissue on these different types of scanners.

We proposed two different frameworks: the first is Intensity, Texture and Morphology based Mitosis detection in Color images (ITM^{2}C) (3); the second is Multispectral Intensity, Texture and Morphology based Mitosis detection in Multispectral images (MITM^3) (4). I'll explain how each works in turn.

Using color as our guide

The ITM^{2}C framework is designed to feature a high detection rate, low incidence of false positives, and good discrimination between mitotic and non-mitotic regions. Its overall aim is to improve the accuracy of mitosis detection by integrating the color channels that best capture the statistical features of mitosis. To do this, it employs three main steps: color channel selection, candidate detection and segmentation, and feature computation and classification (3) (Figure 1).

Step one

Histogram analysis of different tissue components using numerous color channels, blue ratio and hematoxylin images. Histograms where the peaks of the mitotic region are different from those of other regions are selected for further analysis.

At a Glance

- *Mitosis detection is an essential component of many histopathological tests, from detecting cancers to grading disease, but it's challenging*
- *We propose two frameworks that detect mitotic cells in either color or multispectral images*
- *Automated mitosis detection may be a way of overcoming the drawbacks of manual assessment*
- *The future of automated mitosis detection relies on increasing the speed and sampling efficiency of digital analysis*

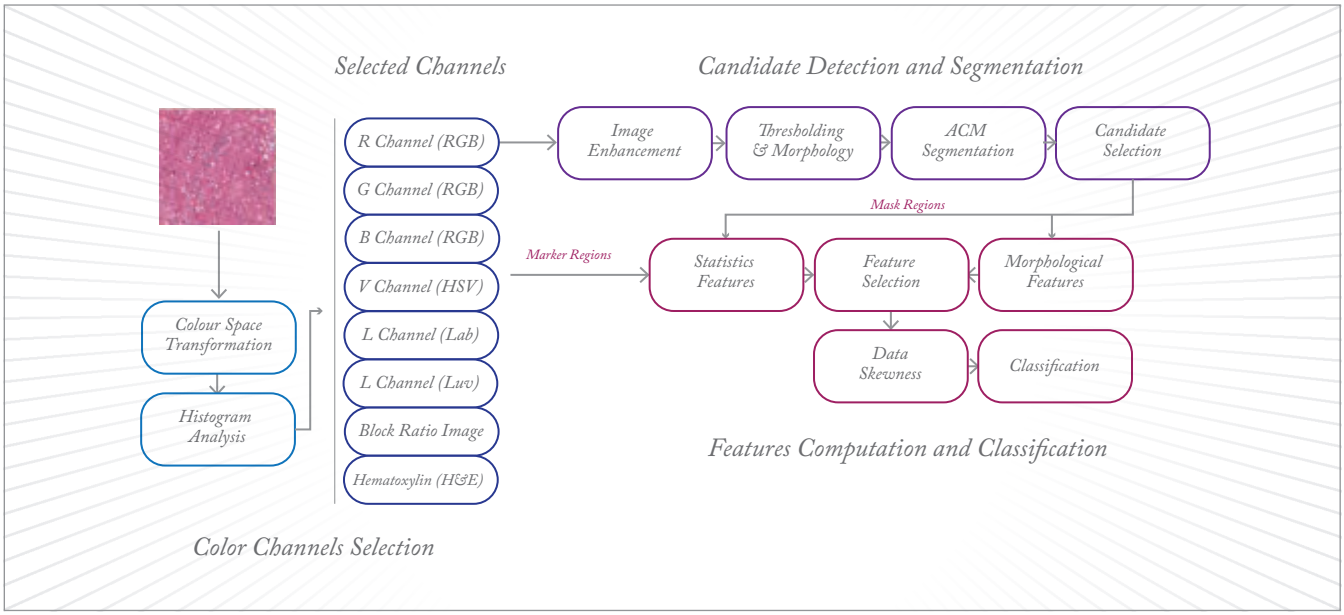


Figure 1. Mitosis detection framework (ITM²C) for color images. ACM, Active Contour Model.

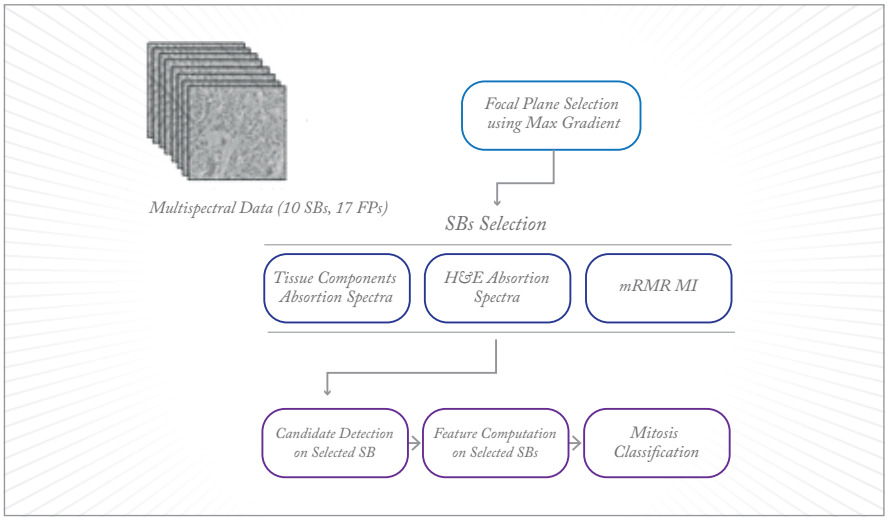


Figure 2. Mitosis detection framework (MITM³) for multispectral images. SB, spectral band; mRMR, maximum redundancy maximum relevance.

Step two

Candidate detection includes smoothing, binary thresholding and morphological operations to generate candidate regions whose boundaries are then further refined. This step is performed using the red color channel (where peaks between regions show the best separation).

Step three

Computation of the features of each candidate region in all selected color channels; a subset of features are chosen to maximize consistency.

Finally, after an extensive investigation to infer the best mitotic classifiers, the candidate region is classed as either mitotic or non-mitotic.

Multiple bands better than one?

The MITM³ framework addresses two important additional questions. First: is spatial-spectral analysis on selected spectral bands – as opposed to on a single band or all bands – satisfactory for efficient classification of mitotic and non-mitotic nuclei? An obvious advantage of using selected bands is the reduced computational and storage complexity. And second: how effective are multiple features for discrimination of mitotic and non-mitotic nuclei compared with using a single feature?

This framework is novel in several ways – it uses three different methods for spectral band selection, it computes morphological and multispectral statistical features (MMSF), and it extensively investigates classifiers and infers the best one for defining mitotic nuclei. Five steps are involved (Figure 2).

Step one

Choosing the most informative focal plane for separating mitotic nuclei from background.

Step two
Selecting relevant spectral bands for detecting mitosis. We suggest three different methods for spectral band selection: relative spectral absorption of different tissue components, spectral absorption of H&E stains, and the minimum redundancy maximum relevance (mRMR) technique.

Step three
Detection of potential mitotic nuclei.

Step four
Computation of a MMSF signature vector of intensity and texture information for each candidate across selected spectral bands. Morphological features are also computed using segmented regions of the candidates and are added to the signature vector.

Step five
Candidates are sorted into mitotic and non-mitotic classes using an L-SVM (linear support vector machine) classifier.

A side advantage to performing simultaneous analyses on multiple spectral bands is that we can investigate whether this yields an improvement in accuracy over using just one or all spectral bands. In addition, both patch- and region-based features can be evaluated for mitotic discrimination; in our case, the framework shows better classification results on patch-based, rather than region-based, texture features.

Our frameworks rank highly among the ICPR MITOS contest results, coming first overall (based on F-measure accuracy score) for multispectral and second for Aperio and Hamamatsu datasets. In addition, the frameworks perform almost equally well on brightlight and multispectral data – a promising result on the way to clinical applications.

Where next?

In the past 10 years, the digital detection, segmentation and classification of nuclei has moved to the forefront of histopathology research. Differences in slide preparation, image acquisition or complexity of tissue structure can often result in a high degree of variability when viewing routinely stained images, which in turn, makes nuclear detection – and in particular mitotic count – very challenging. The little research activity in this area means that we still have some way to go in detecting and segmenting mitotic nuclei to allow us to accurately and reproducibly use this parameter for disease prognosis. We've proposed two frameworks for different types of digital datasets, both of which have been carefully evaluated and have performed very successfully so far. But this isn't the end of our work – next, we plan to expand from a two-class into a multi-class sorting system and then use it to classify all kinds of microscopic objects, from apoptotic nuclei to cancerous cells.

Frameworks like ours can improve the reliability of mitotic activity assessment, which is a key component in the histological grading of cancers. Mitotic counts are traditionally done by visual estimation through a microscope, but this technique has less than optimal reproducibility. Automated mitosis detection offers a quantitative measure to describe tumor proliferation and may be a way of overcoming the drawbacks of manual assessment. Similar frameworks can be applied to other histological characteristics, like nuclear atypia or lymphocyte infiltration, both important parameters in breast cancer diagnosis and prognostic evaluation. In my experience, any laboratory task that involves object detection and pattern recognition can benefit from automation.

And the drawbacks of these frameworks?

The main challenge to implementing computer-aided techniques like the ITM^{2}C and MITM^3 frameworks is that they are computationally expensive; at the moment, mitosis detection in a 0.5 x 0.5 mm image takes 10–20 minutes – an unacceptable amount of time considering that a typical histopathology slide contains a tissue area of about 15 x 15 mm.

In the near future, we hope that increasing the efficiency of digital analysis will improve detection speeds and result in increased use of automated methods. Because this work is so laborious, but so important to the diagnostic and prognostic process, researchers are developing new frameworks to improve the accuracy and reliability of computer-based mitosis detection. These frameworks offer an opportunity to quantify results and ensure reproducibility, but they bring with them new challenges. We need to speed up automated detection to make it a viable option for overworked laboratories, and we need to devise more efficient sampling tools for fast and accurate classification of microscopic objects. Once we have tackled these challenges, though, the future of automated histopathology is a bright one.

Humayun Irshad is Research Fellow at Harvard Medical School, Beth Israel Deaconess Medical Center, USA.

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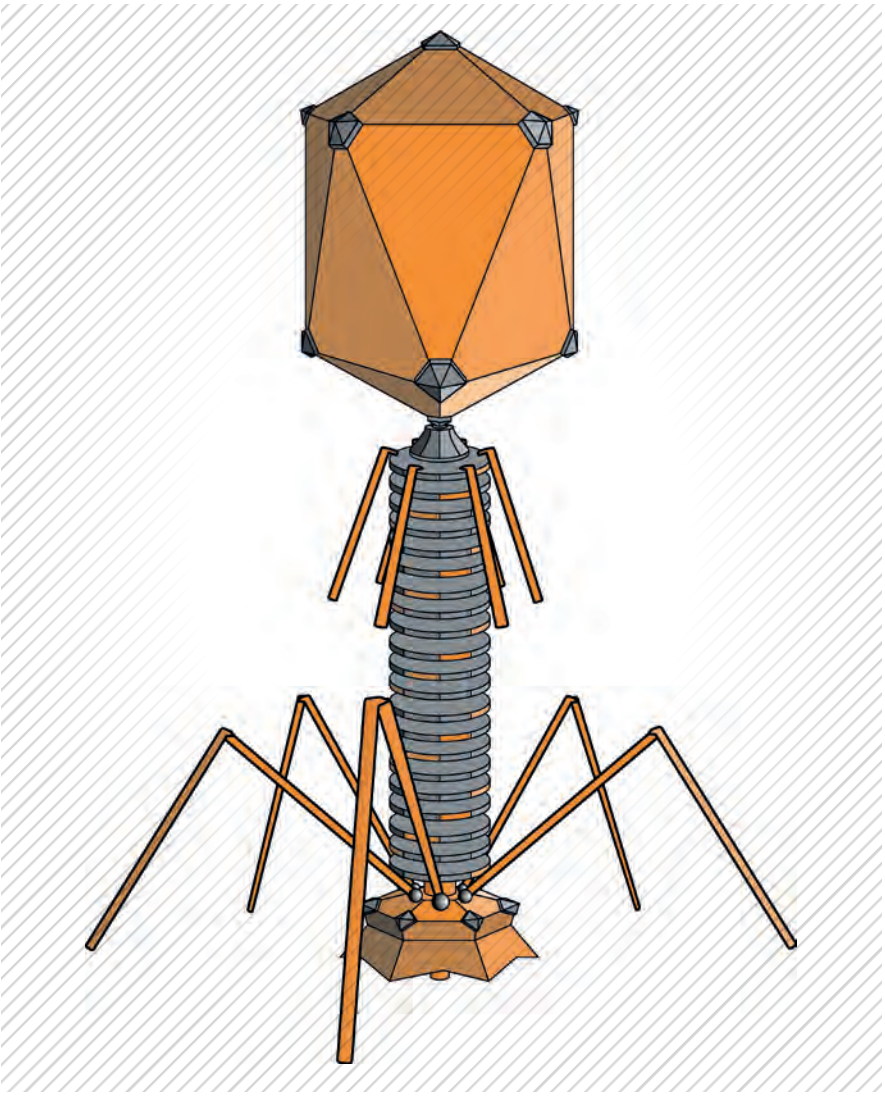

At a Glance

- *Bacterial resistance to antibiotics is a serious and ever-increasing problem*
- *Current methods of testing for drug-resistant pathogens are time- and labor-intensive, which can impact patient treatment*
- *A new method of biosensor-based testing has been developed that can return a result in as little as 10 minutes*
- *Though this new test appears promising, it remains to be seen how well it will translate into clinical practice*

Stopping Superbugs in Their Tracks

A new biosensor technique takes advantage of bacteriophages to rapidly detect drug-resistant pathogens

By Michael Schubert

"The problem [of antibiotic resistance] is so serious that it threatens the achievements of modern medicine. A post-antibiotic era – in which common infections and minor injuries can kill – is a very real possibility for the 21st century." The opening words of the World Health Organization's global report on antimicrobial resistance (1) emphasize the magnitude of this issue, then call for action in developing methods to detect and monitor multiple-drug-resistant bacterial pathogens (2). But detecting these "superbugs" is no easy task, and overcoming them is even more difficult.

One of the first pathogens to be given "superbug" status, methicillin-resistant *Staphylococcus aureus* (MRSA), is also one of the best-known multi-drug-resistant bacteria. MRSA can strike anywhere, but is especially deadly in immunocompromised patients or when it enters the internal organs. Though a problem worldwide, the danger of "superbugs" like MRSA is emphasized in environments where many people live in close quarters. This includes hospitals, prisons and the military – one reason why the United States Air Force has chosen to collaborate with Auburn University on a new method to test for drug-resistant pathogens.

Current methods of detecting drug resistance take hours; biochemical and microbiological assays are long and labor-intensive, whereas DNA- or antibody-based methods require considerable sample preparation and purification, along with time-intensive sequencing protocols. Labs that use plate testing for MRSA need two plates for each test, which are read at 24 and 48 hours so that the final results aren't ready for two full days. Those that use molecular analyzers can speed the process up; PCR-based instruments take only a few hours, but even they require a substantial amount of setup

at the bench. To prevent these kinds of testing delays and the waste of lab resources, a team of researchers at Auburn University have devised a new technique that takes only minutes to identify antibiotic-resistant strains of *Staphylococcus* (3). Designed for the specific recognition and detection of MRSA, the technique includes both the identification of the bacteria and the verification of its drug resistance in real-time. While the technologies involved are not new to biosensor science, they have never before been married in a tandem technique like this one for bacterial testing.

The 10-minute test

The new method takes about 10–12 minutes to identify MRSA strains, a task it accomplishes by taking advantage of bacteriophages. These simple viruses target and kill bacteria, but are benign in humans; the MRSA test uses a strain of lytic phage that specifically targets *Staphylococcus* bacteria while excluding all others. The novelty of the test is in the first step, which uses this bacteriophage as a sensor probe – the lytic phage is transformed into spheroids (which maintains high bacterial capture efficiency, but makes them more suitable for sensors), then transferred onto a quartz crystal microbalance (QCM) sensor as a spheroid monolayer using the Langmuir-Blodgett technique. Once the monolayers were prepared, the researchers tested their biosensors with bacterial water suspensions while measuring changes in resonance frequency and energy dissipation; using those numbers, they were able to determine whether or not the mass density of the monolayer was increasing as bacteria bound to the phage spheroids. They found that all strains of *S. aureus* bacteria interacted with the spheroids to bind to the sensor, whereas other kinds of bacteria did not.

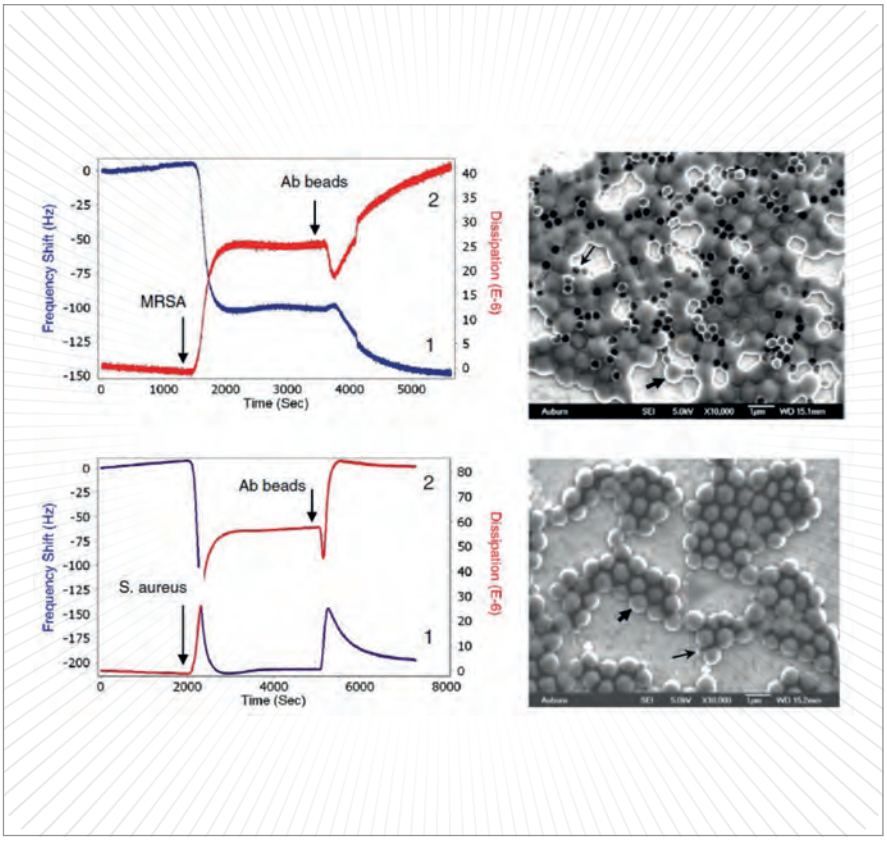

Figure 1. Left, changes in resonance frequency of the phage-spheroid-coated biosensor when exposed first to bacteria and then to anti-PBP2a-conjugated beads (top MRSA, bottom MSSA). Right, scanning electron micrographs of biosensor after assay, with phage spheroids and bacteria bound; at the top (MRSA), the anti-PBP2a-conjugated beads are also bound, whereas at the bottom (MSSA) the beads are not bound (3). MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-sensitive *S. aureus*.

A second step exposes the biosensors to a flow of latex beads, which are conjugated to a penicillin-binding protein (PBP2a)-specific antibody. In this step, the beads will bind to sensors previously exposed to methicillin-resistant strains of *S. aureus*, but not to sensors that were exposed to methicillin-sensitive strains (MSSA). As the sensors are exposed to the bead flow, the changes in resonance frequency and energy dissipation (Figure 1, left) are measured again to capture the change in mass as beads bind to resistant bacteria; it is also possible to obtain a scanning electron

"The new method takes about 10–12 minutes to identify MRSA strains, a task it accomplishes by taking advantage of bacteriophages."

micrograph of the bound bacteria and, where applicable, anti-PBP2a-conjugated beads (Figure 1, right), though it is not a necessary component of the test. This second step provides unambiguous discrimination between resistant and sensitive strains, so that if both steps of the test yield a positive result, it signals specific detection of MRSA.

Can it help avert a crisis?

The need for rapid, effective and sensitive detection of antibiotic-resistant bacteria is growing rapidly as more and more pathogens develop resistance to our most effective drugs. "A crisis has been building up over decades," the World Health Organization warns, "so that today many common and life-threatening infections are becoming difficult or even impossible to treat," (2). The tandem approach can be used not only with MRSA, but with other drug-resistant bacteria as well, and could provide medical laboratories with a quick, cost-effective way of diagnosing multi-drug-resistant infections in patients. Because of its speed and reliability, the test is particularly useful in settings with high population density, where MRSA and other drug-resistant infections are most likely to spread – and where early diagnosis can make a major difference, allowing doctors to treat their patients with the appropriate antibiotics from the start, rather than "flying blind."

Could pathologists use it?

Melissa Andreas, a medical laboratory scientist at a core clinical lab in Oregon, USA, feels that current testing methods are somewhat outdated. "I think molecular techniques are where we're headed," she says, but warns that in order to implement a biosensor test like this one in the lab on a commercial basis, "it needs to be rock solid and easy to use." Even working in a small laboratory, Andreas sees as many as 10 samples a day for MRSA testing and adds that a rapid protocol would ease the burden of testing not only patients showing signs of infection, but also potential carriers of the superbug. "Most of the MRSA assays we do are to check if people are carriers while they're preoperative, and those are a two-day test," she says. "But we also see MRSA show up in the normal course of microbiology testing, especially in wound cultures and urinary tract infections." In standard infectious disease evaluation, the workflow is slightly different, but the time taken to culture bacteria and run panels of tests still results in a turnaround of up to two days. For all applications, a quick test for drug-resistant bacteria would save time and work in the lab and speed up the overall pipeline.

"Whether or not this new, biosensor-based diagnostic test will become the "right test" still remains to be seen."

Michael Prystowsky, chair of the Department of Pathology at Albert Einstein College of Medicine, New York, says that his priority is to get patients the best treatment possible, as early as possible. With that in mind, he's interested in seeing testing times reduced by any means as long as sensitivity and specificity are preserved – whether that's through point-of-care testing, faster sample processing, or other forms of new technology. With this new test, however, he cautions that the nature of the samples used for testing will determine its value; though the test itself may only take 10 minutes, potential requirements for bacterial culturing or other preparative steps may extend the period between taking the initial sample and returning a result. The key to good patient care when dealing with multi-drug-resistant pathogens, he says, is "the right test at the right time to optimize treatment decisions" – and whether or not this new, biosensor-based diagnostic test will become "the right test" still remains to be seen.

Certainly, the test still needs evaluation with real patient samples before it's ready for widespread use. When it can be implemented in clinical labs, the test offers the chance to greatly reduce the time from laboratory to point-of-care without losing the effectiveness or sensitivity of current methods; it's even fast enough for use during surgical procedures. And it paves the way for the development of other applications using biosensors and bacteriophages – for instance, phages might be used as a treatment for drug-resistant infections, or transformed into spheroids to create antimicrobial surfaces for clinical use. Most importantly, the current test was designed to detect MRSA in particular, but its success outlines a new approach to screening.

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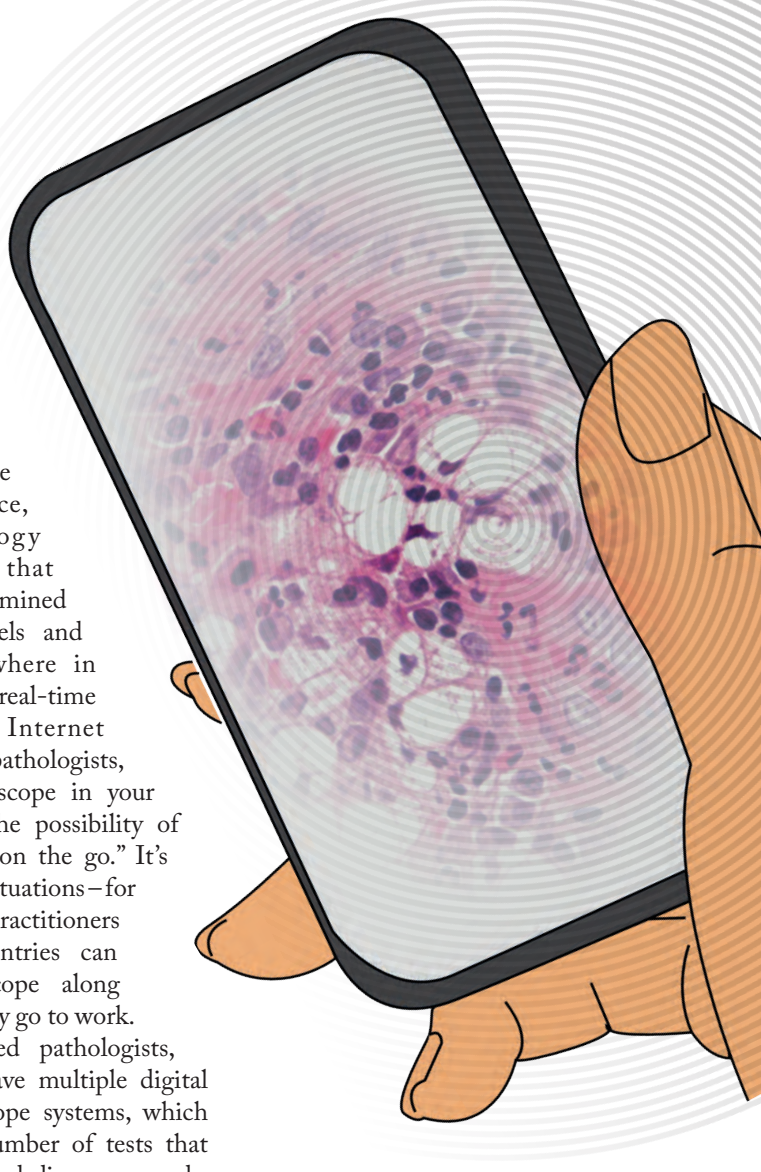
Pocket Pathology

A new method of lens production brings high-quality digital pathology into the realm of the smartphone

By Woei Ming Lee

No more than a hobby in the 17th century, microscopy has transformed over the last few centuries into an ever-growing industry that is forecast to be worth nearly $4 billion by 2017 (1). While the optical technology behind light microscopy has seen little change over the last few years, the digital revolution has not left pathologists behind. Modern imaging technology has taken a quantum leap – nowadays, miniature digital cameras like those found in smartphones are outperforming even dedicated digital compact cameras. Knowing this, it seems inevitable that smartphone cameras will emerge as a new microscopy imaging platform.

A low-cost mobile microscope with a small form factor is pivotal to myriad existing practices not just in medicine, but also in agriculture, geology, ecology and marine biology. In essence, having technology like this means that samples can be examined at microscopic levels and shared from anywhere in the world on a real-time basis, thanks to Internet connectivity. For pathologists, a disposable microscope in your pocket opens up the possibility of making diagnoses "on the go." It's useful in all sorts of situations – for instance, medical practitioners in developing countries can bring the microscope along with them when they go to work. For laboratory-based pathologists, it allows you to have multiple digital automated microscope systems, which can increase the number of tests that can be completed and diagnoses made. The advent of these small, portable microscopes has drawn significant interest from the commercial, medical and scientific worlds, but they all share a fundamental technological and economic barrier – the imaging lenses. Imaging lenses are produced by grinding small pieces of glass or casting molten plastic in molds, processes that require specialized equipment. By re-examining the lens-making process, we break down the barriers and gain access to high-resolution imaging for mobile microscopy.



At a Glance

- *Portable microscopy systems all share the same barriers – the economically and technologically demanding process of imaging lens production*
- *Elastomer lenses formed by hanging and curing droplets overcome these barriers to offer a simple, low-cost lens-making process*
- *Elastomer lenses currently lack the resolution of polymer lenses, but are promising in many primary care fields*
- *As field of view increases and more applications are developed, mobile microscopy will become a game-changer in pathology*

Droplet lenses: nature's design

Nature makes lenses with droplets on a daily basis. Dew forms through the process of condensation, where miniscule drops of water nucleate and coalesce to form millimeter-sized water droplets ("macrodroplets") on a solid surface. These droplets of clear liquid can bend light, acting as lenses. We exploited this well-known phenomenon to develop a new process for creating inexpensive, high-quality lenses.

To begin with, we developed elastomer lenses that, when combined with a standard smartphone camera, can resolve images down to four micrometers. Because the lenses are formed using naturally occurring forces – surface tension and gravity – the cost of production is a mere penny, spent on the materials themselves. So far, we've made lenses a few millimeters thick that have a maximum magnification power of 160 times and a resolution of about four microns – which is about two times lower than the average commercial microscope, but costs over three

Figure 1. The mobile microscopy lens and lighting unit. Left, the lens in place on a smartphone camera. Middle, the lighting unit on its own and, right, attached to a smartphone.

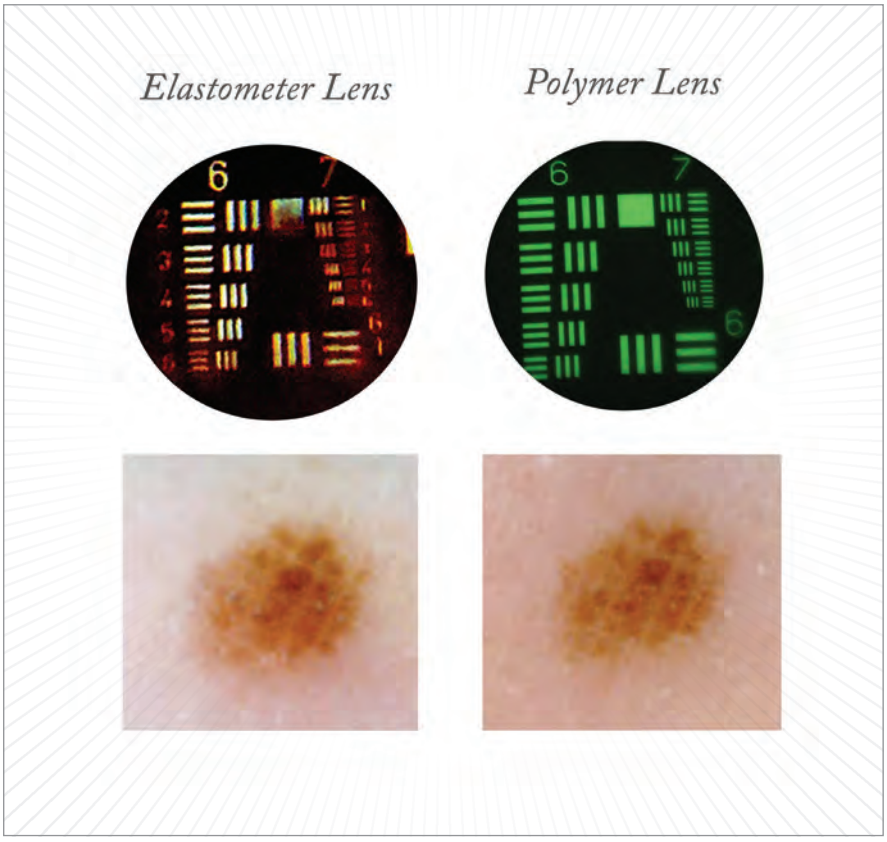


Figure 2. Comparing the performance of the new elastomer lens with a standard polymer lens. Top, light microscopy resolution. Bottom, dermatoscopy of the common mole. Image courtesy of Kar Gay Lim, Macquarie Health.

orders of magnitude less to produce (2). The surprise for us was the level of magnification enhancement we were able to achieve using a very simple lens production process.

All we need is an oven, a glass microscope slide and a common, gel-like silicone polymer called polydimethylsiloxane (PDMS). First, we drop a small amount of PDMS onto the slide and bake it at 70 degrees Celsius for 15 minutes to harden it, creating a base. Then, we drop another dollop of PDMS onto the base and flip the slide over. Gravity pulls the new droplet down into a parabolic shape. We bake the droplet again to solidify the lens, after which we can add more drops as needed to hone the shape of the lens and increase its imaging quality. Current methods of making lenses are difficult and expensive because of the need for specialty lathe or molding equipment (3). Our new method allows us to harvest solid lenses of varying focal lengths just by hanging and curing droplets of different volumes – an easy and inexpensive recipe!

How it works

The lens is designed to be placed directly onto the back of a smartphone camera (Figure 1, left) to take magnified images of samples under ambient light. We've also developed a 3D-printed lighting unit with two mini-LEDs (Figure 1, middle and right), which can be fitted onto the smartphone if better illumination is needed. Even with the lighting unit included, the attachment is more than two times smaller and slimmer than any existing ones – an advance that led me to release its design at Google's recent "Mobile First World" conference, which focused on the global transition from an Internet-based lifestyle to a mobile-based one.

When used as a standard light microscope, our device resolves structures

down to four micrometers in transmission lighting with a five-megapixel camera. This is about two times lower than the resolution a polymer lens can achieve (Figure 2, top). But for dermatoscopy applications, our lenses have very good optical performance on skin (Figure 2, bottom). At the moment, the elastomer lens is interesting commercial parties in the area of skin diagnosis, and the technology can be extended to imaging devices in other primary care fields like otoscopy, ophthalmology and even endoscopy.

Moving to mobile microscopy

Why is it worth using this technology yourself? Cost provides a compelling argument. Mobile microscopes reduce the startup costs involved in creating new pathology services, so that pathologists can begin working in more remote areas without spending more than necessary. With the advent of different mobile health networks, smartphone-enabled microscopes and other tools can be linked to cloud services where patient data are stored and shared among medical professionals through secured networks. The first challenge to overcome, though, is to get pathologists and clinicians to begin adapting their practices to mobile microscopy. Though it's an ideal tool for use in developing countries, most high-resolution smartphones are still fairly expensive, and medical practices in those countries often follow very traditional practices. I think that once first-world countries begin to use mobile microscopes in their clinics, it'll start trickling down to developing countries, where we'll see wider adoption.

At the moment, I feel like pathologists are still waiting to see how this kind of technology will pan out. I know that one of the key issues to overcome in mobile microscopy is to capture a high-resolution image (micrometers) over a large area (centimeters) very quickly, so that rapid diagnoses can be carried out on suspicious tissue. Having this access on a portable device gives pathologists their ideal pathology microscope in a pocket. Mobile microscopes still have a limited field of view, but I anticipate that this concern will eventually be addressed by a combination of more powerful smartphones, inexpensive optics, and better computational processing of optical images. People also like to have different microscope imaging setups (like fluorescence, darkfield, or phase contrast) available in different modules for their smartphones, so expanding the available options might increase the rate of adoption.

"I hope we'll see a dedicated miniature flatbed scanner, based on smartphone technology, in every pathologist's pocket."

A pathology game-changer

I anticipate that we'll develop more and more applications for mobile microscopy, and as we continue to expand what we can do with the technology, it will become more and more popular. My team has recently discovered, for instance, that we can use simple capillary effects to create concave lenses, which can be combined with convex lenses to reduce aberrations and pave the way to creating disposable endoscopy systems based on elastomer lens technology. Another interesting direction we can take is into flatbed scanning – we've already seen the success of flatbed scanners for digital pathology, as they've been widely adopted in major hospitals. In the future, I hope we'll see a dedicated miniature flatbed scanner, based on smartphone technology, in every pathologist's pocket. Once they can start performing flatbed scanning with a system that fits in a pocket, I think mobile imaging technology will become a game-changer for pathology practices. With the almost exponential increase in imaging chip resolution, this could happen within the next five years.

You could say that Antonie van Leeuwenhoek, an unremarkable tradesman, laid a new cornerstone in science by using a homemade high-powered lens to reveal a whole new world beyond our naïve vision. As a result of this discovery and his ingenuity, he gave birth to the field of microbiology through single-lens microscopy. Now, we are moving into an era when every individual can have the microscopic world right at their fingertips – and that includes pathologists, who may one day soon be able to take their laboratories with them wherever they go.

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Smart Oxygen Cuvette for Optical Monitoring of Dissolved Oxygen in Biological Blood Samples

A "smart" oxygen cuvette has been developed by coating the inner surface of a plastic (PMMA) cuvette with sol-gel based oxygen-sensitive indicator material. This new oxygen sensing system monitors the dissolved oxygen in samples for biological and medical applications. Smart oxygen cuvettes provide resolution of 4 ppb units, accuracy of less than 5% of the reading and 90% response in less than 10 seconds.

Background

Different methods have been used to detect the presence of microorganisms in blood cultures. Early detection of such organisms is of primary importance to the selection of appropriate therapies and doses to be adopted for patients. The information collected using such methods helps in the selection of system parameters optimum for detection of the different microorganisms. Some of the changes such as conversion of oxyhemoglobin to deoxyhemoglobin within the red blood cells have been detected using spectroscopy methods, which provide data on growth behavior of organisms. In this Application Note, we explain how a cuvette coated with an oxygen-sensitive indicator acts as a detection system to measure the dissolved partial pressure of oxygen in blood culture systems. We also show the trend in oxygen consumption in response to the increasing density of yeast microorganisms in the blood samples.

Experimental Conditions

The oxygen sensing experiment was carried out using a smart oxygen cuvette. We started our experiment by placing whole goat blood and water in the cuvette. Data logging began at the instant diluted low-level oxygenated blood was placed in the cuvette. Once the oxygen levels were stable, yeast cells were added to the blood in the cuvette. The oxygen quenching was observed over a period of time. After each run all of the dissolved oxygen sensor data was logged. The experiment was conducted three times.

Results

The system was calibrated and the dissolved oxygen levels were monitored when the yeast cells were added and the measurements carried out for approximately 30 minutes. With an objective to study the performance of the smart cuvette while sensing the oxygen levels in the cell culture, we performed a set of experiments varying the amount of yeast dissolved in blood. The oxygen is consumed by the cells faster if the number of cells is greater. Figure 1 shows the performance of the smart oxygen cuvette in measuring the dissolved oxygen levels in cell culture environment with different yeast amounts added to diluted blood.

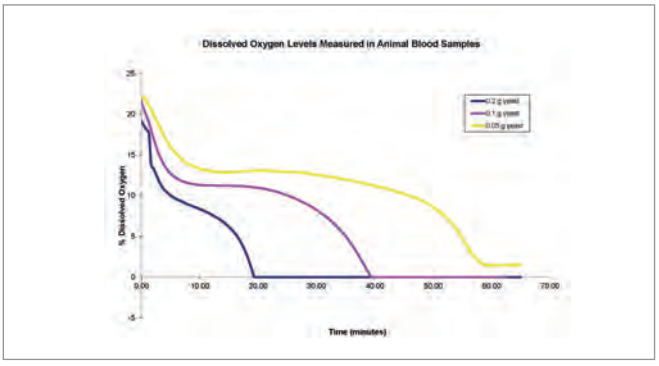

Figure 1. An optical oxygen sensing method measures oxygen consumed by cells when different amounts of yeast are added to diluted blood samples.

Conclusions

A smart oxygen cuvette demonstrates superior measurements of dissolved oxygen in important biological experiments such as those performed in blood culture and bioreactor systems. The integration of smart oxygen cuvettes with advanced phase fluorometry for detection can be used to develop portable systems to measure the presence of bacteria in different blood cultures. Development of a cost effective system would open a new approach to studying the presence of microorganisms in blood culture systems. Systems of this nature could accelerate intervention procedures and help reduce healthcare costs.

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Revving Up Reform

Transformative changes to pathology services are needed now more than ever. Why are they taking so long and how can better collaboration help?

By Jane Kirkup

The UK's National Health Service (NHS) has changed a lot in the years since Lord Carter produced his ground-breaking reports on how pathology services in the country could improve cost-effectiveness and quality (1, 2). The pressures pathology services are under have increased considerably, with more tests being ordered and greater demands for cost savings as the NHS faces a protracted period with little real-term increase in spending. In some areas, new methods of delivering pathology services have been developed in response to the recommendations from Lord Carter's independent panel, but in others, progress has been much slower. The difficulties in getting individual Trusts to collaborate to provide pathology services over a wider area has hindered development.

Could this be about to change? A roundtable chaired by Paul Briddock (policy and technical director at the Healthcare Financial Management Association) was convened to discuss the changes and challenges to pathology service reform. In general, participants thought that the current situation meant there were more reasons than ever for organizations to collaborate and reform services. Here, I present the key discussion points. And although the meeting addressed the situation in the UK specifically, there are many common themes that will strike a chord with pathologists around the world.

At a Glance

- *Eight years on from Lord Carter's report on improving cost-effectiveness and quality of pathology services in the UK, progress has been very slow*
- *Demands for pathology services continue to increase, but many services are still not optimized to cope with the increasing workload*
- *Collaboration between healthcare trusts and private sector partners has successfully facilitated cost-effective and streamlined services*
- *Change needs to happen faster though and this can be driven by better communication and collaboration between pathologists, healthcare trusts, private partners and clinicians*

Save money, but increase productivity

The fact that the NHS needs to find an estimated £30 billion (around €38 billion) in efficiency savings by 2021 could be a strong driver for change, according to Roche Diagnostics UK managing director Christopher Parker. But, he asked, is pathology high enough on organizations' priority lists?

Janet Perry, director of operational finance at Barts Health NHS Trust, thought it was: "In reality we need to be looking for efficiencies across the board – and that includes pathology. There is no area that can be viewed as a low priority for us."

Perry added that there is more willingness to consider new and progressive ways of working in pathology services, such as collaborative partnerships, or contracting out services, than in other areas. However, one concern was that different models and options are still emerging and being implemented, making it difficult for organizations to choose one. "We need to ensure that there is a robust economic appraisal of all the options before deciding on our preferred option," she said.

To the contrary, Colin Carmichael, business development director at Viapath (a pathology partnership involving several London NHS Trusts) felt, "On the provider side, pathology is quite low down the priority list of NHS Trust chief executives and finance directors, and is seen as an area where the difficulties of change are often greater than the financial benefits." The perception was that change was taking far longer than Lord Carter had expected – but what, the panel questioned, are the barriers?

Drive and deliver

What would drive this sort of transformation in other areas? Linking pathology transformation into the broader challenges faced by hospitals is one answer. Alan Goldsman, director of finance at the Royal Marsden NHS Foundation Trust said, "We've spent time focusing on reducing the unit cost of pathology. Perhaps the reason we have not been successful is that we have not been looking for how we can use pathology to drive our quality, innovation, productivity and prevention targets. How can we put it at the center of what we do and help us to reduce waste?"

Lee Outhwaite, director of finance and information at Derby Hospitals NHS Foundation Trust, added, "The critical bit is getting the pathology team onside with how it will improve value, not just reduce cost. We need a much more general narrative about how we can drive quality up."

Many pathology laboratories have made considerable efficiency savings since the Carter reports – but these savings may have reached their limit unless there is consolidation. Charlton said: "We've had some 21 percent of cost improvement programs with each lab making incremental changes and pretty much delivering on this. Now I think

we're at the point where we can't make individual cuts anymore and that will drive collaboration."

The panel agreed that successful collaboration needed a number of factors. One of these was executive buy-in and agreement on the direction of travel. All organizations involved needed to agree on what they wanted to achieve and how benefits should be shared – and to feel they were equal partners.

Timing was also important. There were dangers in putting off change until there was no option; this could lead to a negative approach, which might make the change sub-optimal. Trusts need to have a 'burning ambition' to change, said Briddock, rather than embarking on change from a 'burning platform.'

Carmichael pointed to the failed collaboration in the Midlands that would have involved 40 clinical commissioning groups (CCGs). Individual CCGs have pulled out because of concerns over the clinical and financial benefits the changes would bring. However, in the East of England, three networks of Trusts have been created to deliver community pathology services, showing that partnership and collaborative working can deliver success.

Power of partnership

Private sector partners have successfully facilitated collaborative, cost-saving and streamlined services. One example of this is in the North East of England where three Trusts, The Queen Elizabeth Hospital in Gateshead, City Hospitals Sunderland NHS Foundation Trust, and South Tyneside NHS Foundation Trust, have worked together with Roche Diagnostics to create a hub and spoke model with 'cold' work – up to 80 percent of all the pathology needed by the three Trusts – carried out at one centralized site.

The Queen Elizabeth Hospital in Gateshead was chosen as the centralized site, with the other two retaining facilities to process their own urgent work but sending non-urgent work to Gateshead.

Gaining agreement on the model took a lot of work, and meant overcoming the presumption that the largest site – South Tyneside – would be the site for non-urgent processing. "We made sure that clinical representation was not related to size," said Chris Charlton, pathology services manager at Gateshead Health NHS Foundation Trust. "No one site or discipline had more dominance. This took a huge commitment from each of the sites, but it got us through the hardest part of the process."

New state-of-the-art automated facilities have been developed and installed at Gateshead to cope with the centralized workload and allow faster testing that should result in long-term cost savings for all three Trusts.

Marcus Thorman, chief finance officer at Imperial College Healthcare NHS Trust, outlined his Trust's plans for collaborative working with other local Trusts. "Pathology has been seen as something to deliver significant savings for organizations into the future. And if we collaborate, we think we can save more."

"Trusts need to have a 'burning ambition' to change [...] rather than embarking on change from a 'burning platform'."

Carmichael asked whether those collaborations being developed at the moment would have enough leadership and drive to push them forward. In many cases, it was easier to get agreement about a generic solution rather than an actual model of delivery. It could be challenging to achieve rationalization with many partners involved. Chairman Briddock added all partners needed to change their perception to see the hub as 'our hub', even when it is not in their own Trust.

How many partners is too many? Peter Ridley, director of finance at Royal Surrey County Hospital NHS

"Pathologists have to be more at the center of things – they need to move out of their backrooms and into the clinical diagnostics environment."

Foundation Trust described a pathology service venture with just one other Trust: "This was more manageable and enabled us to prove the concept as a 50:50 venture and then add partners."

Who pays the bill?

The panellists could also see changes on the horizon that will influence how pathology services develop. One of these is the increased interest of CCGs, led by general practitioners, in what they get from pathology services for the money they pay. Primary care accounts for half of the total cost of such services – estimated to be between £2 billion and £2.5 billion (approximately €3–€3.5 billion) a year. Outhwaite described it as a 'disruptive innovation', which had led many areas to think of broader reform.

The question of how pathology is paid for is one area that might benefit from reform. Do payment systems help or hinder transformation of pathology? According to Briddock, "In some places there are simply no incentives for acute providers to work with primary care to manage demand. In fact, a cost per case basis for direct access pathology often means that looking to reduce demand will reduce margin for the acute provider. But we need to take a system-wide approach to getting the right tests done to support optimal patient care."

Trusts are also becoming more concerned about demand management and ensuring that each additional test adds to the clinical picture. Barts Healthcare had tried 'internal recharging' so that the cost of tests was charged to the clinical group that requested them. Perry said the Trust had now suspended the process. "The aim had been to ensure departments controlled their usage of pathology, but it did not provide any incentive for pathology to work with the clinical groups to help reduce demand."

However, the panel agreed that understanding the value of tests throughout the patient pathway is important. Goldsman said the real benefits would come from a dialogue between pathology practitioners and frontline clinicians about how services could change. For example, the projected cost of cancer drugs in the UK was expected to double by 2021 compared with 2010. But many of the drugs under development would only benefit patients with certain genetic characteristics, so testing would be vital.

He said, "Pathologists have to be more at the center of things – they need to move out of their backrooms and into the clinical diagnostics environment. They should be involved side-by-side with clinicians – that is what will transform our services."

To conclude, three key themes emerged. Firstly, change needs to happen more quickly, potentially drawing on some of the examples of successful collaborative partnerships. Secondly, an effective dialogue between pathology providers and clinicians is essential for effective reform management. And finally, there are great opportunities for NHS organizations to bring pathology into the heart of the patient pathway and generate benefits for everyone.

Jane Kirkup is Senior Market Manager, Roche Diagnostics, West Sussex, UK.

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The Next Gen of Histopathology Training

Are we ready to meet the demands of modern clinical practice?

By Jacqueline James and Manuel Salto-Tellez

The 2003 sequencing of the human genome has led to an exponential rise in the incorporation of molecular techniques into clinical practice; the use of high-throughput technologies to underpin activities in modern diagnostic laboratories continues to rise as a direct result (1, 2, 3). This change has cast a huge spotlight on the central role of histopathologists in the healthcare system; the uniqueness of their job and skills puts them at the forefront of personalized patient management, through their ability to assimilate clinical, macroscopic, microscopic, molecular and bioinformatic information into comprehensive morphomolecular diagnostic reports (4, 5). With the increasing demands placed on histopathology services, it stands to reason that there is now an overwhelming need to define new paradigms for the training of the next generation histopathologists so that they can function effectively in the laboratories of the future.

There is a lot to be done in this respect, and here we outline: (1) why the current histopathology training curriculum needs to change; (2) what can be done to address the deficiency in molecular diagnostic training within the confines of the existing five-year training curriculum in the UK; and (3) how we believe histopathology training must be delivered in the near future to meet the demands of personalized medicine. While we are focusing on the UK here, these issues are certainly not unique to the UK, and are affecting histopathology labs around the world.

Why does histopathology training need to change?

Patient stratification and delivery of personalized healthcare is already necessary in many diseases diagnosed with FFPE materials: colorectal cancers in young patients and in the metastatic setting, lung adenocarcinomas, advanced-stage malignant melanomas, gastrointestinal stromal tumours, virtually all sarcomas, lymphomas and gliomas, all breast cancers… In order to preserve the role of pathologists at the center of patient management, it is imperative for future generations that our cellular pathologists are equipped with appropriate knowledge in the techniques and applications of molecular pathology to support the delivery of a modern healthcare service. The goal is not only to understand the use of these tests, but to actively take responsibility for generating the results.

When we think about the actual delivery of a molecular pathology service, it is best to use an integrated model (6) – combining traditional tissue-based morphology and the results from low- and high-throughput molecular testing; the two entities should not be separated. Through an integrated approach, pathology laboratories will be better able to develop capabilities that would take a clinical sample through all of the different levels of interrogation (Figure 1).

While traditional assessment of tissue morphology and phenotype will remain a core skill, it is envisaged that next-generation pathologists will also need to understand and interpret complementary data sets. This battery of information will include data generated from single gene analysis – from high throughput genotypic and molecular analyses and from digital pathology algorithms – with translational and pathological bioinformatics arising as a new subspecialty underpinning many of these aspects of modern pathology. In addition, pathologists will be required to understand and engage with stringent biobank sample quality assurance programs to fully support local and national translational research programs

There will also be increasing pressure for next generation pathologists to understand molecular pathology and diagnostics in the context of clinical trials, specifically in the analysis of biomarkers to stratify patients within a trial (clinical trial diagnostics), or to identify biomarkers useful for predicting patient response to treatment (discovery in clinical trials). Such tests should be performed by appropriately trained diagnostic pathologists operating in accredited laboratories. But even before any molecular analysis is performed in this scenario, it will be critical for pathologists to closely analyze the sample tissue to confirm several important factors, including: that it's the right sample for molecular analysis; that there is an adequate ratio of malignant to non-malignant cells; that there is no evidence of inadequate preanalytical handling; that

At a Glance

- *Personalized medicine and human genome sequencing have generated a sharp increase in the need for specialist molecular pathology services*
- *Current training must change in order to retain the central role of the histopathologist in the healthcare system*
- *Molecular diagnostic training is currently being effectively introduced into existing curricula, and while this has proven effective so far, it has to change to meet rising demands*
- *Future pathology services must include several subspecialists working alongside molecular pathology teams who can suitably interface between research and diagnostics*

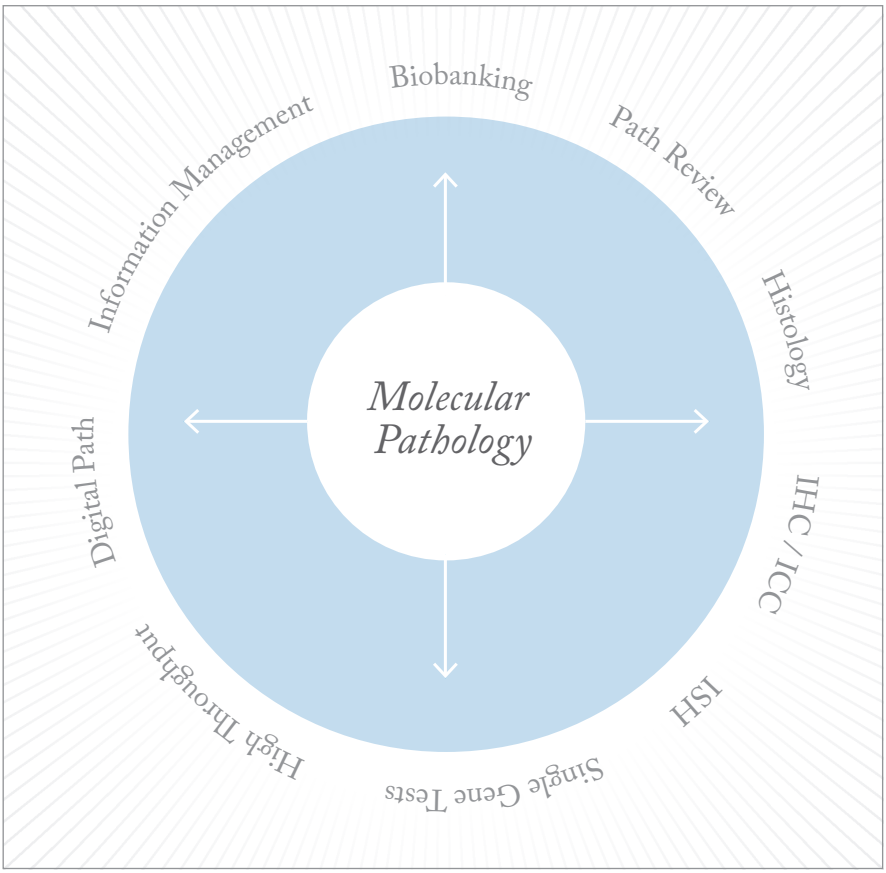

Figure 1. Integrated molecular pathology activities and technologies.

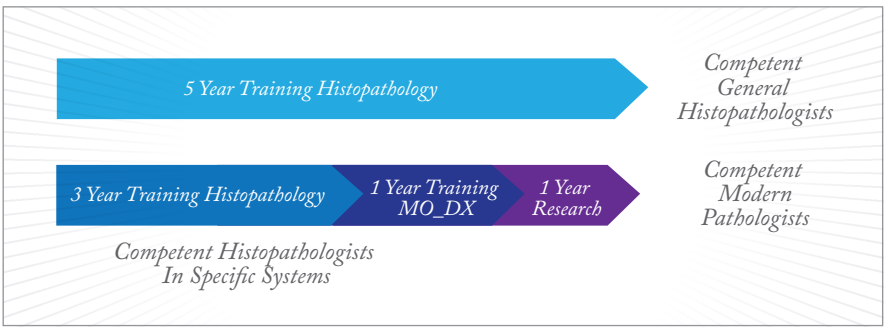

Figure 2. Morphological general excellence versus morpho-molecular competency.

there is no significant pathology present that would interfere with the analysis; that there is no strong morphological evidence of tumor heterogeneity that would lead to analytical bias and that the stage of disease is appropriate for the intended therapeutic approach. So trainees will still need to maintain high-quality microscopic skills.

In addition, pathologists of the future will have to understand how digital pathology can be utilized to guide disease recognition and how automated methods can be employed to score novel and well-established biomarkers. Trainees will need to experience low- and high-throughput genomic technologies and gain an understanding of how molecular testing with deep sequencing techniques, gene expression, gene copy number and methylation profiling can unveil powerful, clinically relevant information. The interpretation of the data generated from all of these molecular tests will require additional knowledge and skills, bioinformatics and biostatistics, populations and cohorts.

How can the existing curriculum be adapted?

In the UK, it has been shown that molecular diagnostic training can be effectively introduced into the existing 5-year histopathology training program (7), and it can be integrated at the most relevant points, throughout its duration in order to satisfy current requirements (Figure 2). This achieves two primary objectives: (1) to equip future practising histopathologists with a basic knowledge of molecular diagnostics; and (2) to create the option for those interested in a subspecialty to gain experience in tissue molecular diagnostics.

In the UK, three stages of training are proposed: In stage A, molecular pathology training is introduced in the first 12 months, and this facilitates preparation for the first part of the Fellowship of the Royal College of Pathologists (FRCPath) examination. During stages B and C of training – around 36–48 months after completion of the first part examination – trainees undertake mandatory 2–3 month attachments. This molecular diagnostics training is delivered as a blend of interactive small group sessions, specialist seminars and practical experience with core competencies assessed and a logbook maintained by the trainee. During this time, trainees are fully exposed to molecular diagnostics audit activity, validation of new tests, external quality assurance tests and research. Trainees also develop a greater understanding of management issues relevant to molecular

testing and are prepared for future consultant practice.

Those trainees who successfully complete the second part of the FRCPath examination are eligible for a further 12-month period of molecular training; this may, for example, be to develop a subspecialty interest in molecular diagnostics. A consolidated 12-month period could provide a pathologist with the armamentarium to become a dedicated molecular diagnostician, equivalent to a 1-year fellowship in molecular tissue pathology. Alternatively a trainee could complete 'superspecialty' training composed of both a subspecialty area in histopathology complemented with molecular training focused on the relevant associated molecular tests (for example, a gastrointestinal pathologist may learn more about the range of molecular tests linked to this anatomical area).

How should future training be delivered?

Unfortunately, we may be reaching the point at which the current curriculum will not be good enough for tomorrow's histopathologists, even with the introduction of snippets of molecular diagnostics training throughout the course of the existing curriculum, as described above. The expanding role of molecular capabilities across healthcare will force current training practices to change dramatically. There is an increasing need for histopathology, like all clinical disciplines, to evolve rapidly to meet the demands of pharma and those of surgical, medical and clinical practice.

It is our recommendation that future training is modular and we believe it's important that pathologists choose if they wish to work in an academic medical center early in their training so that they can make the appropriate choices for them; modular training will allow individuals to decide which areas they want to specialize in so that they remain competent morpho-molecular pathologists. However, we would advise early exposure to academic research so that modern pathologists have the knowledge and experience to become involved in translational biomarker studies in order to help the rapid translation of research results into clinically meaningful molecular tests. The idea that is currently percolating into other areas of medical training is also relevant to pathology, and that is that "academic medicine is a measure of quality of healthcare." So a modular scheme would need to incorporate specific training in molecular diagnostics and provide good exposure to research endeavors.

"In the future, we see integrated laboratories, run by appropriately-trained molecular pathology teams who have the skills to suitably interface between research and diagnostics."

The future is here

We believe modern pathology is poised at a crossroads: between tissue-based hybridization knowledge and broader molecular knowledge; between science and diagnostics; and between present and future. Within the ideal cellular pathology department of the future there will need to be flexibility, variety and integration. Given the ever-expanding remit of the pathologist, tomorrow's pathology team will undoubtedly incorporate good morphologists, good molecular diagnosticians, good translational scientists, good translational bioinformaticians, good clinico-pathological trialists, good digital pathologists and good biobankers. In the future we see integrated laboratories, run by appropriately-trained molecular pathology teams who have the skills to suitably interface between research and diagnostics. This vision is not in the distant future; it's now, and it won't be long before we see pathology services having to make big changes to meet the modern demands of clinical care.

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Committed to Improvement, Committed to Change

Sitting Down With… Fraser Charlton, Consultant Pathologist and Head of Department, Royal Victoria Infirmary, Newcastle Upon Tyne, UK

You're the head of one of the biggest pathology departments in the UK. What are the major challenges?

Dealing with an increasing workload without a matching increase in staffing, while maintaining quality, is a constant problem. Although we've improved productivity significantly, it's getting close to breaking point now.

We're running at nearly full capacity, so if anything goes wrong, we don't have the wiggle room we used to, and with a large department, there is always at least one person absent, for one reason or another. The options of outsourcing specimens or using locums both have significant disadvantages.

I keep banging on about the fact that clinical appointments need to have proper consideration of laboratory impact. We need to get the message across that we can't provide an ever-improving and -increasing service if they don't put something into it.

Is anything being done to deal with mounting pressures?

I think that the central planning of training has been about as successful as central planning was in the former Eastern Europe! As well as insufficient numbers, the recent low national pass rate of the Part 2 FRCPath was creating a backlog of trainees that weren't able to become consultants – I'm very glad to see that improving. However, the numbers are not keeping pace with growth in demand, so we need to find other, more imaginative solutions to the staffing problem. One important thing we've done in Newcastle is to embrace the roles of biomedical scientists and advanced practitioners: as well as performing something like 80 percent of our cut-up, we have several enrolled in the BMS reporting pilot. It's good to have pathology consultants focus on what only they can do, and let other people do the rest.

Has digital pathology technology made it into your service?

We're actively looking at it. I feel it's reached a sufficient level of maturity to be usable, and there are clearly reduced costs for slide storage, delivery and retrieval, as well as potential productivity advantages – networking across a region being a key one, which we're currently trialling at the moment. I also like the patient safety aspect: we have an excellent specimen tracking system that minimizes errors in the laboratory – but when cases land on my desk, there's nothing to stop me picking up the wrong slide! Anything to reduce the likelihood of such errors is very attractive.

How do you improve efficiency now and going forward?

I believe that our lab is one of the best in the country in terms of efficiency; we've really embraced Lean processes and created a culture of service improvement – Dave Evans, Laboratory Manager, and Terry Coaker, Histology Operations Manager, provide superb leadership in this area. There's constant monitoring of different aspects of work of the department; when we notice something going wrong, we promptly investigate and address the problem. It's now the way we work.

Weekly "huddle" meetings with the consultant staff have proved useful; short, frequent, informal meetings improve communication and enable quicker decision-making. It also helps specialists realize that their problems are not unique when they see the stresses across the whole department.

Two things have priority for me in the future: 1) better integration with genetics – I'd like to see pathologists at the hub of tissue diagnosis using *all* the relevant modalities; and 2) to re-establish better links with research – molecular diagnosis is an excellent starting point, because that's where a lot of translational research happens. My ultimate vision is of an institute with cellular pathology, research and genetics in one building, which has proved so successful elsewhere. If the pathology market is opened up to competition, it's difficult for a teaching hospital to compete on the straightforward stuff – but we can do advanced diagnostics that other places can't, and I think that's where we should position ourselves.

What's rewarding about your role?

I enjoy successful service improvement projects – when something tedious becomes trivial, or when you cut through the Gordian knot of something problematic with a simple, elegant solution. It's great when people start coming up with ideas themselves, overcoming the classic mantra of "I'm too busy to think about why I'm too busy." I'm very pleased that, as a department, we have relatively unqualified people coming in and being recognized and nurtured – that's great. You need to have a culture that recognizes the potential in everyone, regardless of position. I've also learnt that service improvement works best when you listen to as many people as possible.

What's the secret of running a successful high-volume pathology department?

I wish I knew! It often feels like you're just limping from one crisis to another – you think, "Well, it didn't all fall apart, so that's good." Like other departments, I'm constantly amazed how much we have managed to achieve with significant, sustained problems in staffing, but I'm also aware that we can't carry on like this indefinitely.

Most of the good things we've done have been because of a commitment to service improvement. For example, a significant reduction in turnaround time was achieved simply by articulating the goal and making everyone aware of it.

The four main things that keep me going are: 1) a sense of humour; 2) a thick skin; 3) constitutional optimism; and 4) a tolerant wife! Not necessarily in that order...

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