JULY/AUGUST 2016 # 21

the Pathologist

It's Our Turn to Talk

What happens when pathologists come out of the shadows to openly communicate diagnostic error?

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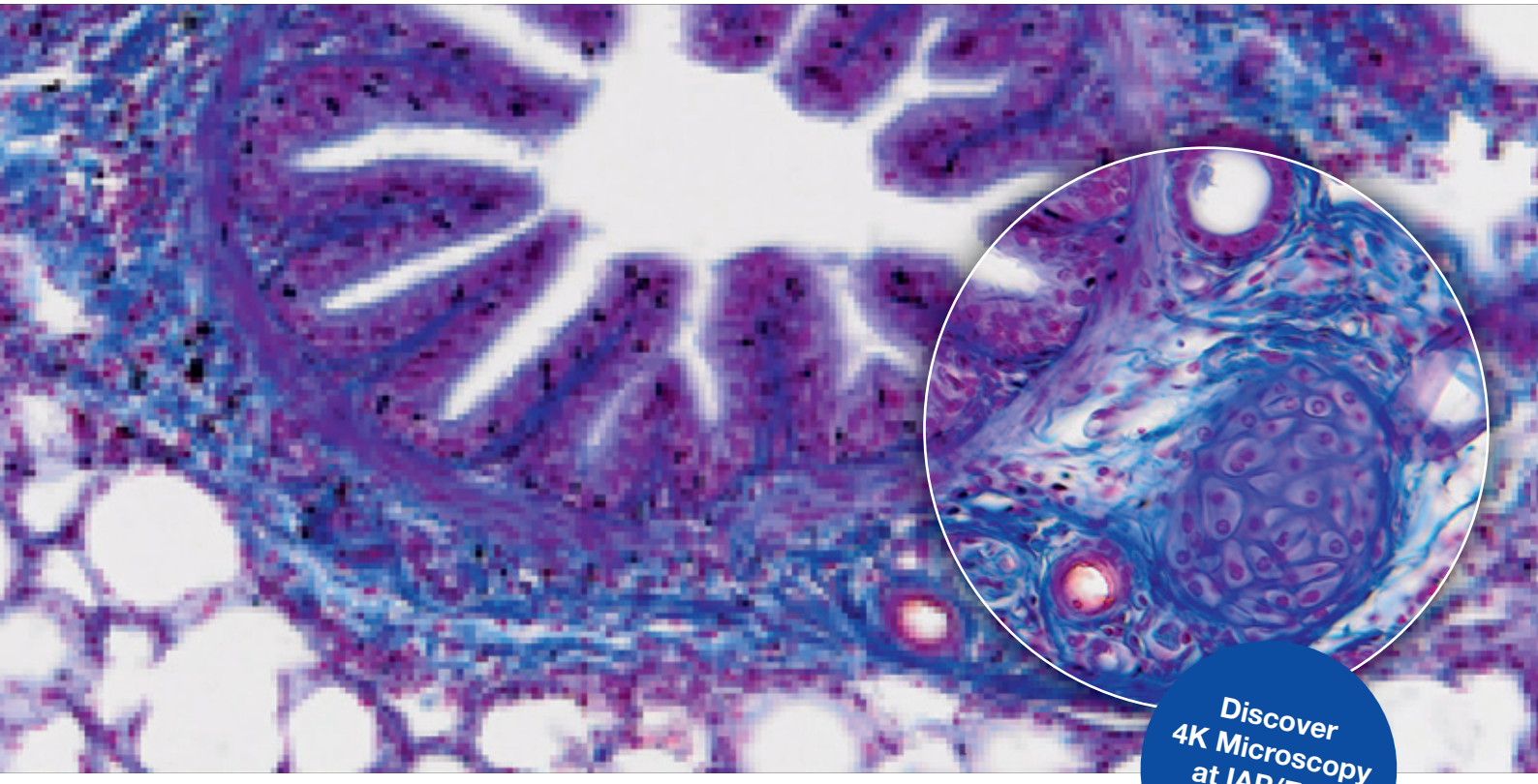

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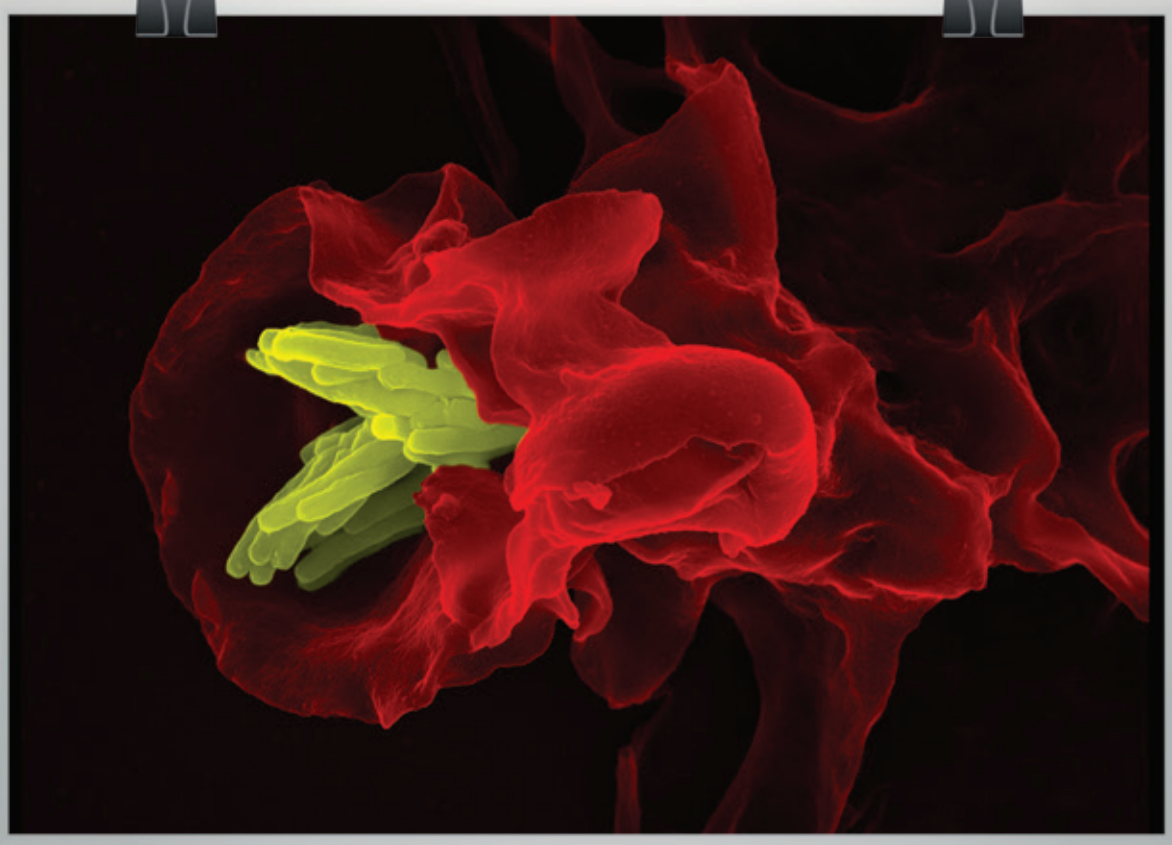

Macrophages are specialized phagocytic cells of the innate immune system that remove diseased cells and non-self objects from the body and serve as antigen-presenting cells. This macrophage (red) is engulfing a *Mycobacterium tuberculosis* pathogen (yellow). The image was captured by Volker Brinkmann of Berlin's Max Planck Institute for Infection Biology using a Zeiss field emission scanning electron microscope (FE-SEM).

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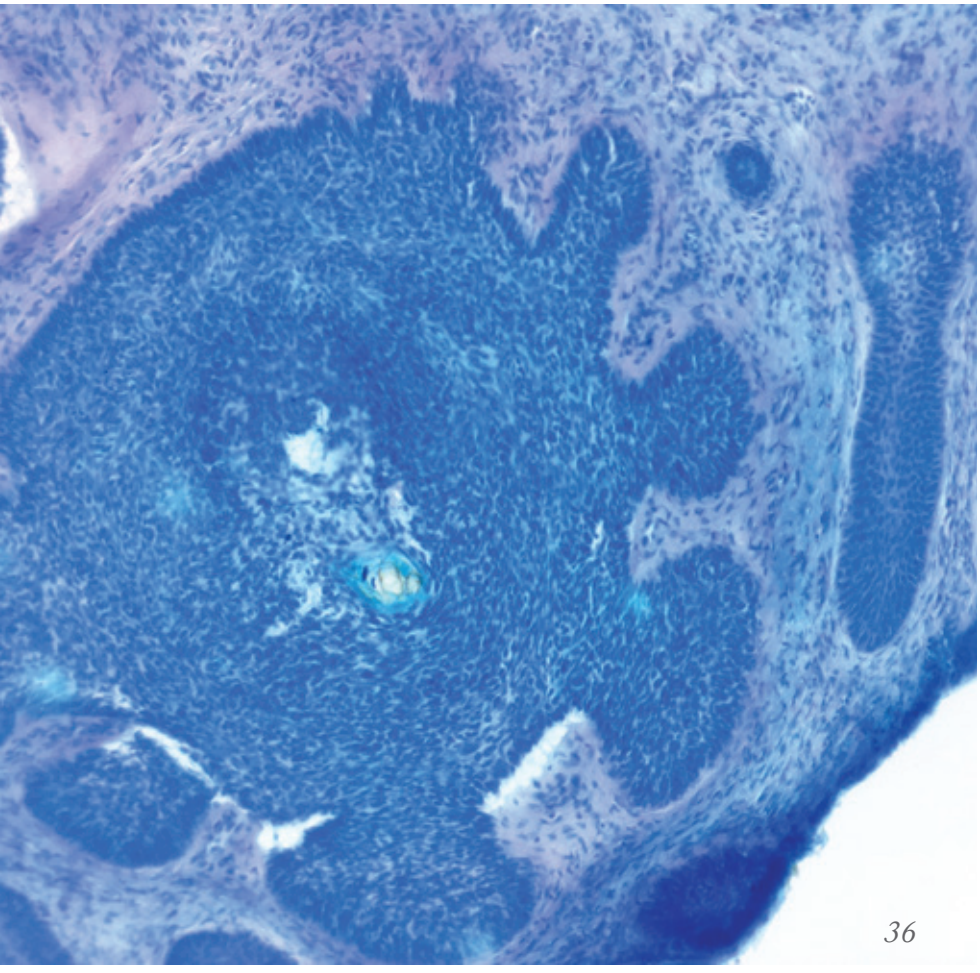
Contents

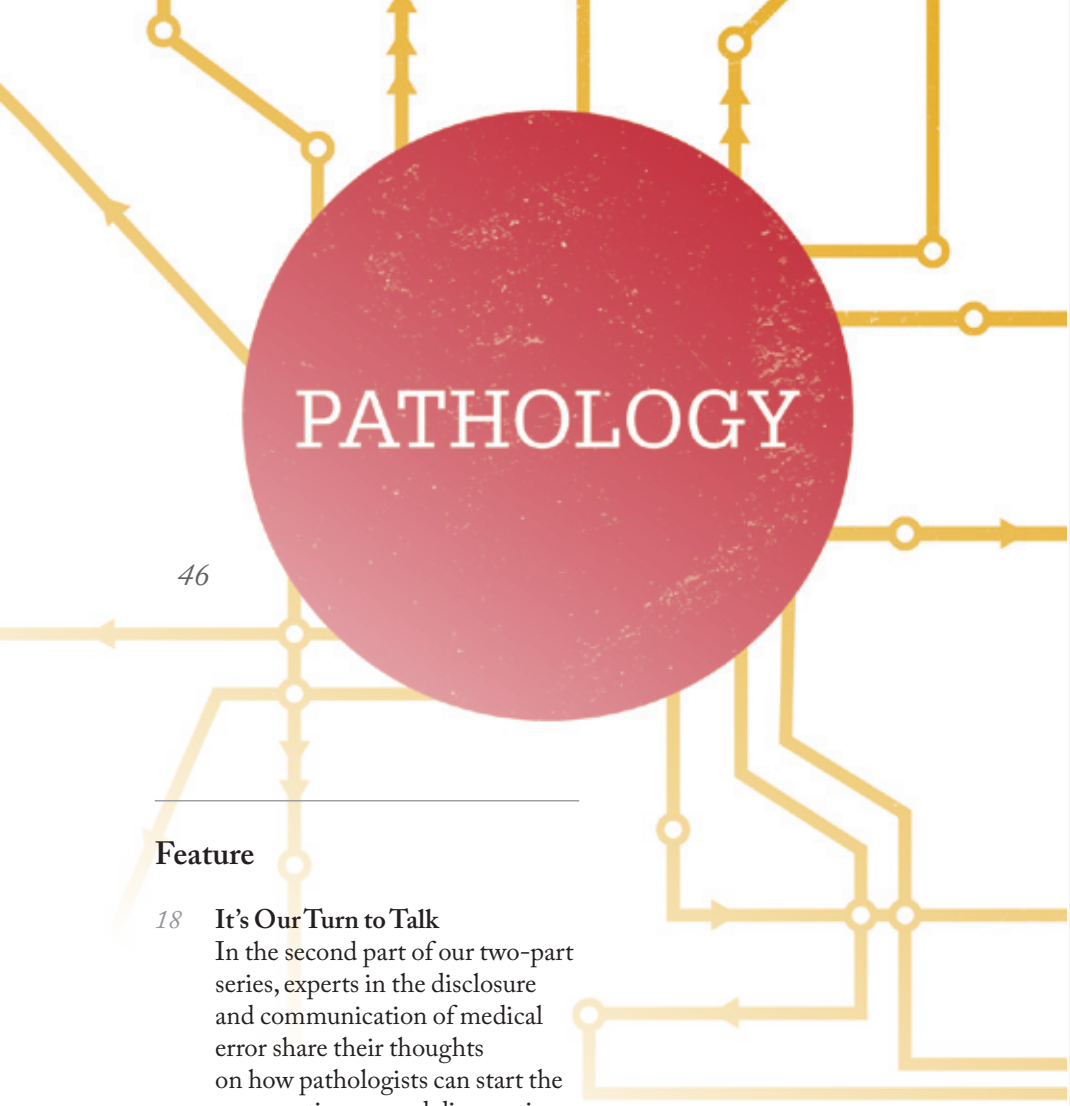


On The Cover

Illustration of the pathologist venturing into unchartered territory and speaking up about diagnostic error.

Upfront

In My View



46

Feature

Next Gen

Profession

Sitting Down With

the Pathologist

ISSUE 21 - JULY/AUGUST 2016

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Too Little, Too Late?

Hollywood needs to wait before it turns the Theranos story into a movie – there's still more to come...

Is anybody else intrigued to see where the Theranos story goes next? Nineteen-year-old Elizabeth Holmes starts a diagnostic company that, 11 years later, is valued at $9 billion – allowing her to boast a net worth of $4.5 billion. It sounds like the stuff of fairy tales or, if things go wrong, nightmares.

Alarm bells have been ringing for quite some time. Not surprising, given that claims of viability and accuracy of its secret but "revolutionary" fingerprick testing technology were based on data never released.

Theranos is now fighting for survival, after US regulators revoked its license to operate its Californian lab. Holmes has been banned from the blood-testing business for at least two years – and a federal criminal investigation is ongoing. All this action comes off the back of a startling revelation uncovered by Wall Street Journal: Theranos' flagship "Edison" technology was not being used to run its single drop diagnostic tests; rather, generic machines were relied upon – and allegedly results were often inaccurate.

Pretty much overnight, Holmes' net worth was revised down to zero by Forbes and Theranos dropped to $800 million. Though corporate statements assured that "corrective measures" would be taken, I thought to myself, "There's no coming back from this." And yet, there I was, sitting in a packed hall at the AACC's annual congress in Philadelphia, eagerly awaiting Holmes' grand entrance – along with over 1,000 others, including national press. It was her opportunity to redeem herself – and I can't deny, I half expected a no-show. Kudos to Holmes, who braved the room full of critics to "lift the lid" on a new technology (note: not Edison). The miniLab, Holmes claimed, will "miniaturize laboratory testing."

The presentation included demo videos and subsets of data, followed by a live Q&A. Though she appeared confident, the data had not been validated or peer reviewed and, if I'm honest, the presentation felt a little like a sales pitch – a risky approach in front of an intelligent audience. I know that Holmes was not there to defend herself or discuss the current investigation, but I felt that some honesty on the current situation would have been welcomed.

"Our hope is to be able to work with all of you in validating and testing [our panels]," she said. "We will work as hard as it takes to be able to realize [our] vision."

Did she manage to convince? Based on the mood in the room, I think she still has a lot of work to do.

Fedra Pavlou
Editor

Upfront

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

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

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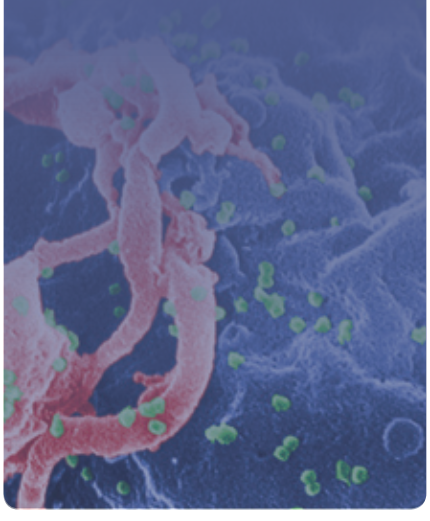
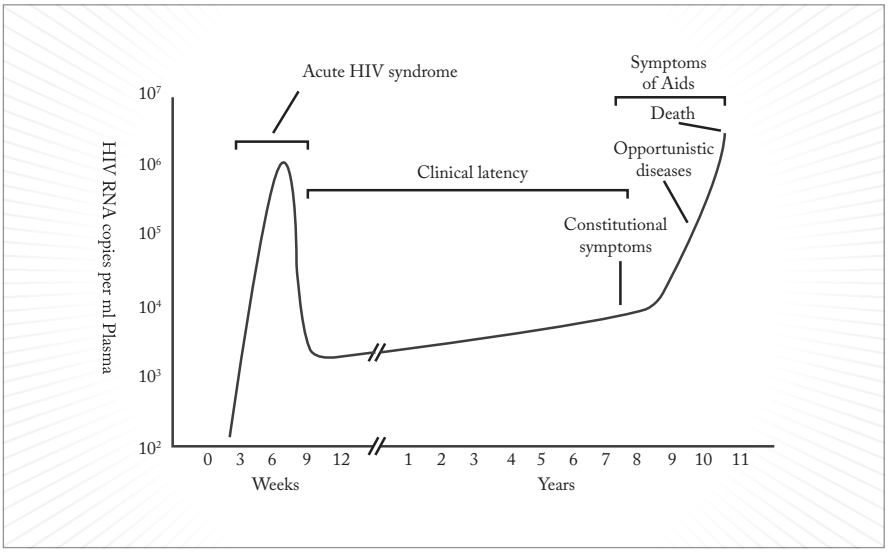


The Secret Life of HIV

Early-capture testing can detect HIV infections before symptoms arise, offering opportunities to decrease transmission and improve treatment

Every so often, a discovery in the world of human immunodeficiency virus (HIV) research will prompt the use of the phrase "Holy Grail." Usually, it's a proposed treatment for the disease, or early-stage work on a possible preventative vaccine. But those may not be the only interventions deserving of a grand title. What if there were a way to detect HIV earlier than ever – during the acute phase of infection, when the disease is both most transmissible and potentially most treatable? A landmark study in the New England Journal of Medicine (1) details a cohort of high-risk individuals whose HIV status was tracked over time with twice-weekly nucleic acid testing, allowing researchers to detect the presence of the virus long before they became symptomatic or began secreting antibodies.

"The common tools for HIV diagnosis utilize the emerging antibody and HIV core antigen as targets of detection," explains senior author Merlin Robb. "A person will have virus in the blood and genital secretions for perhaps a week or more before these tests are sensitive. Testing for nucleic acid of HIV closes that gap and permits the earliest identification of acute infection with HIV." This type of testing is already standard for HIV monitoring in most clinical laboratories and blood banks, but isn't yet commonly used for early capture. Robb would like this to change. "Acute HIV infection is thought to be an era of greater transmissibility, although there is an active debate on the proportion of new cases arising in association with acute infection. There is also increasing information that individuals in acute infection may be the best candidates for testing interventions for cure." If either or both of these hypotheses proves true



The course of an HIV infection over time, showing the concentration of HIV RNA in the blood at each stage of infection (with a noticeable peak during the acute phase). Credit: Jurema Oliveira.

as the researchers collect more data, it will provide motivation to improve nucleic acid testing platforms; current assays are effective, but not portable, and developing smaller, faster tests would allow more widespread monitoring of high-risk populations.

Who is most likely to benefit from early-capture testing? "The highest risk groups for HIV infection are men who have sex with men without use of condoms, and injecting drug users. In some settings, high-risk women would also be ideal participants in frequent nucleic acid testing campaigns." Robb feels that, in these communities, an inexpensive, accessible and reliable diagnostic platform might be able to identify patients in the acute stage of infection – giving doctors the opportunity to intervene to prevent transmission and potentially offer experimental strategies aimed at a cure. The advantages aren't limited to people at risk of HIV, though. "There are many settings where identification of a pathogen which can be transmitted readily with high-grade pathogenicity would be very useful for epidemic evaluation and control. An example would be a nucleic acid testing device for Ebola, which could be carried into sometimes austere epidemic settings."

Robb's work continues – but now it serves a slightly different purpose. Having discovered that patients can be identified early by nucleic acid testing, he's now attempting to turn that to both their advantage and his by offering them the opportunity to start treatment early and participate in research studies assessing reduction of the virus' infectious reservoir. *MS*

Reference

1. *ML Robb et al., "Prospective study of acute HIV-1 infection in adults in East Africa and Thailand", N Engl J Med, 374, 2120–2130 (2016). PMID: 27192360.*

Revealing Recurrence Risk

The deubiquitinating enzyme USP14 may predict endometrial cancer patients' risk of treatment-resistant, potentially fatal recurrence

When diagnosed with cancer, most patients are pleased to hear that their disease is early-stage or low-grade – and most doctors are equally happy to deliver the news. But in endometrial cancer, that information doesn't always bring the relief it would with other diagnoses. That's because a subset of patients with early-stage, low-grade disease experience recurrence for unknown reasons, and those recurrences tend to resist further treatment. How do we know which patients are at risk of a return? We've had no way to tell – until now. Martina Bazzaro and her colleagues at the Masonic Cancer Center have uncovered a biomarker that could potentially predict these recurrences (1).

Deubiquitinating enzymes (DUBs) are important modulators of pathways regulating cell proliferation and chemoresistance. They've previously been linked to cancer initiation, progression and chemoresistance – but now, Bazzaro's research suggests that high levels of a particular DUB known as USP14 indicate a seven-fold higher likelihood of recurrence, meaning that USP14 may be able to serve as a biomarker for recurrence risk. "USP14 is important in regulating the β-catenin pathway, as well as the epithelial-to-mesenchymal transition, both of which are related to chemoresistance in endometrial cancer," Bazzaro explains. Examining a newly diagnosed patient's USP14 levels could lead to more aggressive treatment and follow-up for those at higher risk, ultimately saving lives. It could also offer a potential treatment avenue – not only does USP14 serve as a marker of recurrence likelihood, but when targeted with the FDA-approved inhibitor VLX1570, the viability of chemoresistant endometrial cancer cells was found to decrease.

"The clinical test using USP14 as a biomarker would be staining for it in clinical specimens at the time of surgery and prior to chemotherapy," says Bazzaro. Immunohistochemistry is the simplest way of testing for the enzyme, and the team anticipate that clinical trials will start within the next 18 months. "We will first assess USP14 as a marker for recurrence in prospective clinical trials, and then conduct clinical trials using VLX1570 in recurrent endometrial cancer resistant to conventional carboplatin chemotherapy." Bazzaro also suggests that, because of the similarities between recurrent endometrial cancer and certain types of aggressive ovarian cancer, USP14 testing may eventually be recommended for ovarian cancer too. *MS*

Reference

1. *RI Vogel et al., "USP14 is a predictor of recurrence in endometrial cancer and a molecular target for endometrial cancer treatment", Oncotarget, [Epub ahead of print] (2016). PMID: 27121063.*

The Tell-Tale Gene

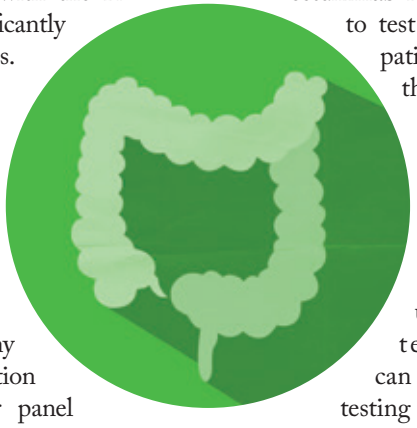
Geoffrey Liu explains how a new blood marker can predict which colorectal cancer patients are likely to respond to cetuximab

Despite all we understand about colorectal cancer, there are still a number of ongoing mysteries. One of these – namely, why up to half of patients receiving cetuximab treatment fail to respond – may be inching closer to a solution. Geoffrey Liu, the Alan B. Brown Chair in Molecular Genomics and an Associate Professor of Medicine, Medical Biophysics, and Epidemiology at the University of Toronto's Dalla Lana School of Public Health, recently published a study revealing that a polymorphism in the *FCGR2A* gene can serve as a biomarker to predict which patients may benefit from cetuximab.

An initial trial conducted a decade ago established that the drug was most effective in patients whose tumors exhibited a *RAS* mutation (1) – but that alone didn't explain the response pattern. The new research builds on that work by indicating that, in patients with wild-type *KRAS*, cetuximab extends survival by an average of 5.5 months in those with two *FCGR2A* H alleles. Patients with one H and one R allele gain only a 2.8-month benefit, and in patients with two R alleles, survival is extended by only 1.6 months (2).

How does FCGR2A function as a biomarker for cetuximab response?

The fragment C gamma receptor (FCGR) is the binding site for immunoglobulins in the antibody-dependent cellular cytotoxicity pathway. Therefore, any monoclonal antibody therapy – including cetuximab – can work through several mechanisms. Although one mechanism is simply that cetuximab "mops" up *EGFR* ligands, there has been more evidence recently that one of its main modes of action is through antibody-dependent cellular cytotoxicity. Binding assays and other functional assays performed by other groups have suggested that there is a differential binding capability dependent on the *FCGR2A* polymorphic variant, with the R allele showing significantly less binding capabilities.



Will there soon be a clinical test for the biomarker?

The translation into a clinical test will not be difficult. As a single polymorphism, it can fall into any number of next generation sequencing or tumor panel tests, the same way that we test for somatic mutations in *KRAS, EGFR*, and other genes.

How might this change the day-to-day work of pathologists involved in colorectal cancer care?

We anticipate that, if further validated prospectively, the *FCGR2A* polymorphism will be performed concurrently with *RAS* mutation testing, the same way that *ALK* translocations and *EGFR* mutations are often reflexively tested in metastatic lung cancer patients. Of course, as both *RAS* and *FCGR2A* are genomic changes, it will be easier to multiplex the testing in metastatic colorectal cancer patients than it is to use genetic testing for *EGFR* mutations and IHC/FISH for *ALK* in lung cancer.

What are your testing recommendations for patients with colorectal cancer?

We don't recommend testing for *FCGR2A* yet clinically. *RAS* testing, however, should be ongoing. We are now in the process of figuring out whether there is an "ideal" patient profile for *FCGR2A* testing, or whether all colorectal cancer patients should be tested routinely.

What are the next steps for your work?

Now that we have found this new association between *FCGR2A* and cetuximab response, we will need to test further in additional patient groups to ensure that our marker is useful across ethnicities and other populations. We will also be developing CLIA-certified methods of testing *FCGR2A* using multiplex technologies that can run *RAS* mutation testing (*KRAS*, *NRAS*, and so on) simultaneously.

Were there any surprises during your research?

We were surprised to find that there were so many challenges in genotyping *FCGR3A* (which was not significantly associated with clinical outcomes). The presence of a pseudogene required us to be careful in our selection of primers and platforms for testing, and we wonder if some of the prior publications on this other polymorphism might have been confounded by inaccuracies generated by this pseudogene.

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1. *DJ Jonker et al., "Cetuximab for the treatment of colorectal cancer", N Engl J Med, 357, 2040–2048 (2007). PMID: 18003960.*
2. *G Liu et al., "Fc-γ receptor polymorphisms, etuximab therapy, and survival in the NCIC CTG CO.17 trial of colorectal cancer", Clin Cancer Res, 22, 2435–2444 (2016). PMID: 27179112.*

Reading the Mind in the Blood

Circulating levels of inflammatory biomarkers may yield clues as to how well patients will respond to antidepressants

When it comes to diagnosis and prognosis, mental health conditions are among the most elusive. What works perfectly for one patient may fail utterly or even make the problem worse for another, and the range of medications available to treat disorders like depression is ever-broadening. At the moment, doctors treat through trial and error, prescribing one type of antidepressant after another until they strike upon the one that works for a given patient. There's currently no better way of doing it – but that may be about to change. Researchers from King's College London have developed a potential blood test to determine whether or not patients with depression are likely to respond to conventional treatments.

The test measures the absolute mRNA values of two inflammatory factors, macrophage migration inhibitory factor (MIF) and interleukin-1β (1). In an initial sample of 142 patients, those who exhibited higher concentrations of the two biomarkers were less likely to respond to standard treatments like selective serotonin reuptake inhibitors or tricyclic antidepressants (see Figure 1). It's possible that inflammation interferes with biochemical and neurological functions required for antidepressant function in some individuals, while others may have genetic differences that affect both inflammation and drug response. To find out more, the researchers will need to expand their work to larger and more varied patient cohorts before bringing the test to the clinic.

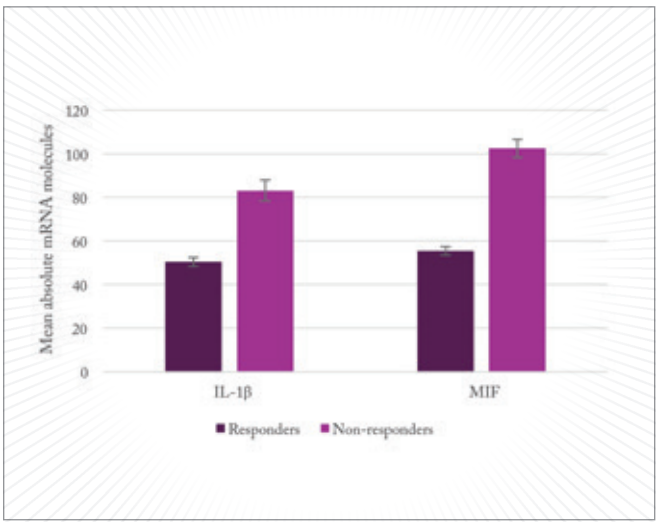

Figure 1. A comparison of the mean absolute numbers of mRNA molecules of inflammatory biomarkers IL-1β and MIF in responders and non-responders to conventional antidepressant treatment.

Carmine Pariante, principal investigator on the study, estimates that about one-third of patients exhibit levels of inflammatory marker mRNA above the established cutoffs. Those are the patients he encourages to seek more aggressive treatment – perhaps by prescribing a less common drug, or by combining depression treatment with anti-inflammatory medication. He said, "We would not want to go on prescribing too much medicine if it's not necessary, but we would want to escalate people sooner rather than later if they need it. (2)". *MS*

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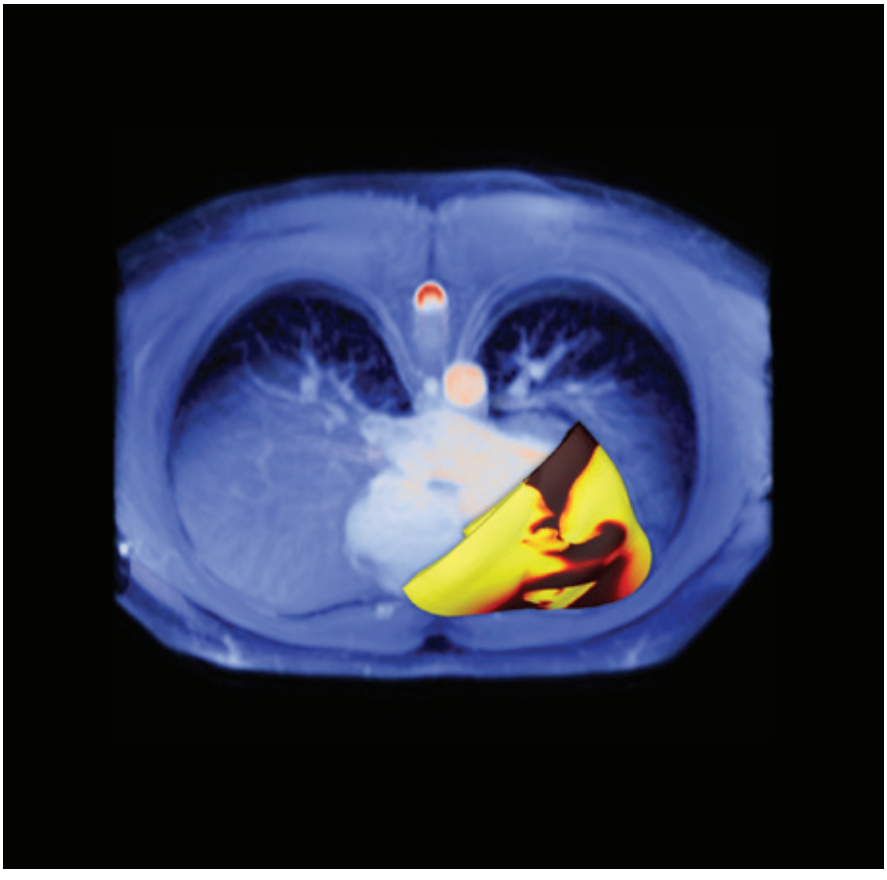
A Virtual Vision of the Future

Noninvasive 3D modeling of damaged hearts can predict future arrhythmias and determine which patients truly need implantable defibrillators

Living with cardiac arrhythmia can be a lot like carrying around an (irregularly) ticking time bomb. It's a problem that can cause sudden cardiac death – but in whom, and under what conditions? Patients who are considered most at risk receive implantable cardiac defibrillators (ICDs) to curb arrhythmia at its onset, but the current methods of determining risk have low sensitivity and specificity, meaning that some patients who need ICDs don't get them, whereas others who don't may undergo unnecessary surgery. Surely there's a better way to stratify patients; that's what Natalia Trayanova and an interdisciplinary team from Johns Hopkins University thought when they developed a "virtual heart" to model and predict cardiac behavior.

"Our goal was to develop a noninvasive, personalized risk assessment tool that has the potential to ultimately prevent sudden cardiac death and avoid unnecessary ICD implantations," says Trayanova. Called the virtual-heart arrhythmia risk predictor (VARP), the simulated heart enables physicians to play out scenarios that manifest the heart dysfunctions of each individual patient, giving them the tools they need to make more accurate treatment decisions (1).



How did they do it? "We constructed 3D computer models of each patient's heart based on MRI scans. The models used the particular geometry of each heart, the location and geometry of damaged tissue caused by previous heart attacks, and representations of the electrical processes within and between the cardiac cells. We then delivered tiny electrical stimuli at many locations in the virtual hearts and watched how the electrical signal propagated through the tissue to see if it caused an arrhythmia," she explains. The process may sound simple, but it wasn't: "Almost every step of the VARP pipeline was a challenge, as this has never been done before using human scans."

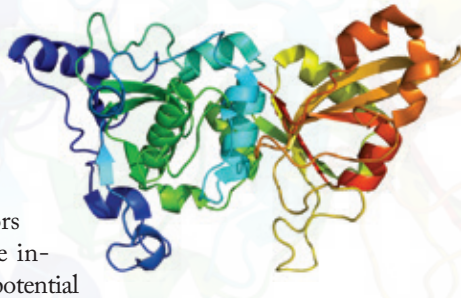
But the work paid off. In addition to being noninvasive, VARP is an accurate predictor of risk – significantly more so, in fact, than the clinical tests currently in use. As a result, the research team intend to demonstrate its capability in larger prospective studies in post-infarction patients, while simultaneously extending the approach to patients with other heart conditions that result in different scarring patterns. "The virtual heart approach has the potential to radically change the process of sudden cardiac death risk assessment and patient selection for prophylactic ICD implantation. It could eliminate many unnecessary ICD implantations and associated complications, benefiting innumerable patients. It could also save the lives of patients with preserved ejection fraction, who could be at significant risk for sudden cardiac death, but are generally not targeted for ICD therapy under current clinical recommendations," concludes Trayanova. *MS*

Reference

1. *HJ Arevalo et al., "Arrhythmia risk stratification of patients after myocardial infarction using personalized heart models", Nat Commun, 7, 11437 (2016). PMID: 27164184.*

Putting a CAPN1 on HSP

The discovery of a new, potentially causative mutation for hereditary spastic paraplegia could lead to better diagnosis, treatment, and understanding of the disease



Hereditary spastic paraplegia (HSP) is a rare, but debilitating, disease. Those who are diagnosed with it – between two and 10 people per 100,000 – experience weakness, stiffness and contraction of the lower limbs, along with a range of possible incidental symptoms including eye issues, deafness, coordination problems and cognitive defects. And there are as many suspected causative genes for HSP as there are presentations of the disorder; over 70 "spastic gait genes" are known, along with others that produce similar phenotypes. But even the myriad genes aren't enough to explain all cases of the disease, and many families exhibiting the HSP phenotype remain undiagnosed through generations. Recently, scientists at the Montreal Neurological Institute identified a new gene that could help diagnose patients with unexplained HSP symptoms.

"Our study shows that homozygous or compound heterozygous mutations in *CAPN1* cause autosomal recessive HSP," says Ziv Gan-Or, who led the study (1). "They are probably responsible for 1–2 percent of HSP patients. Although we cannot determine the exact mechanism, our results show that it is possibly related to the stabilization of microtubules." But even without understanding the mechanism of disease, could the newly identified gene be useful in the clinic? "*CAPN1* mutations can be immediately included in the panels of genes that are currently being sequenced in clinical lab tests," Gan-Or says. "However, since we are the first to demonstrate a role for *CAPN1* in HSP – and specifically for only four mutations in the gene – it is possible that such clinical tests will identify variants of unknown significance." He advocates for more studies in different HSP cohorts in order to identify additional pathogenic *CAPN1* variants, and suggests that the entire coding region and exon-intron boundaries of the gene should be fully sequenced in clinical tests.

HSP is a very heterogeneous disease, and patients with mutations in the same gene can present with "pure" HSP (involvement of the lower limbs and bladder only), or with complex forms that include various other neurological symptoms. Most of the patients in the initial cohort of 20 families exhibited complex HSP with ataxia, but Gan-Or says it's likely that other symptoms can occur in *CAPN1*-associated HSP. "There is no specific patient profile, so we recommend that every HSP patient with autosomal recessive inheritance, as well as single affected individuals in unaffected families, should be tested for biallelic *CAPN1* mutations, regardless of the clinical presentation."

Some of the paper's authors have already begun a more in-depth examination of the potential disease mechanism behind *CAPN1* mutations. Gan-Or and his colleagues, on the other hand, are focused on identifying more genes that cause HSP. "Although more than 70 genetic loci are known to be involved, many families remain genetically undiagnosed – which means that other, still unknown genes are potentially involved." Ultimately, their aim is to increase our overall genetic understanding of the disease to aid not only the diagnosis, but eventually also the treatment and counseling of patients and their families. *MS*

Reference

1. *Z Gan-Or et al., "Mutations in CAPN1 cause autosomal-recessive hereditary spastic paraplegia", Am J Hum Genet, 98, 1038–1046 (2016). PMID: 27153400.*

In My View

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

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

Contact the editor at fedra.pavlou@texerepublishing.com

Only Gene Deep

Advances in genomics are certainly thrilling, but let's not forget that a tumor is more than a bundle of genetic information

By Han van Krieken, Chair of Pathology, Radboud University Medical Center, Nijmegen, the Netherlands

As histopathologists, we try to understand disease by looking at tissues. We see a snapshot of cells in their tissue environment. We can see whether they are normal or abnormal, whether there are too many or too few cells, how they are organized and how they interact. We can localize enzymes and proteins, measure expression levels, determine DNA alterations, and so on – and by bringing all this knowledge together, we can form a fairly complete picture of the disease that manifests itself in the tissue. These efforts provide the patient and the treating physician with information that can be used to choose the best possible treatment (or no treatment).

In this era of genetics, we are increasingly able to sequence the DNA of individuals and tumors, which allows us to quickly diagnose many different diseases that are caused by changes in genes, such as cystic fibrosis or Noonan syndrome. For cancers, we get information on the gene alterations that drive the tumor; for example, *c-erbB2* amplification or *ALK*-fusions. Increasingly, it is suggested that whole genome sequencing will replace traditional forms of diagnosis. Indeed, if a child with an intellectual disability comes for a diagnosis, physical examination is already replaced by DNA analysis. And I was informed that in Hong Kong, where the incidence of *EGFR* mutated lung cancer is quite high compared with western countries, lung cancer is already diagnosed using genetic tests on blood samples in patients with inaccessible pulmonary lesions; if an *EGFR* mutation is found, it is regarded as sufficient evidence that the patient should be treated using an anti-EGFR approach. But in my view, although sequencing is an important diagnostic tool with much potential, it will never give the complete picture.

An example: it was recently shown that the cells within a tumor the size of a ping-pong ball will carry a total of 100 million mutations, with only a few of those mutations present in the majority of cells (1). Not only does this finding indicate that tumor heterogeneity on the cellular level is enormous, but also that complete sequencing of tumors provides us with so much data that it becomes useless. Quite interesting, of course, but not surprising for pathologists. In fact, that the nuclei in cancer cells are extremely variable compared with normal cells has been one of the most important criteria a pathologist uses when making a diagnosis of cancer for more than a century...

Furthermore, a tumor consists of not only neoplastic cells but also stromal cells, such as fibroblasts, inflammatory cells, endothelial cells and others. There is enormous variation in the ratios of these cell types between tumors – variation that has been shown to relate to treatment response and survival of the patient. Such variation cannot be found by sequencing the tumor or even the germline DNA.

Genes act through proteins, but

proteins are not only modified by genetic mechanisms. Indeed, proteomic approaches are likely to give even more information, but replacing genomics with proteomics (which will take quite some time) will also not tell the whole story. Cells and tissues are so complex that we cannot fully understand what is going on by extracting only the genes and proteins. Spatial orientation, communication between cells, composition of tissues are all critical.

To that end, analyzing tissues with the microscope will remain an extremely cheap and fast way of providing useful information. But I am also convinced that we can benefit from new approaches in this field to extract even more information; for instance, deep-learning approaches – where standard tissue image analysis is supplemented with new information based on automated quantification of structures and protein levels – have great potential.

Of course, sequencing of tumors has given us a lot of valuable information – and will continue to do so – but we must remember that many other factors are equally important. As we all know, we are more than our genes – and a tumor is more than its genetic make-up.

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To Err Is Human

How can we harmonize testing to prevent diagnostic errors?

By W. Greg Miller, Professor of Pathology, Virginia Commonwealth University Medical Center Richmond, Virginia, USA

Harmonization of laboratory test results is one of the most pressing issues in laboratory medicine. The landmark 1999 report from the US Institute of Medicine "To Err Is Human: Building a Safer Health System" emphasized the importance of clinical practice guidelines to standardize decisions and treatments. Using guidelines was not new in 1999 but has assumed increasing importance in the practice of medicine. A 2015 follow up report from the Institute "Improving Diagnosis in Health Care" again emphasized the importance of guidelines and stressed that cooperation among the healthcare team, including laboratory professionals is essential to reduce diagnostic errors.

Neither of these reports recognized that laboratory test results frequently vary depending on the measurement procedure or laboratory performing the test. Consequently, diagnostic errors are possible when non-harmonized laboratory test results are interpreted using fixed decision values in clinical practice guidelines. For example, parathyroid hormone results varied four-fold across different laboratory measurement procedures, yet a guideline recommended the drug Cinacalcet to treat calcium and phosphate imbalance in chronic kidney disease when the parathyroid hormone exceeded a fixed value (1). Urine albumin to creatinine ratios of 30 mg/g (3.4 mg/mmol) and 300 mg/g (34 mg/mmol) are almost universally used in guidelines to identify micro- and macro-albuminuria in diabetes or hypertension, despite a 45 percent difference in median results among different laboratory measurement procedures for urine albumin (2). Steroid hormone measurements such as testosterone and estradiol have 100 percent or more variability among different measurement procedures making clinical guidelines difficult to develop or apply (3).

A substantial infrastructure has been developed to provide tools and procedures for harmonization of laboratory test results (4). The International Standards Organization (ISO), for example, has standards for reference materials, reference measurement procedures, and reference laboratory services. The Joint Committee for Traceability in Laboratory Medicine (JCTLM) reviews specific components of reference systems that conform to one of the ISO standards and lists those that meet the criteria. Measurement procedure producers use these approved reference systems to establish calibration traceability for the measurement procedures used in medical laboratories. At present, the JCTLM lists reference methods for 79 analytes and reference materials for 162 analytes. However, no reference system exists for most of the 1,000-plus medical laboratory tests. Clearly, our profession has a challenge to fill this gap so that more test results can be harmonized.

In principle, calibration traceability to reference systems should produce harmonized results among different measurement procedures. Unfortunately, some analytes with reference system components remain non-harmonized. One of the main reasons for ineffective harmonization is lack of commutability of reference materials with authentic clinical samples (4). Commutable reference materials are those that have the same relationship for results between different measurement

"One of the main reasons for ineffective harmonization is lack of commutability of reference materials with authentic clinical samples."

procedures as do clinical samples. Calibration traceability to commutable reference materials effectively harmonizes results for clinical samples. Unfortunately, a number of older JCTLM listed and other international reference materials are not commutable, so when they are used for calibration traceability the results for clinical samples do not agree among different measurement procedures (4). JCTLM now requires commutability validation for reference materials intended to be used as calibrators for medical laboratory tests. Therefore, all providers of reference materials should ensure commutability for new reference materials.

Another challenge for harmonization is the large number of analytes for which there are no reference system components available. This problem was addressed at a conference in 2010 (5) and mechanisms are now being developed by the International Federation of Clinical Chemistry and Laboratory Medicine, the International Consortium for Harmonization of Clinical Laboratory Results and ISO to use international consensus harmonization protocols to achieve agreement for clinical sample results among different measurement procedures.

An interesting challenge for implementing new calibration schemes to achieve harmonized test results is conformance to regulatory requirements. Many countries have regulations that require measurement procedure manufacturers to resubmit for approval when a test has been recalibrated to conform to international harmonization recommendations. Our profession needs to collaborate with regulatory agencies to streamline and lower the cost for approval of harmonized measurement procedures – such realignment of calibration is clearly in the best interest of good medical care. New measurement procedures should be required to demonstrate calibration traceability to approved reference systems, when they exist, rather than simply demonstrating agreement with another measurement procedure already on the market.

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Driving Down Diagnostic Discrepancies

Establishing a proactive strategy for case reviews could help reduce errors

By Raouf Nakhleh, Professor of Pathology, Mayo Clinic Florida, USA

Making a correct diagnosis in surgical pathology depends on many things, including the pathologist's knowledge and experience, clinical correlation, standardized diagnostic terms, confirmatory ancillary testing, and targeted case review. To help streamline the process, the College of American Pathologists (CAP) and the US Association of Directors of Anatomic and Surgical Pathology (ADASP) have released error-reducing guidelines for selective case reviews (1). The CAP-ADASP recommendation is that pathology departments should formalize a quality assurance-based review process – and for reviews to be completed in a timely manner to avoid any negative impact on patient care. Other recommendations include document case reviews that are relevant to their practice and to monitor and record results continuously. And, finally, if there is poor agreement within a defined case, there should be steps for improving the situation.

Clearly, case reviews can detect diagnostic

discrepancies, some of which are real errors that could affect patient care. There is some evidence that targeting problematic areas in pathology may be more effective in detecting discrepancies than by performing random case reviews. Indeed, many pathology departments already have review policies for selected types of cases, such as esophageal dysplasia and glial neoplasms. The guideline's main recommendation is for departments to evaluate the material they see and establish a policy to review cases as a proactive measure to reduce diagnostic error. This may be based on the specimen type (for example, breast biopsy) or on a disease process (for example, esophageal dysplasia).

Importantly, I'd like to draw attention to the following considerations for determining which – and how – cases should be reviewed:

- Reviewing pathologists should formulate their diagnosis independently and without influence from others.
- Reviewing pathologists should have sufficient expertise in the organ system/diagnosis case that they are reviewing.
- Reviews should include negative cases to detect potential false-negative cases.
- Targeted case reviews of selected organ systems/diagnoses are more efficient at detecting discrepancies than random reviews.
- A review of cases before sign-out could be used to build collaborative teams and improve pathologists' skills. This has also been shown to reduce amended report rates.

The type of review is highly dependent on the practice size and the expertise of the pathologists. A review system is easier to implement in an intermediate-sized group (approximately 10 to 15 pathologists), for example. In such a practice, most pathologists tend to be generalists with specific interest and involvement in a subspecialty area. Often, individuals with subspecialty interests will serve as the point person to their clinical counterpart and they will actively keep up with the literature for that organ/system. These individuals are excellent case reviewers because they are able to convey any new knowledge regarding peculiarities of reporting or new ancillary testing before sign-out. I would, however, recommend that before an "expert" signs-out any material, it is reviewed (hopefully) by another expert pathologist. Larger groups may have more flexibility to review cases depending on the number of specialists available within a particular subspecialty.

In smaller groups, expertise specific to an area (neuropathology, medical renal pathology, etc.) or specimen type (bone or soft tissue tumors, for example) may not be available and so they will send out some specimens to a consultant. However, smaller groups should develop some mechanisms for case reviews that they see and manage. For example, cancer cases will be signed out and referred to a larger institution for definitive therapy and review. I'd like to suggest that evaluating and documenting these external reviews could serve as a minimum together with those cases reviewed during in-house clinical conferences. Of course, in the future, pathologists may use digital pathology to share a case with others in real-time, giving them the opportunity to discuss it with another pathologist who is an expert in that specimen. In the meantime, there is still a lot of work to do in establishing robust case review procedures.

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It's Our Turn to Talk

Pathologists, Patients and Diagnostic Errors – Part II

In the first of this two-part feature (1), we discussed the reasons why disclosure of diagnostic errors can be so problematic. But we also noted that most physicians want transparency. What are the best ways to release their inhibitions and help them kick-start these difficult conversations? In the final installment of this feature, experts in the disclosure and communication of medical errors share their thoughts on how pathologists might explore what will be – for many – uncharted territory.

By Nick Miller

In last month's feature (1), Michael Laposata (Chairman, Pathology Department, University of Texas, Galveston) exhorted his colleagues in the pathology community to take their place as valuable, indispensable members of the diagnostic team – "It's our turn," he asserted. We also drew attention to the factors that may have discouraged physicians from medical error disclosure in the past: injured pride, shame, fear for one's reputation and livelihood, a lack of confidence in one's own ability to communicate technically complex results to patients and physicians, and an absence of any kind of pre-existing relationship with the patient from which to start a conversation. Awareness of these factors – as well as an appreciation of the scale and impact of medical errors in general and diagnostic errors in particular – has led to programs that seek both to encourage open communication and to support physicians who engage in such communication. Indeed, it may be that we are witnessing a cultural shift in healthcare organizations, resulting in greater willingness to explicitly endorse full transparency and to support it with training programs. Here, in the second of a two-part feature, we discuss these developments and how they might affect the error disclosure environment for pathologists and patients alike.

Disclosure protocols: where do we stand?

For many years, one of the most fundamental barriers to medical error disclosure was the lack of a body of clear, broadly accepted protocols and guidelines. This impeded transparency, and therefore also hampered system-wide learning and improvement, not least with regard to diagnostic procedures. As the Institute of Medicine (IoM) report points out (2): "Conducting analyses of diagnostic errors, near misses and adverse events presents the best opportunity to learn from such experiences and implement changes to improve diagnosis." Yael Heher (Anatomic Pathologist and Director of Quality and Safety, Department of Pathology, the Beth Israel Deaconess Medical Center and Harvard Medical School, Boston) is clear on this point: "Systems learning is really important – we should examine the error from a systems perspective, honestly look at system vulnerabilities, and design quality improvements to reduce risk of error recurrence."

Without accepted disclosure systems, it's impossible to generate reliable national metrics and wide-ranging safety improvements. In addition to helping measure the problem, effective disclosure protocols give physicians much-needed guidance on how to go about communicating – when, how and to whom – when they are involved in a medical error.

Recognition of the impact of the guideline deficit is now leading to the development of medical error reporting protocols in different institutions and countries. Laura Zwaan (Assistant Professor, Institute for Medical Education Research, Rotterdam), who helped develop error disclosure guidelines for a Dutch hospital, confirms, "More and more of these protocols are being developed, certainly in the Netherlands but I believe also worldwide." And Thomas Gallagher (Professor and Associate Chair, Department of Medicine, University of Washington, Seattle) points out that well-accepted guidelines, such as the CANDOR toolkit (4) and resources from the Collaborative for Accountability and Improvement (5), have recently become available.

Michael Laposata makes specific recommendations regarding the ideal formal disclosure pathway for diagnostic errors. Having a dedicated error disclosure function in each institution, Laposata suggests, would get pathologists out of an awkward position. He recommends that the internal evaluation should involve a person who has a role dedicated to patient safety and a clear understanding of the varying diagnostic challenges of different clinical situations – and who is supportive of physicians faced with such challenges. This would result in a more nuanced appreciation of diagnostic error – one that recognizes that there are degrees of error as opposed to a simplistically binary "mistake/no mistake" approach.

In this context, Laposata cites the IoM's suggestion of a "standard of avoidability," which would take into account the relative difficulty of diagnosis. With this approach, negligence (where the error is inexcusable) would be at one end of the scale; at the other end would be cases where diagnostic criteria are less clear-cut and circumstances more complex, and where some instances of error are almost unavoidable. The increased granularity provided by this standard of avoidability approach, Laposata asserts, would ameliorate some of the concerns surrounding error disclosure – such as litigation fear (see next section).

> "We had a hard time finding (error disclosure) guidelines, which surprised us. It's a huge problem." Michael Laposata

> "Our specialty organizations have been silent on how to deal with these issues . . . it would be nice if international organizations identified steps that should be followed in error disclosure." Suzy Dintzis

Cultural environment – litigation, reputation, career

Developing efficient and supportive disclosure guidelines, however, will be of little benefit if healthcare professionals are too scared to use them, for example because of concerns over malpractice litigation, reputational damage or loss of livelihood.

In Europe, litigation does not seem to be a major concern – at present. According to Cordula Wagner (Executive Director, Professor of Patient Safety, Netherlands Institute for Health Services Research, Utrecht), "We are aware that litigation could turn into a problem, but are keen to avoid going in a direction which could tempt physicians to engage in defensive medicine or cover things up because of litigation fear." This is why Laura Zwaan is pleased to see that the Netherlands' biggest liability insurer has recently developed and distributed its own guidelines on error disclosure. As she points out,

having an insurer endorse a disclosure route should allay the fear of liability. And Wagner emphasizes the utility of a discreet incident reporting system to which only the institute has access. "People from outside can't see it, so if there is some kind of safety issue, people feel safe in reporting it."

But perhaps more fundamental than litigation fear, in many countries, is the pressure brought by a punitive organizational culture. In many healthcare organizations, the prevailing mentality, says Zwaan, is one of "If you're trying your best, you won't make any errors," But that's not true. "Everybody makes errors," says Zwaan. She continues: "We need to reassure healthcare professionals that errors can happen to anyone."

In the litigation-rich environment of the US, physicians may particularly welcome systems that are perceived to foster transparency without jeopardizing individuals' careers. The AHRQ-administered Patient Safety Organization (PSO) program and the Patient Safety and Quality Improvement Act (PSQIA – passed by Congress in 2005) were intended to confer privilege and confidentiality protections to patient safety information shared with PSOs (2). Through the PSO program, healthcare organizations can voluntarily – and, in theory, safely – disclose safety data to the PSO and receive advice on error reduction strategies. The idea is that the PSQIA confers privilege and confidentiality protections to healthcare organizations that share specific types of patient safety information with PSOs. For example, under the PSQIA, adverse event information reported to a PSO is protected from disclosure in medical malpractice cases (2).

Progress in implementing the PSO program is said to have been slow, however, and the actual impact of the program on patient safety and error disclosure remains unclear (2). Indeed, Gallagher relates that there has been some concern that this system may actually inhibit disclosure of errors to patients, because of the significant legal penalties attached to disclosure of error information that has been provided to a PSO: "The PSQIA has not had a major positive impact on communication with the patient about errors," he says. Thus, fears relating to the consequences of disclosure may still trouble healthcare professionals even under the PSO system (2).

In response to this situation, de facto disclosure systems are being developed in some parts of the US, at least at the local level. These take the form of "safe table" forums, where healthcare professionals can discuss safety experiences in an open but legally-protected environment (2). Outcomes from such meetings, however, are not truly transparent – they are not shared beyond the organization concerned – and hence do not benefit the broader community.

Hence, some believe that additional strategies are required. For example, with regard to diagnostic errors, one of the recommendations of the IoM report is to develop an organizational culture in which all healthcare professionals feel that they can safely identify and learn from such errors: a so-called "just culture, " which accepts that healthcare is complex and that people make mistakes. This type of culture should – without tolerating reckless behavior – console those who make errors, coach those who have at-risk attitudes, and only punish those who are reckless (2).

Somewhat ambitiously, the IoM suggests the need for change in the actual legal system in the US, citing the theoretical advantages of "administrative health courts." These bodies – which permit non-judicial mechanisms of investigating and resolving cases of medical injury – would allow quick and equitable compensation without adversarial litigation. Furthermore, they would be based on the standard of avoidability approach noted above – not fault or negligence. This non-punitive philosophy is anticipated to help disclosure.

> "Part of the aim is to make physicians aware of how you could explain the error, and when you say sorry, what kind of words you could choose."
>
> Cordula Wagner

The administrative courts concept is likely to face resistance, however, from stakeholders that benefit from the current tort-based system (2). Hence, the IoM favors a Communication and Resolution Program approach (CRP), such as that developed by the Massachusetts Alliance for Communication and Resolution following Medical Injury (MACRMI) (See Sidebar "Simply the Right Thing to Do"). The suggestion is that this is a more pragmatic way of giving physicians comfort that error admission would not automatically lead to accusations of incompetence or even negligence, as well as of providing systematic support and guidance in error communication and consequent safety improvements.

Communication and resolution programs (CRPs): a proven success

CRPs are intended to provide a means of not only improving medical error disclosure, but also speeding up and making more equitable the system for compensating the patient for

Key Take-Home Messages

1. Define protocols

Define error disclosure protocols and create a function for disclosure and support for pathologists; effective disclosure protocols protect both patient and physician.

2. Instate a communication and resolution program

Some of the most effective disclosure protocols may be associated with Communication and Resolution Programs (CRPs); these support transparency and safety improvements without victimizing caregivers, and may be transformational in their impact.

3. Communicate directly

Direct communication with patients can be difficult; pathologists should seek support from colleagues and other institutional resources at the start of the process. Formal training programs are likely to be of benefit in the longer term.

4. Decrease frequency of litigation

CRPs emphasize the importance of patient communication; such dialogs, when accompanied by genuine empathy and efforts to address the cause of the error, are said to provide relief for patient and caregiver, and may decrease frequency and scale of litigation.

5. Inspire a change in culture

Pathologists should contribute to the cultural shift towards transparency by accepting that errors often arise from systemic problems and situational complexity rather than carelessness, and by identifying areas where systemic improvements could enhance diagnostic outcomes.

6. Reinforce criticality of pathologist's role

Pathologists should ensure that their critical contribution to the diagnostic team is reinforced by developing and maintaining strong communication channels with other members of the healthcare team, and by providing them with the information they need – in understandable form – so as to optimize patient care.

any harm suffered. Ultimately, CRPs are intended to improve patient safety. The fundamental idea is to create a culture in which early reporting of adverse events is the norm, where discussing the occurrence and effect of such events with patients is fundamental, and where the disclosure process leads to system-wide improvements where necessary. "CRPs emphasize the strong link between transparency and patient safety," says Gallagher. "They posit not only the importance of early event reporting and open communication with the patient, but also a thorough event analysis – using up-to-date approaches – to understand the root causes, followed by development of prevention plans and proactive offers of financial compensation for patients who have been harmed by an error."

> "Data show that transparency actually decreases litigation."
>
> Yael Heher

Laposata adds, "With CRPs, we get early reporting of an adverse event, we work through it internally, and then we openly communicate with the patient." Gallagher, who runs the Collaborative for Accountability and Improvement (5), a collection of stakeholders committed to supporting the development of CRPs, continues: "The essential ingredients of a communication and resolution program include a robust adverse event reporting system, because CRPs depend on having a reporting system that clinicians will use to report events immediately – you can't resolve cases that you don't know about."

This all sounds fine in theory, but what kind of outcomes can we expect from CRPs in real life? Won't increased transparency just lead to more disgruntled patients, and perhaps more lawsuits? In fact, it seems that CRP-associated increased error reporting actually results in fewer malpractice claims, as well as an improved safety culture (2). Gallagher points to encouraging data from programs at the University of Michigan and the Lexington VA Medical Centre in Kentucky; for example, the frequency of lawsuits, the time to resolution of claims that were filed, and the amounts that were paid were significantly reduced in the Michigan model. The suggestion, he adds, is that these programs have succeeded in reducing litigation costs not by improving the way they handle lawsuits, but by fundamentally improving the quality of care. In other words, institutions that participate in these programs may be harming fewer patients. More specifically, in terms of measurable outputs, a survey of plaintiffs' lawyers

dealing with the University of Michigan Health System (6) suggested that 71 percent had settled cases for less than they had litigated, 86 percent said transparency allowed them to make better decisions about which claims to pursue, and 57 percent admitted they turned down cases they otherwise would have pursued (See Infographic "The Proof is in the Program").

Similarly, the experience of MACRMI may be instructive (6). MACRMI developed a CRP termed CARe – Communication, Apology and Resolution – which, in brief, is intended to emphasize the principles of disclosure, apology and fairness (See Sidebar "Simply the Right Thing to Do"):

- disclose information when an unanticipated adverse outcome occurs, such information ultimately to include the results of any investigation of the event, explanations of its occurrence and proposals to avoid recurrence;
- apologize where appropriate;
- proactively offer fair financial compensation where appropriate, without the patient having to file a lawsuit.

MACRMI describes the effect of CARe as "transformational," claiming that it has changed the error resolution system from reactive to proactive, and has replaced adversarial attitudes with advocacy, secrecy with transparency, and denial with apology and healing. Furthermore, a culture of individual blame has been replaced by a focus on system improvement, they say, and isolation of affected parties (including the physicians) replaced by supportive assistance (6). The effects of CARe introduction therefore seem to be highly encouraging, and unsurprisingly MACRMI is now promoting the dissemination of its CRP model throughout Massachusetts (2) (See Sidebar "Simply the Right Thing to Do" and Infographic "The Proof is in the Program").

The patient communication predicament

Notably, CRPs emphasize communication with those who have suffered as a result of a medical error. This is in line with the IoM's view on the importance of resolving diagnostic errors through dialog with patients; indeed, patient communication is intrinsic to the IoM definition of diagnostic error: "A diagnostic error is the failure to (a) establish an accurate and timely explanation of the patient's health problem(s) and the failure to (b) communicate that explanation to the patient." In fact, the inclusion of communication failure as a key component of diagnostic error distinguishes the IoM definition from other definitions. Thus, the IoM report asserts that patients are central to reducing the incidence of diagnostic error; improved diagnosis, the IoM suggests,

requires the establishment of partnerships between healthcare professionals, patients and their families (2).

And there are reasons to welcome these kinds of partnerships – open communication with patients is said to benefit doctors, patients and healthcare providers alike. Suzy Dintzis (Associate Professor, Anatomic Pathology, University of Washington, Seattle) reports that pathologists who have disclosed a medical error tend to feel positive about the experience and to experience some personal relief at having taken this step. For the patients, having open, personal communication channels – and, critically, an appropriate apology – seems to defuse the situation, making them less likely to feel victimized or ignored, and therefore less likely to pursue litigation. Indeed, institutions with an open disclosure policy may have lower numbers of litigation cases brought against them (See Infographic "The Proof is in the Program"). "Data show that transparency actually decreases litigation," Heher points out.

Zwaan agrees: " For patients, disclosure is incredibly important. The family always wants to know what happened, why it happened and what's going to be done to prevent it happening again." If patients get this information, Zwaan says, they often don't see any need to file a complaint; thus, open and honest communication can prevent pain for everybody. Dintzis adds, "Disclosure to patients engenders trust in the system; if they feel something is being hidden from them, it's very damaging to the relationship between patient and medical system." And Wagner reiterates that patients aren't always motivated by financial compensation so much as by the need to understand; to get an apology; to see that the mistake has

Simply the Right Thing to Do

The Massachusetts Alliance for Communication and Resolution following Medical Injury (MACRMI) (7)

What?

MACRMI is an alliance of patient advocacy groups, teaching hospitals, insurers, and state-wide provider organizations committed to the implementation of Communication, Apology and Resolution (CARe) programs following medical injury.

Why?

CARe is intended to foster transparent communication, sincere apologies and fair compensation in cases of avoidable medical harm, and emphasizes data capture and communication. It explicitly acknowledges that communications around adverse events are often serial – a process, not a one-off.

How?

Communicate what you know when you know it; don't speculate, but do contract to disclose more information as it becomes available; remember that sharing empathy is always appropriate. Form a small group of professionals at the institution who are dedicated to managing communication around adverse events and call on them if you find that you need to engage in that kind of communication.

Ken Sands, one of the founders of MACRMI, tells us more…

What inspired the creation of MACRMI?

We were aware of pioneering US institutions which had initiated aggressive communication around adverse events, i.e., which supported open communication with the patient regarding both the event and the actions necessary to resolve the matter. We wanted to explore the possibility of a similar initiative in the Massachusetts community. But it's difficult to make changes of this type and scale; we decided we'd have a greater chance of success if we brought together all the stakeholder groups – hospital administration, physicians, the legal community, the local medical society – and acted as a community.

How did you get started?

One problem we encountered at the outset was that every hospital in the US has a slightly different system – for example, academic or not, nature of university relationship, malpractice insurance coverage model. In this situation, we had to prepare the ground a little. In fact, we spent a year doing a readiness assessment for the state of Massachusetts, beginning with some US government-funded surveys to establish whether stakeholders would be interested in pursuing this kind of transparency program. That evolved into a series of conversations with the different stakeholders. And in the end, we demonstrated that there was a critical mass of support, which allowed us to move forward with MACRMI.

Fundamentally, MACRMI has created a setting where many different stakeholders have agreed on transparency goals, and have committed themselves to address the challenges that different institutions may face in implementing transparency. Our key aim is open communication around medical errors.

resulted in changes that will prevent recurrence; and generally to rebuild their trust in the medical profession.

Indeed, patients who have sued often have been motivated by the perception that the truth was hidden from them (6). Conversely, evidence suggests that disclosure generally reduces the intent to sue, promotes more favorable settlements, and reduces the size of the award (6).

Heher suggests that physicians sometimes may be afraid to have the opening conversation with the patient, perhaps because they may feel that they should have an explanation at the start of the disclosure process. "But we've found that patients prefer you to be honest and say that you're not yet sure what happened, but that you're looking into it," she says. Gallagher agrees, "The more time that passes without the patient receiving a satisfactory explanation is adding insult to injury."

An effective transparency culture will permit the establishment of processes that improve patient safety. Although there are some differences of detail between disclosure processes in different institutions, it seems that the majority of them adhere to a number of key steps. Gallagher is clear on the three main components of the disclosure process: information sharing, emotion handling and follow-up.

The first of these involves giving the patient the information they need in order to understand what happened to them. This may not happen immediately, of course; as discussed above, error disclosure is a process. Cordula Wagner is clear: "You must inform the patient within 24 hours. You may not know exactly what has happened, but you can let them know that an investigation is underway and when to expect further information." Ken Sands (Associate Professor of

We prefer the term communication as opposed to disclosure, because communication implies more of a two-way process of understanding. So at MACRMI we've created standard ways of disseminating information, standard protocols for people to follow, and a forum to discuss challenging situations or cases. The MACRMI system is exemplified by our Communication, Apology and Resolution (CARe) program.

Can you explain the CARe approach?

It emphasizes standardization of data capture. We apply standard algorithms to examine adverse events; the object is to establish if there was significant harm, and if so, to what extent it was preventable, and therefore what should we include in our communication with the patient. One of the ways our program may differ from others is the emphasis on "communication always." In our experience, much patient dissatisfaction – and malpractice risk – arises from patients not receiving a timely communication about an unexpected event. That's the case even if the event turns out to have been unavoidable – and in fact most of the events we deal with are non-preventable. Appropriate communication with patients when something unexpected happens, however, reduces the risk of escalation.

Our main message to the broader audience of clinicians is this: if you find yourself in this situation, call for help, because it can be tough to do without support. Our key principles include to communicate what you know when you know it, but not to speculate; and do contract to disclose more information as it becomes available. And it's always appropriate to share empathy. That's different from apology, which is acknowledging ownership of that adverse event. Finally, remember that transparency is a process; communications around adverse events are often serial.

After three years of MACRMI, how have things changed?

It's been a great success. Our surveys show that over 90 percent of clinicians who have participated in the MACRMI program are supportive of our model and prefer it to any other way of trying to address an adverse event. We're still analyzing the patient data and pay-out data, but at present it seems that we are bringing difficult adverse event cases through to resolution in a timeline of say 3–6 months – as compared with 3–6 years if we went through the usual legal system. We expect to see that our financial performance has also improved.

And the next steps?

We want to see the MACRMI program continue to expand. We started out with six participating hospitals; about a year ago we had eight; and as of about a month ago we had 12 hospitals in the MACRMI program. We're also seeing increasing support in the legal community, and have begun identifying lawyers who support the MACRMI model in adverse event claims. When a hospital or a patient shows interest, we can refer them to lawyers who can understand how MACRMI works; that's another service we can add that will help increase the acceptance of this model.

Medicine, Harvard Medical School, Boston) asserts that an effective disclosure protocol should comprise a series of communications, starting with telling the patient that something went wrong and contracting to update them when more information is available. The next communication might be about what exactly went wrong, and the subsequent meeting might provide more information on how and why the event happened. Finally, says Heher, the patient should be provided with the root cause analysis, i.e., the institution's analysis of the event – how it happened, and why.

And the third component, says Gallagher, is follow-up, which ultimately may include offers of compensation. Towards the end of the process, Sands says, the communications are about establishing if the patient suffered any loss. This may involve working with the malpractice insurer over a period of months before meeting again with the patient to address financial compensation, if any. "That again is a negotiation that occurs over a period of months," he says.

The generally inclusive approach of CRPs is notable (6). Thus, among the lessons learnt during three years of CARe program implementation by MACRMI is that institutional risk management officers, patients (and/or their relatives) and the insurer should all work together to resolve the issue (6). In addition, MACRMI advises that patients should have attorneys during resolution conversations, and to this end the CARe program provides patients with a suggested attorney list (6). The trend is clear: disclosure is a process in which all parties collaborate and communicate, and in which the vulnerable parties are supported.

Training towards transparency

It seems, then, that there is a growing momentum behind the shift to transparency. But, given that pathologists are generally unprepared or reluctant to communicate directly with patients (1), how can they be supported in this movement? As Zwaan notes, "Healthcare professionals can definitely use help to communicate appropriately, and support regarding what to do and how to do it." And Heher emphasizes the importance of bringing resources to people at the front line; in particular, she recommends bringing experts to advise healthcare professionals on how to have conversations with patients, and on who should be involved. "People who attempt it without support might find it difficult," she says. "It's not just junior doctors, it's also established pathologists that need tools." Heher suggests, at a minimum, providing healthcare professionals with an understanding of the key pieces of information that need to be exchanged during medical error disclosure. "Give them some tools and some language to help them formulate that information," she advises. Wagner advocates making it easy for healthcare professionals by providing them with a pocket-sized card with reminders of what to say, what not to say, and a timeframe for actions. "That's the way we've started doing it, and it works fine," she asserts.

> "Disclosure protocols should support not just the patient, but also the "second victims" - the healthcare professionals themselves." Laura Zwaan

> "Just as you can't learn how to play golf by watching the golf channel on TV, you can't learn how to have these conversations effectively without the opportunity to practice them." Thomas Gallagher

> "I felt like I had finally been heard . . . and if that had been the end of the legal pursuit, that would have been fine with me."
> Patient Jennifer, after CRP-style communication (6)

One key tool in the support system is specialized training. Zwaan reports that the same Dutch liability insurer that developed error disclosure guidelines has also developed a training program, and she herself has contributed to the development of similar programs. "Communication of errors is very hard," she says, "so training is definitely helpful." Role play may turn out to be an essential part of the training process. Wagner and Zwaan advocate training with a "fake patient," an actor, to prepare for error disclosure. "Part of the aim," says Wagner, "is to make physicians aware of how you could explain the error, and when you say sorry, what kind of words you could choose."

The Proof Is In the Program

Communication and Resolution Programs

University of Michigan Healthcare System (inception 2001)

- **81%** of plaintiffs' attorneys changed their approach to meet Michigan approach
- **90%** of plaintiffs' attorneys recognized change since inception
- **81%** of plaintiffs' attorneys said their costs had reduced
- **71%** of plaintiffs' attorneys settled cases for less than they had litigated
- **57%** of plaintiffs' attorneys turned down cases they otherwise would have pursued
- **86%** of plaintiffs' attorneys said transparency allowed better decisions regarding which claims to pursue

Based on 2006 survey data of 51 plaintiff's attorneys; data quoted by Richard Boothman (6)

MACRMI (inception 2012)

Participating hospitals

6 (2010)

8 (2015)

12 (2016)

90%
participating clinicians supportive of MACRMI

Timeline to resolution of litigation cases

pre-CRP
3-6 years

post-CRP
3-6 months

Based on MACRMI survey data (analysis ongoing) (6)

Similarly, the University of Washington runs a course in communication skills each year, part of which is focused on error communication training through role play. Dintzis explains, "We break the residents and fellows into groups of three: one plays the patient who has been seriously harmed, another plays the pathologist disclosing the error to the patient, and the third is an observer." The value of this simulation is evident both in objectively measurable improvements and in the subjective improved confidence among participants. "When people take our course, the thing that they remember is that role play," says Dintzis.

Gallagher also has experience in the training process. Removing the reflex to keep quiet after an error, he says, is one of the key aims of the training that he and his colleagues provide. Their object is to foster a mindset such that when physicians are involved in a significant medical error, their instinct will not be to keep the event to themselves, but to find someone at the hospital who can help establish what happened and support communication with the patient. "We also offer additional training, for example, regarding the financial resolution of these cases," says Gallagher, emphasizing the holistic approach taken by his institution.

And Gallagher has a final point to make, one that should offer comfort to physicians who find themselves in a disclosure situation inasmuch as it recognizes the enormous emotional distress that accompanies these events – first and foremost for the patient, of course, but also for the clinician. Gallagher

Now It's Your Turn . . .

How can pathologists contribute to the various components of the disclosure process? Should they play an active role? Gallagher is clear: "We operate as diagnostic teams; just as pathologists are critical to the diagnostic team, so they should also be critical to communicating with patients when there's been a diagnostic error." He asserts that the most important first step for pathologists involved in a diagnostic error is to contact the treating clinician. "Make sure the clinician has accurate information that they can convey to the patient, but also offer to come with the clinician when communicating with the patient." Dintzis concurs: "It's really important to improve communication channels between pathologists and clinicians, and to cultivate understanding among the care team." Ensuring that the pathology report contains exactly what the clinician needs to provide optimal care for his or her patient would, Dintzis says, have the added benefit of preventing the kind of errors that can arise through miscommunication. And Heher emphasizes proactivity: "Ideally, in a culture of patient safety you want pathologists to be able to proactively flag up errors, as opposed to reacting to cases identified by patients or clinicians."

It may feel uncomfortable, says Gallagher, but pathologist involvement in error disclosure brings many benefits. "They can probably explain what went wrong more effectively than the treating clinician, and it gives the pathologist the opportunity to apologize to the patient directly, which we know is something patients really care about." Heher expands on these points. "Delegating a technical explanation to someone with little subject expertise results in the loss of two things: firstly, a correct and coherent explanation of what happened, and secondly, empathy from someone closely involved in the error – and that kind of empathy transfer can be healing for the patient."

But pathologist participation may require an act of will; as Heher notes, it is too easy for pathologists to sit back and let disclosure communications pass them by. It's especially easy to delegate communications to the clinician, who already has a relationship with the patient. "We have the option of one-way communication – we issue a report, somebody reads it – but the world is changing and we need to catch up and start participating in disclosure, not only around adverse events, but in response to the molecular era of medicine."

Gallagher urges pathologists, if they are to take away just one point, take this: "If you find yourself in an error disclosure situation, you should reach out to your organization in advance of that discussion and get help." By far the most common reason for these conversations to go poorly, he says, is a lack of planning and preparation.

Ken Sands has similar views. "The right way to approach error disclosure is with significant institutional support and collaboration, especially for pathology, which is not patient-facing – few pathologists will know how to approach patients during error communication." As Sands says, a well-constructed CRP will support clinicians. "Either it makes physicians comfortable with the communication process or it designs alternative pathways for that communication."

Zwaan concurs and sees a role for the hospital complaints officer, who could mediate the session, to lead it, or just to give some advice on how to go about disclosure. Dintzis agrees. "We need to educate pathologists on how to exploit the resources available in their own institutions – risk managers, patient advocates, and so on – rather than trying to do it on their own."

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admits, "Healthcare organizations don't always do a good job of supporting clinicians after errors – that's not only bad for the clinician, it also affects the quality of care they deliver to subsequent patients." Indeed, the idea that an effective disclosure protocol should protect the physician as well as the patient is increasingly accepted. As Gallagher says, "Programs should also incorporate care for the caregiver." Zwaan concurs, stating that disclosure protocols should support not just the patient, but also the "second victims" – the healthcare professionals themselves.

And that is why the efforts of the individuals and organizations mentioned in this feature surely can only be good, not only for patients, but also for physicians of every stamp – including pathologists.

The last word . . .

So, as the transparency movement gathers momentum, what are the key features of medical error disclosure and patient communication that physicians should remember? And what are the key take-home messages for pathologists who may need to deal with a diagnostic error?

One point is that consistently transparent error communication implies an organizational culture that supports this philosophy. The extent to which error communications give physicians cause for concern, suggests Wagner, "depends on the culture of the whole institution, and the culture within one's group of direct colleagues." Organization-wide cultural shift may require systemic actions that are beyond the gift of any one person; equally, however, each member of the institution can contribute to such change. As Heher says, "We need everybody to be on the same cultural page and to accept that the idea is not to judge others, but to enable transparent communication and hence to define clear goals for improving patient safety."

To that end, the IoM provides some specific suggestions for helping this cultural shift to take root in pathology departments (2):

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- identify high-priority areas where improvements would significantly improve diagnosis; for example, focus on the most common diagnostic errors, on "don't miss" conditions that could lead to critical harm if overlooked, and on diagnostic errors that are easy to address;
- accreditation organizations and Medicare should require that healthcare organizations monitor the diagnostic process to identify, learn from and reduce diagnostic errors and near misses;
- provide systematic feedback on diagnostic performance to healthcare professionals;
- routinely undertake post-mortems on a subset of patient deaths to check for diagnostic errors.

Key to establishing this type of culture is to introduce guidelines and systems that provide safe environments such that errors can be voluntarily reported without the threat of legal discovery or disciplinary action. This in turn will provide invaluable support to disclosing physicians and enable healthcare organizations to learn from diagnostic errors – and to introduce measures to address and prevent them (2). The examples provided within this article are evidence that establishment of very focused and supportive guidelines and programs can have a very positive impact for all and even reduce litigation – in a litigious society! But more importantly, the overall result is one of a reduced incidence of diagnostic error leading to patient harm, and a better quality of working life for healthcare professionals and, in particular, for pathologists.

Nick Miller is Associate Editor of The Pathologist.

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All in the Mind

What is actually going on when the decision-making process goes awry?

By Olga Kostopoulou, Reader in Medical Decision Making, Imperial College, London

I fell into the field of medical error research after a cognitive psychology PhD. For my thesis, I investigated how operators identify, or fail to identify, faults in industrial process control systems – for example, as in the contribution of human error to the Three Mile Island accident. Towards the end of my PhD, the medical error field became very prominent, and I ended up working on a project exploring the decision making of oral surgeons regarding the removal of asymptomatic third molars. That was at the School of Dentistry at Cardiff University.

Today, my specific interest and area of expertise is in the field of diagnostic error. Accurate diagnosis is the heart of medicine – it's what makes a doctor an expert. I've done most of my research with UK family doctors, so it's possible that my findings apply mainly to them; I suspect, however, that much will also be applicable to hospital doctors and other healthcare professionals. After all, our minds all work in the same way.

One characteristic of human decision-making common to most is that once we think we've identified the right cause, our minds may not remain open to other possibilities. We elicit hypotheses by reference to cases we know of, by considering the selection of patients that we've seen or that our colleagues have told us about. And once we have mentally structured the problem in a specific way, it can become very difficult to restructure it, to think of other solutions. I and others have found that the starting hypothesis is very important to the ultimate outcome of the diagnostic process – that is, for the actual diagnosis and subsequent treatment decisions. For example, one of our recent studies showed that, if doctors had not explicitly considered the possibility of cancer at the start of the diagnostic exercise, they were much less likely to diagnose it at the end of the consultation and refer the patient to a specialist.

So there's good evidence to suggest that this initial hypothesis-generation stage, right at the start, is very important for the final outcome of the diagnostic process. If we have the wrong hypothesis in mind to begin with, we may subsequently elicit the wrong information, and in addition we may not appropriately account for all

observed information. The net effect may be that we only confirm what we are already thinking. Therefore, if we want to improve diagnostic decision-making, we should focus on supporting this initial stage – subsequent interventions may be too late.

One mechanism by which an initial, incorrect hypothesis persists throughout the diagnostic investigation is pre-decisional information distortion. This may result in a bias towards collecting the wrong information, but mainly it leads people to change the value of new information in an attempt to support their existing leading hypothesis. It occurs because the human mind seeks consistency; we like to have coherence between our hypothesis and the data we observe, and one way we do this is by altering the meaning of these data to fit our hypothesis.

So, to summarize, there are some generic mental processes at play. First of all, from the start, we are continuously trying to elicit causes behind what we observe – usually on the basis of whatever little information is available. If we see someone in the street behaving strangely, we immediately generate hypotheses about why this might be – and it's exactly the same in a diagnostic situation. Secondly, pre- or post-decisional information distortion is a widespread characteristic of human judgement. And the difficulty in restructuring a mental representation – in setting aside the first hypothesis to think of other causes – is another generic characteristic of decision-making. That's why I believe we should make diagnostic decision support systems available very early in the process, before healthcare professionals formulate and start testing their own hypotheses. Having an external system that interrupts you early on, before you go down the wrong path, might be a fruitful approach.

In fact, this is something that we're working on at the moment – a decision support system that slots in at the start of the diagnostic process. There are many commercial diagnostic support systems, and they are all based on the healthcare professional inputting as much data as possible, from which the system generates a list of possible diagnoses. So these systems only come into play after the doctor has collected a lot of information, by which time a favored hypothesis has already been generated. By that time, we may be missing the boat; the user will already have a bias as to what the diagnosis is, and so may not have asked all the right questions, or may not have correctly interpreted the answers, and therefore the information provided to the diagnostic support system may be incorrect – because of a bias towards a given hypothesis. As I said, it's hard for people to change their minds late in the process. For all of the above reasons, we believe that existing decision support systems may come too late in the process, and therefore we have developed a prototype diagnostic support system that intervenes at an early stage. At present it's aimed at improving diagnostic accuracy in family clinics, but we can see it having applicability in other clinical fields too, such as emergency medicine. Hopefully we'll get funding to continue developing this system.

The idea of it is to get healthcare professionals to be more open-minded, to reverse the intuitive way of going about diagnosing and get physicians to be more analytical right from the start. But really we need to be thinking about how we can facilitate this kind of thinking at medical school, rather than trying to persuade experienced doctors to change the way they think late in their career!

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Small, But Mighty

Does microscope portability always mean a compromise in image quality? Possibly not…

By Andrew Monk

Picture a laboratory and many of us get the same image: a set of benchtops crowded with equipment from thermocyclers to hot plates. Dominating the scene is the king of the lab, a large microscope with a bulky stage, illuminator, and perhaps even a computer or digital camera attachment. We've all seen – probably even worked in – laboratories just like this. But this kind of setup doesn't work for everyone, especially pathologists who are "on the road" teaching, training, or working in remote field environments. Those pathologists need an entirely different kind of microscope – but unfortunately, their options to date have not been great. Portable microscopes usually mean a compromise on image quality, whereas the instruments that could provide the detail and resolution needed for definitive diagnosis are too large, sensitive, and resource-intensive for field use. It's clear that we need a better solution – and that's where I hope our new take on field microscopy comes in.

We have developed the ioLight microscope (iolight.co.uk), which is small enough to fit in a jacket pocket, yet produces images that we believe are comparable with the ones from a full-size laboratory microscope. The microscope unfolds for use, so when it's in its working position, the optical head that houses the lens and camera is rigidly supported over the stage and the bottom illuminator. The optical system uses mobile phone components to keep the cost down – and thanks to the quality of modern mobile phone parts and the microscope's careful design, ioLight can achieve 1 µm resolution.

At a Glance

- *Current microscopes, both optical and digital, tend to offer either high-resolution images (<1 µm) or easy portability – but rarely both*
- *Devices that can be taken into remote field situations or used for teaching often lack stages, stands and illuminators – features necessary for capturing high-quality images*
- *We have developed a new model of digital microscope that uses a foldable design to combine sample support and illumination with portability*
- *Devices like these pave the way to not only better patient care – especially under difficult conditions – but also teaching, training and public engagement*

It started with a casual conversation…

My co-founder Richard Williams and I are experienced entrepreneurs and have been involved in a number of startup ventures together. At the beginning of 2013, we sat in a pub together, wondering what to do next. All the best startups are based on a change in the market, and we were excited by the fabulous quality of the latest tablet and mobile phone displays. How could we best take advantage of that to create new and useful technologies? We considered cameras and endoscopes, but ultimately, we decided that there were already enough good – and widely available – examples of those tools. That's when we noticed that the only microscopes available were low resolution, poor quality, or needed a separate stand and illuminator to produce great images, which meant that they weren't really portable.

From our optics experience, we knew we needed a microscope with a proper stage to hold the sample still; otherwise, there was no way to get a resolution better than 1µm. The stage needed two illuminators: one to light biological samples from below, and a top illuminator for opaque samples. It also needed an optical system that was easy to set up well. Laboratory microscopes are quite complicated to set up properly, but we wanted ours to be a device that anyone could use in the field, even if they had no special training.

Conventional optical microscopes are rigid and robust. They produce great images, but they're heavy and tall, so they're very difficult to move around. You also need to add an expensive camera to record images onto a computer, which makes the system even less portable. Digital microscopes are a little different; inexpensive ones are easy to obtain – you can even find them on Amazon – and are great for looking at big subjects like bugs and skin lesions, but not well suited to smaller things. Why? Conventional digital microscopes are handheld, and you can't hold your hand still enough for 1 µm resolution. Adding a stand makes the microscope just as bulky and inconvenient as an optical microscope, and if you then tack on a stage to hold the sample still and an illuminator to light it correctly, you've got a device that's anything but portable. Our aim was to fill the gap by developing something that was small enough to be handheld, but could image subjects right down to the size of a single cell – and we managed to achieve it (see Figure 1).

Challenging conventions

While we were working to develop the prototype, the biggest problem we encountered was how to design a flat, pocket-sized microscope with its optical head suspended rigidly above a stage. Several designs and experiments showed that the microscope had to fold, which clearly goes against years of experience indicating that microscopes have to be very rigid to deliver high-resolution images. Previous successful optical field microscopes like the McArthur and

the Lensman are rugged, monolithic devices that produce good images in all climates – but we were aiming for something different. We wanted a device that didn't have to be held up to the eye for viewing (making it difficult to manipulate the slide), didn't require a tripod, and incorporated image and video capture directly into the device instead of requiring a separate camera. This research led to ioLight's patent application for a high-resolution, portable digital microscope.

We particularly wanted our microscope to be wireless. Nobody wants to carry wires in the field – and nowadays, everything is wireless! The problem with that, though, was that we also wanted high-definition video – and to make it harder still, we wanted zero delay in the wireless video, because focusing a microscope with a two-second delay (standard on most wireless video systems) would be very frustrating! It turns out that this is quite a difficult combination to achieve. We had to engage an expert software team to help, but in the end, we managed to create exactly what we wanted: a microscope with no wires, no delays, and no penalties paid in the form of video quality.

How does it work? Once the microscope is turned on and its mast unfolded, it creates its own Wi-Fi network to connect to the user's iPad, where the ioLight app is installed. The user can then place a slide or sample on the stage over the bottom illuminator. Coarse focus is achieved by manually adjusting the microscope's camera head; fine focus adjustments use a digital slider in the iPad app. The app also controls illumination, letting the user adjust both top and bottom illuminators on a brightness scale from 0 to 4. Once the image looks right, simply capture a still photograph or video using the app – it's stored directly in the iPad's gallery for record-keeping or sharing for long-distance consultation.

The world in your pocket

We expect the new microscope to change the day-to-day work of any professional involved in education or outreach. It's easy to use and travel with, and it can send images to mobile devices in real-time, so that a group of people can review and discuss an image at the same time. The utility of a function like that as a teaching tool is clear – and not just for training early-career pathologists, but even for non-scientists. Young people, for instance, associate more closely with phones and tablets than they do with traditional microscopes, and we've had great success with children as young as eight. It might not seem relevant to pathology at first glance – but this kind of engagement is vital in getting young people interested in pathology without letting the specter of the old, clunky microscope get in the way.

In the clinical setting, the microscope is great for explaining diagnoses to patients. Biopsies can be checked quickly while the patient is present, allowing them to be reassured on the spot, or letting doctors decide when to prioritize further analysis of a sample. In remote clinics, a portable device like this is useful, not just because you can take it anywhere, but because once you've captured an image, you can share it immediately with colleagues anywhere in the world for an expert opinion that might not be available on the ground. I believe that this will be a particularly important application in developing countries where resources are limited. Where power can be intermittent, the ioLight has another advantage: it can run for four hours or more on its internal battery and additional battery power can be provided by a standard external USB power pack. One day, perhaps, pathologists will carry such microscopes all over the world to provide quick, expert diagnoses in the unlikeliest of places.

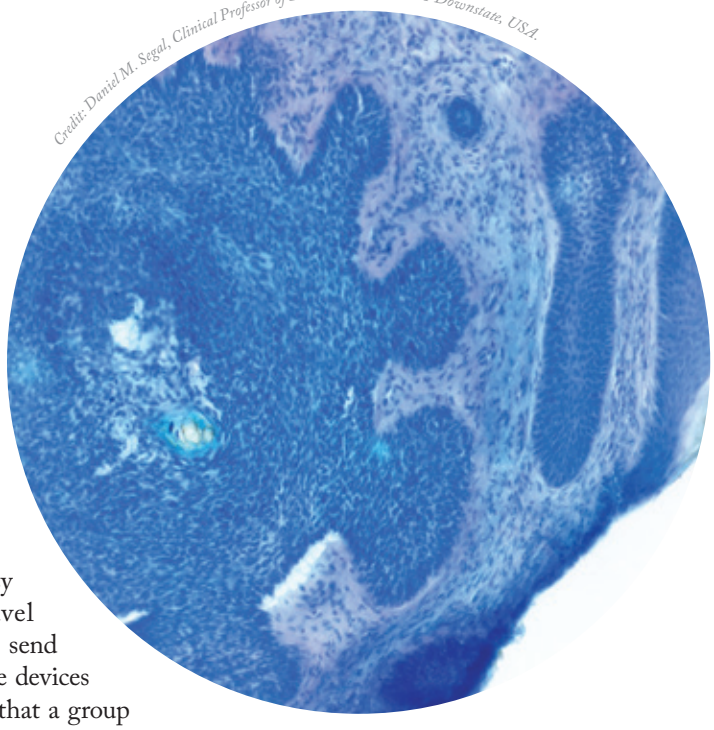


Figure 1. Basal cell carcinoma captured using the ioLight microscope.

Of course, that won't happen immediately. We've just this month started manufacture of the microscope, but we're looking forward to evaluating it for clinical use soon. It has already been evaluated for white blood cell counting using a Neubauer chamber. At the moment, we're also working with a pathologist who is using our prototype in outreach applications like a "Colorful Pathology" display in local public science shows.

Although the real test of the new device's utility will come with a move to full-time clinic use, so far, reactions to it indicate that a high-resolution, portable digital pocket microscope is exactly the tool many pathologists and laboratory scientists have been waiting for!

Andrew Monk is a co-founder of ioLight Limited.

Connecting the Dots to Developmental Disorders

Growth charts that track the formation of neural connections may be able to identify patients at risk of ADHD and other neurodevelopmental disorders

By Daniel Kessler

Growth charts are a time-honored tool among pediatricians and other professionals who work with young patients. But some types of development are harder to track than others – and variables like capacity for sustained attention, which can be confounded by any number of outside factors, are among the most complex. So how can we improve our ability to detect potential deficits? A new kind of growth chart – one that uses brain imaging to map children's neural network development against their age – may offer a solution (1).

At a Glance

- *Untangling developmental data poses challenges for researchers and diagnosticians, because children change in so many different ways at the same time*
- *Mapping brain connectivity againstage reveals a standard developmental curve – and can identify patients who deviate from those norms*
- *Measuring neural connections isn't easy, but using resting-state fMRI and breaking the possible pairs into meaningful components simplifies the task*
- *Upcoming challenges include validating the method in larger datasets and applying it to neurodevelopmental disorders*

Growing inspiration

Working with developmental data can be really challenging; children are constantly growing and changing in so many ways that it's difficult to tease apart which changes are meaningfully related. For example, we get taller at the same time as our vocabularies grow – but it's unlikely that they have a meaningful connection, except that they both change as we age. We had a similar challenge with changes to the brain and children's increasing capacity for sustained attention; we knew both were developing, but were the two meaningfully related?

After some thinking, my colleagues Mike Angstadt, Chandra Sripada and I realized that if we thought about the problem from the perspective of growth charting, what seemed like a challenge was actually a strength! When we see that children who are underdeveloped in one way (like sustained attention functioning) are also underdeveloped on another measure (like brain network development), we have reason to believe there's a meaningful link. Sometimes, age and maturation are treated as "nuisance" variables in science – meaning that they're perceived to obscure, rather than illuminate, information – but in this case, we wanted to embrace maturation. We wanted to use a developmental perspective to obtain a more complete picture.

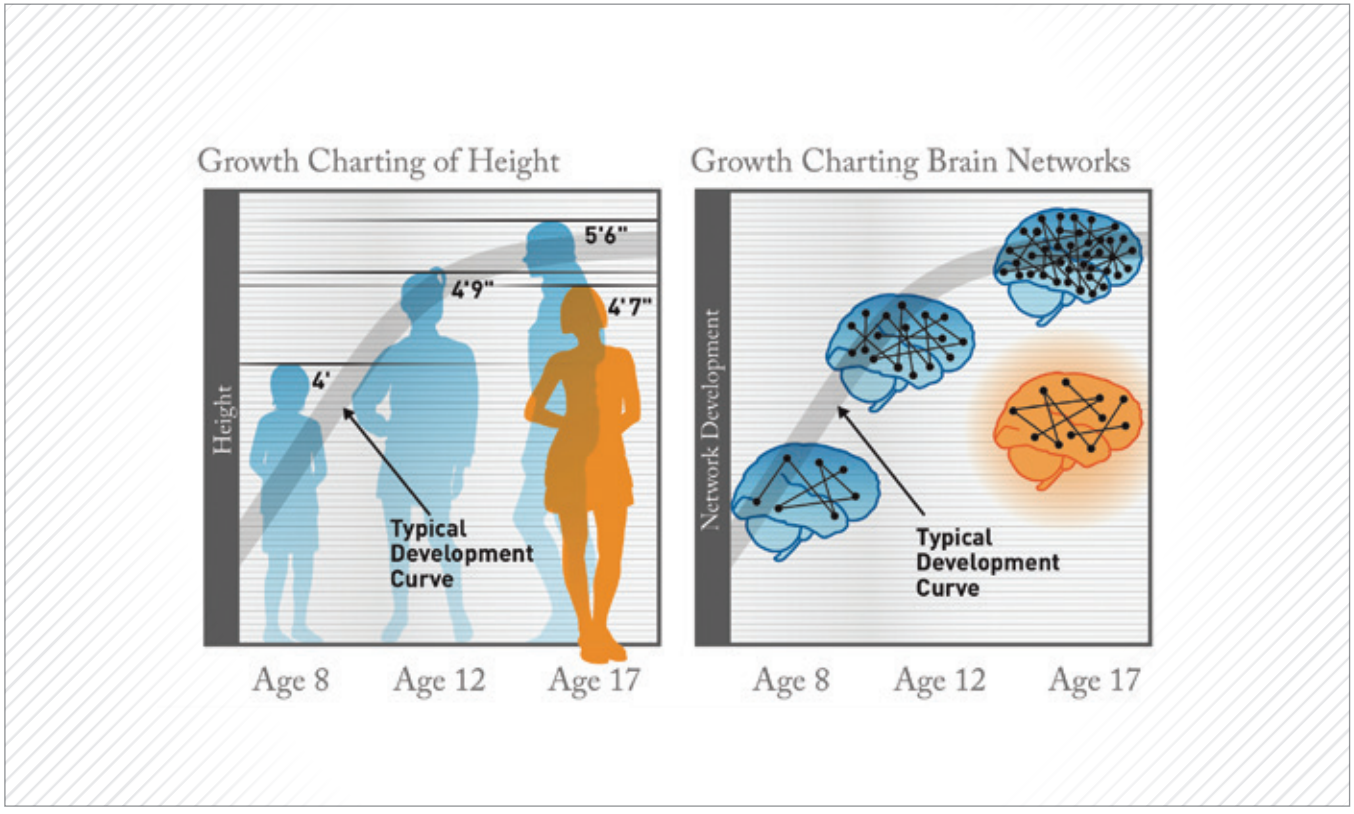
MRI: made to measure

We needed a way to measure brain connectivity before we could track it and relate it to attention. Fortunately, in the recent past, neuroscientists have become very interested in understanding brain connectivity. The approach that we used involved so-called "resting state fMRI." Resting state functional magnetic resonance imaging (fMRI) is a technique in which, rather than taking a picture of a patient's brain using an MRI scanner, we take a movie – filmed while the patient is at rest and free to think about anything they like. Next, we assess connectivity by looking at the patterns of co-activation; that is, what regions of the brain seem to turn on and off at the same time? In contrast, what regions have a more antagonistic relationship where when one turns on, the other turns off? Using correlations, we get a "connection score" for each possible pair of brain regions that tells us how functionally connected they are.

The next challenge we encounter is that, because we track about 1,000 brain regions, there are a staggering number of connections – over half a million! We can't possibly growth-chart every single connection, and even if we could, how would a pediatrician begin to make sense of it? Instead, we use a statistical method that takes these hundreds of thousands of connections and, by finding consistent patterns, breaks them into a small number of meaningful chunks (which we call "components"). We make growth charts of these components. So far, we've found that they can reliably predict attention performance.

Brain in balance

An intrinsic connectivity network, or "ICN" for short, is functionally defined as a collection of brain regions that all seem to turn on and turn off together at the same time. ICNs were discovered through the use of resting state fMRI, and since that time, a lot of fantastic work has characterized where these networks are and what they do. This prior work helps us to understand the patterns of brain changes we see. If you think of each brain region as a person, then ICNs would be circles of friends.



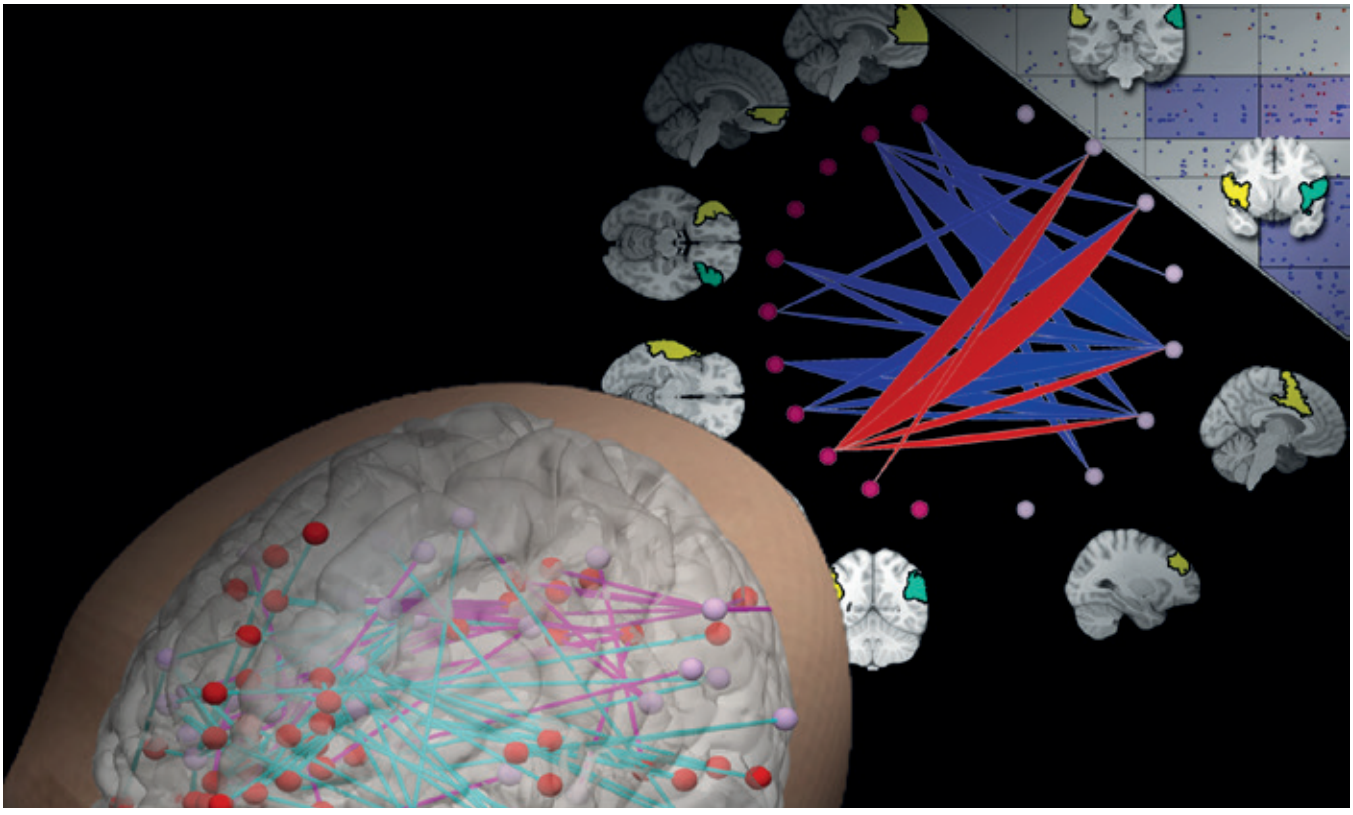
Pediatricians use growth charts (left) to chart patients' progress along a typical development curve. A similar growth chart can be applied to neural networks (right) to compare an individual patient's brain development with that of the population. Blue: typical development; orange: impaired development.

"After some thinking… what seemed like a challenge was actually a strength!"

Many of the regions in the ICN are often close together, but just like friends, some brain regions can keep in touch over great distances.

We were interested in understanding how relationships both within and between ICNs related to maturation and attention performance. In our particular case, there were a few networks that we expected to see based on prior work in adults. One network, the "default mode network," seems to be involved in inwardly-oriented states like daydreaming. On the other hand, there are a few key attention networks that activate during externally-oriented tasks like doing homework. These two sets of ICNs can interfere with one another, and in healthy adults, we believe that an important aspect of attention functioning is having the default mode network "get out of the way" of the attention networks. In fact, previous research has shown that if we look at instances of lapsed attention during a task, we'll often see the default mode network lighting up and getting in the way. For this reason, we expected that changes both within and between these two sets of networks would be important for explaining attention functioning – and we were excited to see that this was indeed the case.

Although our research group is particularly interested in understanding attention deficit hyperactivity disorder (ADHD) and related issues like attention and self-control, we think that the same type of ICN analysis would naturally extend to other neurodevelopmental disorders. In fact, that's the direction we think the field is headed: A 2014 publication in Neuron (2) urges us to think developmentally about the functional architecture of the brain and how it relates to problematic conditions. That's why, as we run follow-up studies



to validate our findings, we've made our connectivity pattern maps available online so that other researchers can use them to examine their own datasets.

Connectomes in the clinic?

Although this type of growth chart is still a long way from seeing the clinic, we think it has a lot of promise. Unfortunately, MRI scanners – which we used in our study – are expensive and not widely available. We'd like to take the insights we've learned so far and try to apply them to data from electroencephalogram (EEG) machines, which are much cheaper and more common in everyday clinical settings. If the approach translates to EEG, it might offer a useful diagnostic tool for physicians to better understand the sources of attention problems. We're still learning a lot about the brain, but it's my hope that, if we can identify what goes wrong in a specific individual's brain, we can provide much more targeted treatment and support. For example, suppose that your child is struggling to pay attention in class. Neurologically, this could indicate a problem in that the default mode network is intruding on the attention networks – or it could just be an issue with how the attention networks are doing their jobs. You'd take your child to a pediatrician, who would order an EEG to score your child on growth charts for brain networks that have been identified as attentionally relevant. The doctor would then combine this information with a wealth of other data – for instance, reports from parents, teachers and the child themselves – to make a diagnosis and determine a treatment plan. That scenario is still a long way off, but I can imagine a future where a physician, armed with brain network growth charts, could prescribe treatments that target the specific brain problem, rather than the general behavioral problem.

Daniel Kessler is a Research Computer Specialist in the Department of Psychiatry at the University of Michigan, USA.

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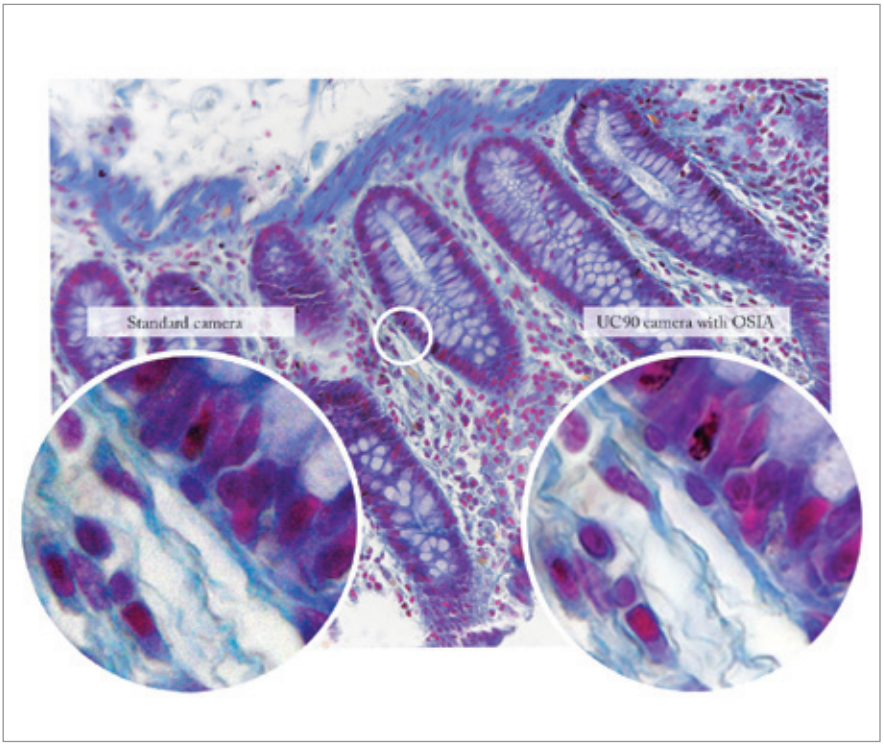
Entering the Era of 4K Microscopy

Presenting new opportunities for working on-screen alongside the oculars, 4K digital technology is revolutionizing microscopy cameras.

Since the emergence of digital microscopy for pathology, on-screen operation has presented a valuable way of working alongside the oculars. Presenting new opportunities for pathologists, 4K digital technology is revolutionizing microscopy cameras. While high resolution provides images both larger and more detailed than previously possible, 4K Microscopy cameras also implement additional technological advances for unprecedented image quality. Pathologists can now enjoy fast, comfortable and user-friendly on-screen operation – enhancing sample evaluation, facilitating effective collaborations and engaging the audience during presentations.



See the details, not the noise. 4K Microscopy with active noise reduction technology makes it possible to capture details that would otherwise be blurred by noise. (Olympus UC90 camera; Specimen: Human colon)

Enhanced on-screen sample analysis

While oculars undoubtedly provide the most life-like view of the sample, working over long time periods can be uncomfortable and slow, and on-screen visualization provides a complementary and comfortable alternative. In fact, 4K Microscopy has now advanced image quality to a standard where the information captured in a digital image rivals that seen through the oculars. Saving time by lessening the need to confirm observations with the oculars, pathologists are increasingly relying on both modes of visualization. 4K Microscopy technologies work in real-time to provide life-like color and cancel out image noise, revealing lifelike details. In addition, these same technologies facilitate daily operation, for quickly navigating across the sample, and enable pathologists to find the desired image focus on the first try.

Effective communication

Sharing detailed and accurate information is vital for effective collaborations. This is facilitated by 4K Microscopy, which combines a higher resolution with a large field of view to display structures on-screen both in detail and in context. Further advancing the analysis of larger regions, 4K Microscopy speeds up digital image stitching, requiring far fewer single acquisitions to form detailed and informative panoramic images.

Through these capabilities, the life-like images acquired with 4K Microscopy enables pathologists to communicate and display results in their best light during presentations or teaching sessions, engaging the whole audience. Complementing the use of multi-headed microscopes, a large group of scientists can easily view and discuss the sample with clarity and understanding, with simply a standard microscope fitted with a 4K camera and a large 4K screen.

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Liquid Biopsy and NGS: Teaming Up to Take Cancer Apart

Liquid biopsy is generating a lot of interest among the laboratory and clinician communities as a technique that enables research into tumor evolution. But, how is its use impacting the work of those in the lab, and how might it fit into the pathology lab in the future? We consider the pathologist's and oncologist's perspectives.

The Pathologist's View

Jose Machado, Director, Genetic Diagnosis Laboratory, Institute of Molecular Pathology and Immunology (Ipatimup), University of Porto, Portugal

What is your background and what kinds of tests does your lab perform?

I'm a molecular biologist by training. In my lab, we perform ~20,000 tests annually, of which 7–8 percent are molecular tests for cancer – occasionally comprehensive gene panels, but mainly single biomarker tests to predict therapeutic response. We usually look at *KRAS*, *NRAS* and sometimes *BRAF* in colorectal cancer; *EGFR*, *ALK* and sometimes *BRAF* in lung cancer; *BRAF* and sometimes *KIT* in melanoma; *KIT* and *PDGFRA* for gastrointestinal stromal tumors; and *JAK* mutations, chromosomal translocations and other alterations in hematological malignancies. At present, we only see liquid biopsy samples when tissue samples are not available, but that's changing, and I expect to see lots of liquid biopsy samples very soon.

How useful is the liquid biopsy technique?

The main advantage is speed. Using liquid biopsy samples, you can analyze the tumor molecular profile without the need for other techniques, so it helps you provide results for research in a shorter amount of time. You don't need any unusual equipment, so it's easy to incorporate it into the normal workflow. Liquid biopsy is also very useful when you're trying to understand the effect of therapy on a research sample. For example, lung tumors often relapse after EGFR tyrosine kinase inhibitor (TKI) treatment, and usually have an *EGFR T790M* mutation. Treatment exists for this mutation profile, but first you have to show that T790M is present. As tissue biopsy usually isn't feasible in these cases, liquid biopsy can serve as a powerful tool to advance thinking.

What are the advantages of the liquid biopsy–NGS combination?

We're still in the early clinical research phase, but we've found it to be a robust technique. Since implementing it, we've been collecting liquid biopsy samples at specific time points and analyzing them by next generation sequencing (NGS). Research shows that NGS techniques are able to detect mutations both in the expected genes and also in many other cancer-associated genes in the panel – p53 for instance. Furthermore, the mutation abundance in liquid biopsy samples correlates well with the tumor burden measured by clinicians in their research. It's a sensitive technique too. Concordance studies with ~500 tumor samples in our laboratory have shown over 95 percent sensitivity in detecting mutants in the primary tumor. You can increase or decrease sensitivity by reaction optimization; we can call variants of frequency ~0.1 percent in a wild type background, which is fairly good. Again, it's easy to fit liquid biopsy-NGS into a standard laboratory workflow, which is a big plus.

For a single biomarker, like T790M, PCR methods are still useful; however, as more resistance-associated alterations are identified, we'll need to detect multiple mutations at once. The need for multiplex techniques such as NGS will grow, and techniques optimized for liquid biopsy – like the Oncomine Lung cfDNA Assay (see Figure 1 and Table 1) – will have a place in clinical research.

Where will liquid biopsy fit in the laboratory of the future?

I think it may become a routine procedure in three main applications:

- Liquid biopsy research is well-suited to better understanding how a tumor changes after initial treatment. This understanding may, in the future, help us to select second-line therapy.
- As a replacement to tissue biopsies, particularly where speed is important and in situations where tissue biopsies are difficult
- To study tumor evolution during treatment and to use research findings to inform anticipatory second- or third-line therapy according to the molecular evolution of residual disease.

Going forward, molecular biologists, pathologists and oncologists must work closely to clinically contextualize liquid biopsy-NGS data, and thus to avoid drowning in a sea of genetic and molecular information.

The Oncologist's Perspective

Nicola Normanno, Director of Cell Biology and Biotherapy Unit, INT-Fondazione Pascale, Department of Research, Naples, Italy

How useful is the liquid biopsy technique from your perspective?

In liquid biopsy sample analysis, we are starting to see an important improvement: obtaining the samples is less invasive and less expensive compared with tissue biopsy samples.

In the future, the real outcome of this advantage may be that liquid biopsy sample analysis is accessible for more tumor types, at more pathology labs. These outcomes may be most clear for analyses where tissue samples are often not available.

What are the advantages of the liquid biopsy–NGS combination?

Tumors are highly heterogeneous, and every tumor that responds to targeted treatment eventually will become resistant. We can observe in research that each mutation may offer the potential for therapeutic intervention. Single mutation techniques, however, will not provide you with the information that you need to follow the molecular evolution of the tumor; techniques like NGS will be essential to the generation of a comprehensive molecular portrait of the tumor. Today, a liquid biopsy-NGS combination enables research to build understanding of tumor evolution. In the future, this understanding may guide therapeutic options.

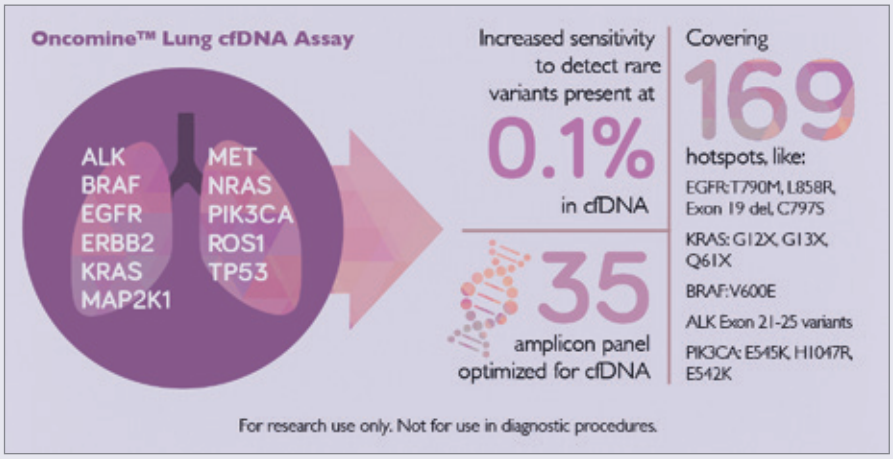

Figure 1. Overview of the Oncomine Lung cfDNA Assay.

Sample	*EGFR E746_A750delELREA*	*EGFR L858R*	*EGFR T790M*	*EGFR V769_D770insASV*	*KRAS G12D*	*NRAS A59T*	*NRAS Q61K*	*PIK3CA E545K*
0.1% HDX	*0.06*	*0.17*	*0.06*	*0.10*	*0.22*	*0.17*	*0.15*	*0.10*
1% HDX	*0.72*	*1.07*	*0.75*	*0.74*	*1.14*	*1.15*	*1.15*	*2.29*
5% HDX	*4.52*	*4.86*	*6.32*	*3.97*	*6.34*	*6.11*	*6.94*	*5.29*
100% WT	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*

Table 1. Variants called from Horizon cfDNA Multiplex Reference Set. All eight mutant hotspots were called at 0.1%.

Advancements in liquid biopsy-NGS are adding to our understanding of tumor resistance. As new targets are detected, we can imagine a future without chemotherapy. Ten years ago we wouldn't have believed that this was possible.

Liquid biopsy-NGS still requires further research and validation, however; circulating tumor DNA can come from many sites, whereas tissue biopsies samples are localized; they portray the situation in a small piece of tumor. Nevertheless, we find that liquid biopsy-NGS data are often confirmed by other techniques.

How do you see it being used in the future?

I believe that liquid biopsy-NGS research is starting a new era of personalized medicine for cancer. It enables a better understanding of tumor heterogeneity, and it's improving the field of oncology. However, we need external assessments to confirm that our results are reliable and may be useful for guiding treatment in the future. There's still a lot of work to do before this approach is routine in the clinic.

Also, we'll need to get better at managing information. The complexity of liquid biopsy-NGS tumor heterogeneity data may be difficult for medical oncologists to handle, so pathologists must contribute to the professional interaction and help us – oncologists and others – to interpret the data. If pathologists don't take on this proactive role, it will be difficult for us to transfer the growing number of benefits of these new discoveries to cancer therapy.

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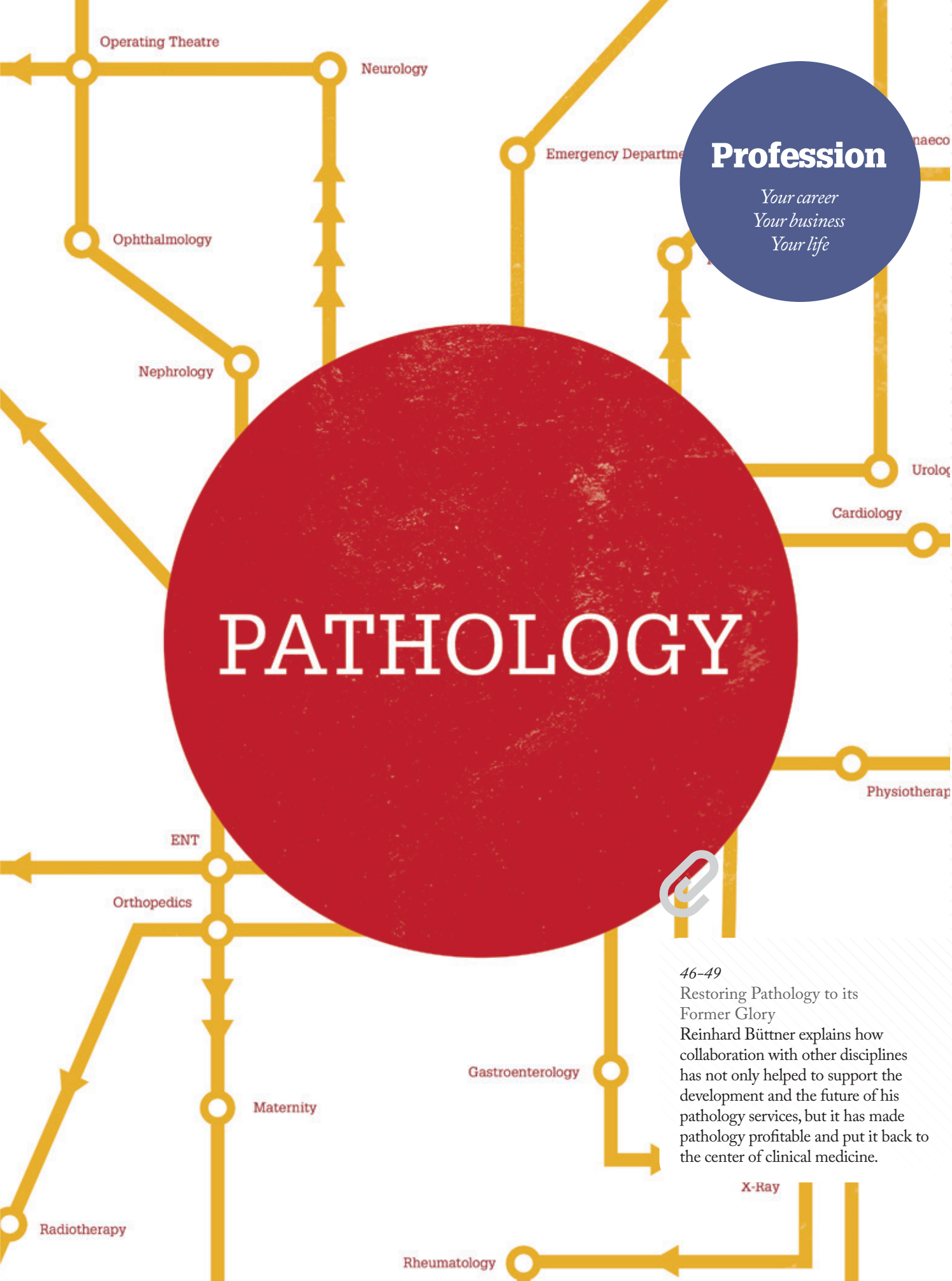

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Restoring Pathology to its Former Glory

Molecular pathology is becoming ever more key to our work – so pathologists must engage in education and collaboration to keep our discipline central to medical science

By Reinhard Büttner

The face of pathology is changing as fast as its disciples can keep up. With molecular techniques rocketing to the forefront and digital pathology becoming an increasingly significant part of the laboratory professional's workload, it's obvious that the word "pathology" no longer means what it did just a few short years ago. What hasn't changed, though, is pathology's status as a key component of medical research – so how can we restore it to its former glory and bring it back to the center of the biomedical sciences?

At a Glance

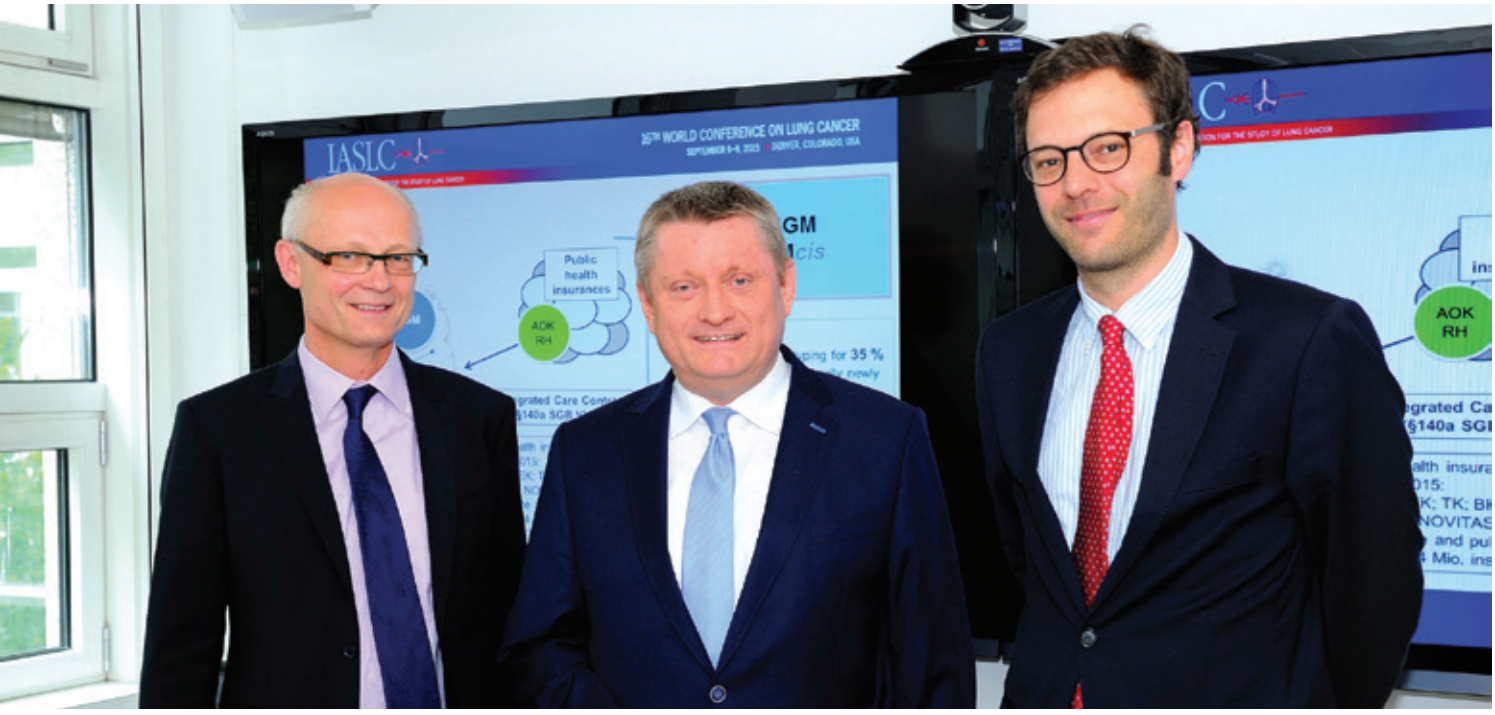
- *Pathology sits at the interface of research and clinical diagnostics – and as such, pathologists need a thorough knowledge of practical science, as well as medicine*
- *As genetics and genomics become an increasingly significant component of modern pathology, collaboration between pathologists and geneticists is crucial*
- *Pathology is not just scientific, but economic as well, and it's important to consider how services can add value and bring in funding for the laboratory*
- *All of these things contribute to bringing pathology back to the center of medical science and encouraging collaboration with researchers of all disciplines*

The genome generation

When I first took up pathology in 1986, I was immediately fascinated by the possibility of combining research and clinical diagnostics. It was a time of discovery for many oncogenes and genomic defects driving oncogenesis. Personally, I was following up the (incorrect) hypothesis that ras oncogene activation might also arise from amplification and translocation, and for that project, I was trying to establish Southern blotting in the pathology department at the University of Aachen in Germany, where I worked. That's when I realized my complete ignorance of practical science – a lack of knowledge I needed to remedy to be an effective pathologist. As a result, I spent almost four years as postdoctoral scientist, splitting my time between the University of Munich's Gene Center and the University of Texas MD Anderson Cancer Center. After my sojourn in the United States, I returned to Germany much better educated and ready to take on new challenges: first a pathology residency at the University of Regensburg, and then the establishment of my own research group in molecular pathology. Ever since, I have been trying to understand the molecular basis of morphology and oncogenesis – a curiosity that has led my laboratory to successfully pioneer the cloning of a number of homeobox genes and receptors.

After establishing a collaborative research group investigating mechanisms of cell death funded by the DGF (German Research Society), I was appointed full professor of pathology at the University of Aachen in 1999 and then, two years later, became chair of the pathology department at the University of Bonn. But around 2010, it became clear to me that next generation sequencing and comprehensive cancer genotyping held tremendous promise for pathology, so I decided to move to the University of Cologne, where I saw a chance to turn that promise into reality. My colleagues and collaborators there shared my strong vision for molecular medicine, and the Comprehensive Cancer Center CIO Cologne was – and still is – Germany's best place for translational cancer research. Molecular pathology plays a huge role and, ever since I started work here, the hospital's CEOs have massively supported new initiatives. For instance, along with oncologist Jürgen Wolf and molecular geneticist Roman Thomas, I founded the Genomic Medicine Network (Netzwerk Genomische Medizin, www.ngm-cancer.com), now by far Germany's largest initiative for comprehensive cancer profiling. Over the last five years, the Network has analyzed more than 20,000 cancer genomes in order to funnel patients into appropriate targeted therapies. That's a lot of patient benefit!

I think that collaboration with genetics is crucial for diagnostic pathology's ongoing development. Discovering the genomic basis of pathological changes in tissues has become a reality in daily practice. To that end, my colleagues and I have allied with genetics to create a special Center for Familial Cancers. By analyzing the mutations that occur in our patients' tumors, we frequently find that they suffer from predispositions to cancer – and as a result, we funnel a number of patients into the Center for further evaluation and treatment. This kind of collaboration is not only good for those patients, but also great for scientific advancement, so I hope we see much more of it going forward. In fact, we regularly host guest pathologists and scientists from all over the world. I invite every pathologist who wishes to share



From left to right: Reinhard Büttner (Institute for Pathology, Cologne), Hermann Gröhe (Minister of Health, Germany), Roman Thomas (Institute for Translational Cancer Genomics, Cologne).

our philosophy to spend some time with us, learn how we run our department, and take home any knowledge they find useful!

Making pathology important and profitable

I think our most important accomplishment is that we have brought pathology back to the center of clinical medicine, at least in oncology. No patient at the University Hospital is treated without in-depth pathology analysis and discussion in a multidisciplinary tumor board. If a pathologist is not present, the board will not make decisions. We've also reinstated pathology as one of the most scientifically productive departments at the hospital – and we're productive in other ways as well; I believe that the Genomic Medicine Network now serves as a blueprint for molecular oncology, and will eventually guide the formation of a national network for cancer patients.

I never think about balancing scientific productivity with the business of pathology – I just listen to my instincts and curiosity. I feel that if you're always thinking about business and profits, you're going to lose your spirit. Somehow, despite its casual nature, my approach has been the basis for both economic and scientific success, making pathology one of the most profitable departments at our hospital. To give you an example, in 2014, we were running out of resources for multiplex cancer genome profiling due to the end of a grant. We decided to continue testing without reimbursement because we had great faith in it, both scientifically and for the sake of our patients. As a result, by the end of the year, profits in my department had fallen by €1 million and our administration was getting increasingly nervous. Luckily, many German insurance companies eventually realized the benefits of what we were doing – they asked for an expert opinion and came to the conclusion that reflex testing of multiple oncogenic alterations in lung cancer by NGS is economically more efficient than sequential single biomarker testing and also beneficial for patient outcome. And we started to receive regular reimbursement from an integrated care contract (a specific contract reimbursing a health service selectively for a group of healthcare providers, in our case Pathology, at our University together with hundreds of lung oncologists in Germany), providing substantial revenue for the hospital. It has always been our philosophy to do the things we believe in. We owe thanks to our administration for their continuous support in whatever we choose to pursue, but as you can see, the results have been great so far.

The system by which molecular biology services are reimbursed in Germany is

Coming to Cologne

XXXI Congress of the International Academy of Pathology (IAP) and 28th Congress of the European Society of Pathology (ESP)

Who?
The International Academy of Pathology (IAP): a group dedicated to advancing pathology worldwide through educational exchanges, including hosting international meetings, providing news bulletins, allocating funds, and maintaining a council of representatives. The European Society of Pathology (ESP): a group dedicated to advancing European pathology by providing such services as governance, funding, the journal Virchows Archiv, and postgraduate courses through its European School of Pathology.

What?
A joint venture between the IAP and the ESP, this year's congress has the motto of "Predictive Pathology, Guiding and Monitoring Therapy." It focuses on the future role of pathology as a strong partner for all other clinical specialties (a role too often overlooked) and on recent developments in diagnostics, particularly in molecular pathology.

Where?
The Kölnmesse, Cologne, Germany.

When?
September 25 to 29, 2016.

What is your role in this year's IAP/ESP congress?
I'm involved as a convener for lung pathology (along with Bill Travis and Lina Carvalho) and as former president of the German IAP and Cologne's most senior local pathologist. I've helped organize the lung pathology track of the conference, participated in organizational and financial meetings, and helped plan the social and cultural events.

I am very happy that the ESP and the IAP have allied to organize a joint meeting like this. I hope we're setting a new standard; the next European IAP meeting in Glasgow in 2020 will be joint with the ESP again, and I'd like all future IAP meetings in Europe to be the same. I also think, though, that this particular conference is an important step forward for the German IAP's international involvement, and a good opportunity for us to encourage as many international pathologists as possible to come to our country. Many pathologists, especially those early in their careers, aren't fortunate enough to be able to travel to such meetings – so it's important to establish financial and organizational support for the next generation, and to ensure that we make up-to-date, high-level educational programs available to them.

What support is being made available to young pathologists to attend events?
One example is the Vladimir Totovic Foundation, a charity we recently started whose vision is to support the central role of pathology in medicine, and especially to support young doctors and scientists who see their future in pathology. There are three main tools we're using to achieve those aims:

- First, one internationally renowned pathologist each year is awarded the Vladimir Totovic Prize (€5,000) and presents the Totovic Lecture on their work at the Annual Meeting of the German Division of the IAP.
- Second, we provide research and educational support for young pathologists moving from abroad to Germany, or from Germany to overseas laboratories. Last year, we awarded three stipends to fellows from Bosnia, Italy and Syria.
- Third, we create travel grants to enable young pathologists to attend international meetings. This year, we're focusing on bursaries for the IAP/ESP congress in Cologne, but we've also previously given awards to enable attendance at the United States and Canadian Academy of Pathology and Asian-Pacific IAP meetings.

By ensuring that early-career pathologists can attend, and that our programming is of the highest quality, we aim to make the joint IAP/ESP conference the world's largest scientific and educational event in pathology – and, at the same time, to establish pathology as an interdisciplinary diagnostic subject. My personal goal for this year's congress is to present pathology to the entire world as the most fascinating life science there is! Our key message is: pathology is a young science and young scientist will guide future medical sciences.

changing right now. At the moment, there are still problems with it; new therapies are being introduced without reimbursement of the biomarkers. The integrated care contract I mentioned earlier, established within the Genomic Medicine Network, provides a convenient solution, which is why I'm so happy that other German university hospitals are now joining a similar national network. With the help of the German Cancer Aid, the plan is that 16 other molecular pathology platforms in Germany will be enabled to perform multiplex NGS diagnostics and serve interdisciplinary, genomically-informed tumor boards for innovative and targeted therapies.

"If a pathologist is not present, the board will not make decisions. We've also reinstated pathology as one of the most scientifically productive departments at the hospital."

I strongly believe that university departments are true drivers in molecular medicine. However, as pathology is now more involved than ever in clinical decision-making, it's also needed in regional hospitals farther from universities. We've established a model for combining local presence and connecting local units to big centers, which we follow in our own hospital; our department is connected to a wide variety of regional departments in a 110-kilometer radius from Siegen to Luxembourg. For some, we provide the entire anatomical pathology service, including staffing. In other cases, we serve as preferred collaborators and receive histology slides and perform molecular services.

Encouraging healthy competition

There's clear competition between Germany's major universities in terms of scientific performance. For example, part of our scientific funding from the Ministry of Science and Technology is based on our performance in comparison to other university hospitals, and part of the funding provided by the medical faculty is based on scientific output in comparison to other departments. But that's not the only source of rivalry these days; there is also severe competition between university, regional and private hospitals for patients and services. Pathology is no longer purely scientific – it's economic now as well, and we regularly analyze our department's performance with a team of financial controllers.

We also go outside the standard scope of our work by providing extensive pathology services in Luxembourg. It's a very small country that lacks a university hospital, and – like so many other places – it has a hard time attracting enough medical students to the field of pathology. Cologne has a long tradition of supporting Luxembourg (a few places at our medical school, for instance, are always reserved for students from Luxembourg), so we help out with pathology at the Labaratoire National de Santé (LNS). The LNS is now under the direction of Fernando Schmitt, a good friend and visionary pathologist and cytologist, who shares our philosophy with regard to molecular pathology and is eager to collaborate with us. At the moment, we're establishing direct links between our patient information systems so that we can work together even more closely and effectively.

The pathology of the future

At my institute, we have recently moved to very comprehensive hybrid capture gene panels in molecular diagnostics. For hereditary cancer patients, whole exome sequencing will also be an appealing option in the future. Genomic and proteomic technologies are taking their place next to histology as crucial techniques for the pathology lab – so it's increasingly important for pathologists to receive appropriate training in molecular pathology, so that they understand these analyses.

Digital pathology is another incoming revolution. We will be able to steer our workflow much better, work outside the lab whenever necessary, and see a trend toward more quantitative work on digital slides. As pathology becomes entirely digital, I anticipate a wide range of new capabilities – things like three-dimensional organ reconstruction from slides, or merged morphologies generated by overlaying histology, molecular data, radiological images and functional imaging. All of these are fascinating possibilities, but they'll require large datasets, and pathologists will need a more robust understanding of electronic data handling than ever before.

I think that, a decade from now, the average pathologist will need both a strong science background and solid training across almost all areas of medicine. They'll be working in teams rather than alone, and they will spend a lot of time in interdisciplinary clinical boards. I also anticipate that pathology will return to its former place as a central discipline for medical research – and pathologists themselves will become key collaborators with scientists of all kinds.

Reinhard Büttner is Professor and Chairman of the Institute for Pathology at the University Hospital Cologne, Center for Integrated Oncology, Cologne, Germany.

Marker of Excellence

Sitting Down With… Professor Anthony Whetton,
Director of the Stoller Biomarker Discovery Centre, Manchester, UK

How did you get involved in the biomarker field?

My focus has been leukemia research since 1984. I began working with proteomics in 1999, and then moved into biomarker discovery, simply through wanting to do the best possible research for the most clinical impact. We soon started using our proteomics platform outside leukemia – for example, biofluids analysis – to identify markers relevant to cancer. Consequently, we applied for £13 million Medical Research Council (MRC) funding to develop the Stoller Biomarker Discovery Centre, which is now the largest clinical proteomics center in Europe.

How difficult was it to muster the resources needed to win the MRC grant?

It relied on teamwork. First, we pulled together stratified medicine groups with expertise in psoriasis, lupus, arthritis, and cancer – everything starts with clinical need. Then we co-operated to show the MRC that we had the ideal basis for development of a transformational biomarker discovery platform. But it took 4–5 iterations before we got the award, and each one was more difficult than the last. I still find it hard to believe that we succeeded!

You have 13 mass specs – why have you chosen to invest so heavily in this technology?

It's the best technology for discovery proteomics, and the instruments get better and more sensitive every year; for example, it's clear that SWATH-MS markedly increases efficiency. So we concluded that the industrialization of proteomics would be best-served by adopting mass spectrometry (MS) technology. There are other approaches to proteomics – for example, antibody arrays – but we think MS is best for biomarker discovery.

How important are collaborations to you?

We've always sought collaborations to identify disease-associated biomarkers, and we continue to invite collaboration on biofluid and tissue sets from other centres. One collaboration with Tessa Holyaoke at the University of Glasgow has led to a potentially curative strategy for chronic myeloid leukaemia (1) which I hope will soon be in clinical trials. That development could not have happened in either institute alone.

How long does it take to develop a new biomarker into a clinical CDx?

Too long – about 10 years. One problem is that samples aren't collected early enough in the clinical study, due to issues such as cost, time and availability of research nurses. But another point is that you need a very well-regulated laboratory environment, including a recording regime which passes regulatory scrutiny. At the Stoller Centre, we work to the highest relevant standards as early as possible. This will compress the period between biomarker discovery and clinical application – our target is to bring four biomarkers to the clinic in the next five years. Our quality regime is aimed at meeting international standards – including MHRA, FDA and EMA requirements – and covers MS, antibody-based assays, sample storage, laboratory information management systems and informatics.

Is global investment in biomarker research reflected in approvals of new CDxs?

No – the rate of biomarker regulatory approvals isn't changing, perhaps because biomarker development is so hard. You must address issues including statistical surety, sensitivity, specificity – which must be very high to support a biomarker launch. You cannot afford to get it wrong. It's just not acceptable to have a high false positive or negative rate.

What will be the impact on healthcare budgets of increased CDx use?

There are obvious clinical and health economic benefits to using a biomarker test to assess responsiveness before or just after initiation of treatment. For example, if you treat patients with expensive biologics, at £10,000/ year, for months before you know whether they respond to it, that's not good for the health service, the taxpayer or the patient. But biomarkers help to get the right drug to the right patient at the right time. There are good exemplars of this in leukemia – for example, in CML you test for the chromosomal translocation encoding BCR-ABL, which indicates treatment with tyrosine kinase inhibitors.

What role does informatics and big data play in biomarker development?

Informatics tools support digitization of the proteomic map for any individual, and association of the map with an electronic healthcare record. And that allows you to identify false positives and false negatives and develop the test surety. Furthermore, future CDx will not rely on single markers, but will use algorithms to derive information from multiple measured factors, and this too will require informatics capabilities. Applying informatics to proteomic data will allow accommodation of co-morbidities, concomitant medications, and other confounding factors, thus enabling development of algorithms with high sensitivity and surety.

How important is pathology expertise?

It's a fantastic asset! We absolutely need pathology expertise to move from the lab to clinical usage as swiftly as possible. That's why we applied for and obtained another £3 million from the MRC to build the pathology node, led by Tony Freemont, which takes our discoveries and translates them into something of clinical value. This integration of expertise will allow us, ultimately, to improve healthcare outcomes for everyone.

Reference

1. *SA Abraham et al., "Dual targeting of p53 and c-MYC selectively eliminates leukaemic stem cells", Nature, 8, 534, 341–346 (2016). PMID: 27281222.*

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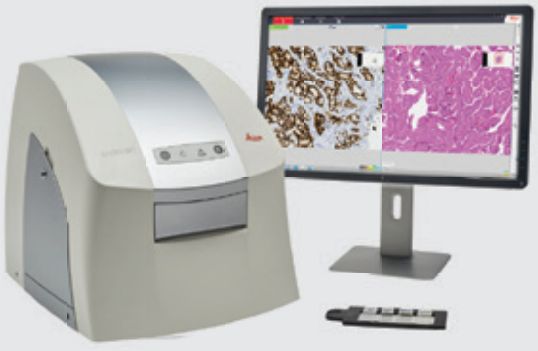

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